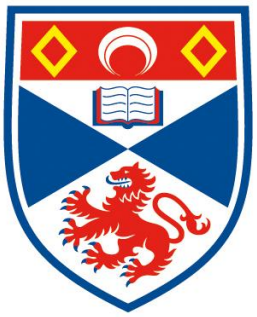
ORGANOCATALYTIC FUNCTIONALISATION OF CARBOXYLIC ACIDS USING ISOTHIOUREAS

Louis Christian Morrill

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews

2014



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This thesis is submitted in partial fulfilment for the degree of PhD at the University of St Andrews

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Acknowledgements

Firstly, I would like to thank my supervisor, Professor Andrew Smith for giving me the opportunity to work within his research group and for all his support and guidance throughout my undergraduate and postgraduate degrees. I am also very grateful for the help of our collaborator, Dr David Fox at Warwick University for his patience and expertise with regards to the kinetic and computational work described in this thesis.

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Abstract

This thesis describes investigations into the ability of isothioureas to act as organocatalysts in formal [4+2] cycloadditions between carboxylic acids and various Michael acceptors *via* C1-ammonium enolate intermediates.

Initial research focused upon establishing optimal reaction conditions to affect the asymmetric intermolecular formal [4+2] cycloaddition between a range of arylacetic acids and α-keto-β,γ-unsaturated esters, giving *anti*-dihydropyranones in high yield (49-87%) and with excellent diastereo- and enantioselectivity (up to 98:2 dr, up to 99% ee). This represented the first time that carboxylic acid derived ammonium enolates have been successfully applied towards an intermolecular reaction process.

Subsequent studies utilised trifluoromethyl enones as Michael acceptors, forming a range of C(6)-trifluoromethyl *anti*-dihydropyranones with good diastereoselectivity (up to 95:5 dr) and enantioselectivity (up to >99% ee). Detailed mechanistic studies were carried out, revealing that the process was stereospecific, with the diastereoisomer of product formed dependent upon the configuration of trifluoromethyl enone used. A variety of product derivatisations were demonstrated including those which introduce additional trifluoromethyl-bearing stereogenic centres with high diastereoselectivity. Kinetic studies indicated that this Michael addition-lactonisation process is first order with respect to both *in situ* formed anhydride and catalyst concentration, with a primary kinetic isotope effect observed using α,α-di-deuterio 4-fluorophenylacetic acid. DFT computational studies support a rate-determining formation of a reactive ammonium enolate prior to a stereochemistry-determining enone conjugate-addition step.

The isothiourea-catalysed α-amination of carboxylic acids with low catalyst loadings (as low as 0.25 mol%) using *N*-aryl-*N*-aroyl Michael acceptors was demonstrated, forming a range of 1,3,4-oxadiazin-6(5*H*)-ones or hydrazide products with excellent enantiocontrol (typically >99% ee). Notably, the scope of this methodology was expanded to allow the direct functionalisation of carboxylic acids bearing α-heteroatom and alkyl substitution for the first time. The synthetic utility of the hydrazide products was demonstrated through their derivatisation into a range of bespoke functionalised *N*-aryl-α-arylglycine derivatives in high enantiopurity (up to 99% ee).

Isothiourea-mediated functionalisation of 3-alkenoic acids was shown to occur regioselectively, giving products derived from α-functionalisation of an intermediate C1-ammonium dienolate in a range of formal [2+2] and [4+2] cycloadditions. Formal

[4+2] cycloadditions with either trifluoromethyl enones of *N*-aryl-*N*-aroyl diazenes allow access to products in high diastereo- and enantiocontrol (up to 95:5 dr, up to 99% ee). The simple, two-step elaboration of stereodefined hydrazides into aza-sugar analogues without erosion of enantiopurity has also been demonstrated.

2-Arylacetic anhydrides were also demonstrated as useful precursors for the formation of C1-ammonium enolates in isothiourea-mediated Michael addition-lactonisation processes. Trifluoromethylenones, α-keto-β,γ-unsaturated esters and *N*-aryl-*N*-aroyldiazenes are reactive Michael accceptors in this process, with HBTM-2.1 (5 mol%) readily promoting heterocycle formation with high diastereo- and enantiocontrol (up to 95:5 dr, up to >99% ee). This protocol offered a useful and practical alternative to the *in situ* carboxylic acid activation method, in which by-product formation and the amount of sacrificial base used is minimised.

DHPB was shown to promote the one-pot synthesis of 2,4,6-subsituted pyridines bearing a readily derivatised 2-sulfonate functionality from (phenylthio)acetic acid and a range of α,β-unsaturated ketimines in moderate yields (40-66%). Functionalisation of the 2-sulfonate group *via* various methodologies allowed the rapid assembly of both novel and biologically relevant pyridines.

Publications

The work described in this thesis has formed the basis of the following peer reviewed publications to date:

1) "Isothiourea-Mediated Asymmetric Functionalization of 3-Alkenoic Acids", L. C. Morrill, S. M. Smith, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem.*, 2014, **79**, 1640-1655.
2) "2-Arylacetic Anhydrides as Ammonium Enolate Precursors", L. C. Morrill, L. A. Ledingham, J-P. Couturier, J. Bickel, A. Harper, C. Fallan and A. D. Smith, *Org. Biomol. Chem.*, 2014, **12**, 624-636.
3) "Isothiourea-Mediated One-Pot Synthesis of Functionalised Pyridines", D. G. Stark, L. C. Morrill, P-P. Yeh, A. M. Z. Slawin, T. J. C. O'Riordan and A. D. Smith, *Angew. Chem. Int. Ed.*, 2013, **52**, 11642-11646.
4) "Isothiourea-mediated asymmetric Michael-lactonisation of trifluoromethylenones: a synthetic and mechanistic study", L. C. Morrill, J. Douglas, T. Lebl, D. J. Fox, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2013, **4**, 4146-4155.
5) "Catalytic asymmetric α-amination of carboxylic acids using isothioureas", L. C. Morrill, T. Lebl, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2012, **3**, 2088-2093.
6) "Organocatalytic Functionalisation of Carboxylic Acids: Isothiourea-Catalysed Asymmetric Intra- and Intermolecular Michael Addition-Lactonisations", D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc*., 2011, **133**, 2714-2720.

Abbreviations

Ac	Acetyl
app.	Apparent
ASAP	Atmospheric solids analysis probe
aq	Aqueous
Ar	Aromatic
atm	Atmosphere
ATR	Attenuated total reflectance
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
br	Broad
BTM	Benzotetramisole
Bu	Butyl
Bz	Benzoyl
c	Concentration
C	Celsius
CAN	Ceric ammonium nitrate
cat.	Catalyst
Cbz	Carboxylbenzyl
CI	Chemical ionisation
Cy	Cyclohexyl
cm	Centimeter
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
decomp.	Decomposition
DFT	Density functional theory
DHPB	3,4-Dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole
DIBAL-H	Di-*iso*-butylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine

DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diasteroisomeric ratio
EDG	Electron donating group
ee	Enantiomeric excess
EI	Electron impact
eq	Equivalent molar quantity
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HOMO	Highest occupied molecular orbital
HBTM	Homobenzotetramisole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IPA	Isopropanol
IR	Infrared
ITU	Isothiourea
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium di-*iso*-propylamide
LHMDS	Lithium hexamethyldisilazide
LRMS	Low resolution mass spectrometry
LUMO	Lowest occupied molecular orbital
M	Molar (i.e. mol dm^{-3})
MM	Molecular mechanics
m	Multiplet
m	*Meta*
Me	Methyl
Mes	Mesityl

MHz	Megahertz
mg	Milligram(s)
mL	Millilitre(s)
mol	Mole(s)
mp	Melting point
MS	Mass spectrometry
M. S.	Molecular sieves
NBS	*N*-Bromosuccinimide
NCAL	Nucleophile-catalysed Aldol-lactonisation
NFSI	*N*-Fluorobenzenesulfonimide
NHC	N-heterocyclic carbene
NMM	*N*-Methylmorpholine
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
NSI	Nanospray ionisation
o	*Ortho*
oct	Octet
p	*Para*
PG	Protecting group
Ph	Phenyl
ppm	Parts per million
PPY	4-Pyrrolidinopyridine
Pr	Propyl
PS	Polymer supported
q	Quartet
quant.	Quantitative
quint	Quintuplet
R	Alkyl
rt	Ambient (room) temperature
s	Singlet
sat.	Saturated
sept	Septet
t	Triplet/time

t	*Tert*
T	Temperature
TBS	*tert*-Butyldimethylsilyl
Tf	Triflyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Tetramisole
TMS	Trimethylsilyl
TS	Transition state
Ts	Tosyl
ZPE	Zero point energy

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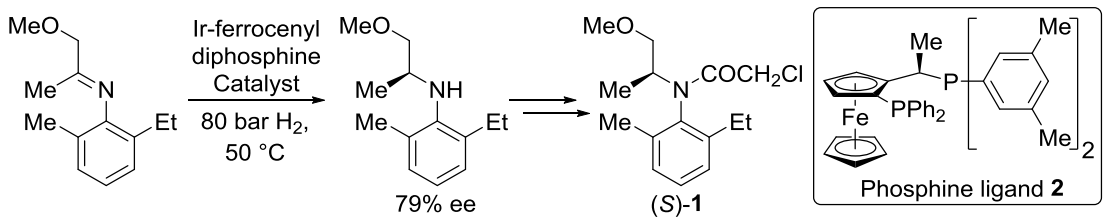
Chapter 1: Introduction

1.1 Asymmetric Catalysis

In many biological systems it is known that the two enantiomers of a chiral compound are recognised as different substances and often produce biological responses distinct from one another. There are documented cases, such as the sedative thalidomide which was withdrawn from the market in 1961 due to being identified as the cause of birth defects, in which one enantiomer of a drug when administered has the desired therapeutic effect while the other enantiomer causes adverse biological effects.[1] It is therefore important to be able to prepare pharmaceutical compounds in exclusively one enantiomeric form (100% enantiomeric excess) or the U.S. Food and Drug Administration agency – who treat the presence of the undesired enantiomer as an impurity – will withhold drug approval. A variety of ways exist to access one enantiomeric form of a chiral compound including traditional methods such as chemical resolution and the use of chiral auxiliaries.

Despite the merits of these approaches a particularly appealing, yet challenging field is asymmetric catalysis that aims to use chiral catalysts in sub-stoichiometric quantities to create enantiomerically pure products. The potential economic advantages of this approach over stoichiometric methods are clear, and this is reflected by the explosion of interest in developing new catalytic asymmetric processes suitable for application on industrial scale. There are currently a number of such processes operating in industry, many of which use transition metals. A leading example is the industrial synthesis of Metachlor (*S*)-**1**, a popular herbicide, which includes within its synthesis the hydrogenation of an imine using iridium and a chiral ferrocene-derived phosphine ligand **2**. The process yields over 10,000 tonnes of product a year from only 34 kg of iridium (Scheme 1).[2]



Scheme 1: Industrial asymmetric synthesis of Metachlor (*S*)-1.

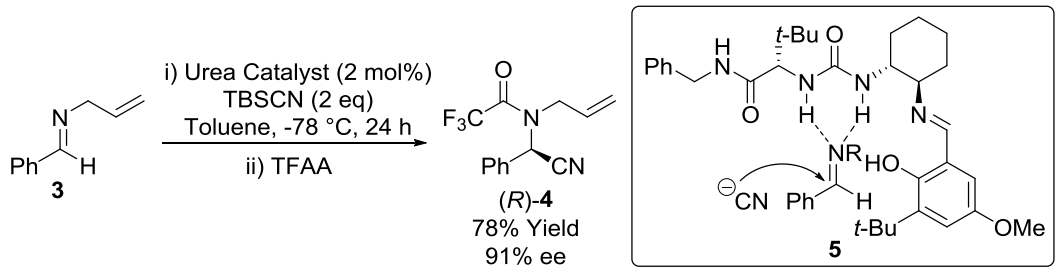
1.1.1 Organocatalysis

Although the field of enantioselective metal-catalysed processes had been well established, until around the year 2000, relatively few processes had been communicated which make use of organic molecules to catalyse asymmetric reactions. Organocatalysis is an attractive alternative to metal-catalysed processes due to the inherent benefits of using organic molecules as catalysts such as their typically low sensitivity to moisture and air, low cost and toxicity along with being easily handled and readily accessed from the chiral pool.

Organocatalysis is typically defined as the acceleration of a chemical reaction by addition of a substoichiometric amount of an organic molecule which does not contain a metal atom,[3,4] and can be divided into four main types of activation modes: Brønsted acid, Brønsted base, Lewis acid and Lewis base.

1.1.1.1 Brønsted Acid Catalysis

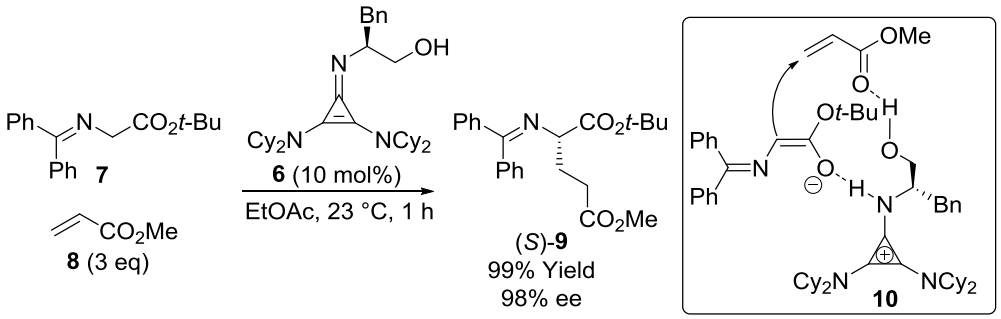
In Brønsted acid activation the catalyst initially donates a proton to the substrate (Brønsted base) and subsequently imparts asymmetry *via* hydrogen bonding or tight ion-pairing.[5] Typical catalysts that operate by this organocatalytic reaction mode are ureas, thioureas, BINOL derivatives, phosphoric acids and more recently phosphoramides. Jacobsen is one of the pioneers in this field and in 1998, illustrated how chiral ureas could be used as Brønsted acid catalysts for an asymmetric Strecker reaction by lowering the LUMO of the imine *via* hydrogen bonding to the substrate.[6] Reaction of imine **3** with TBSCN in the presence of TFAA and a chiral urea derivative gave cyanated amide (*R*)-**4** in 78% yield and 91% ee *via Si*-face attack of cyanide on the LUMO activated imine **5** (Scheme 2).



Scheme 2: Brønsted acid-catalysed Strecker reaction.

1.1.1.2 Brønsted Base Catalysis

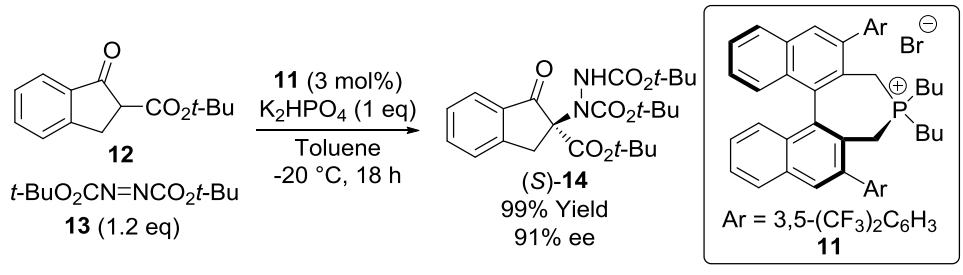
Brønsted base catalysis involves the initial deprotonation of the substrate (Brønsted acid) by the catalyst and asymmetry results from a tight ion-pair between the protonated chiral catalyst and the deprotonated substrate.[7] Many catalyst architectures have found application as Brønsted bases including Cinchona alkaloids, thioureas, amidines and guanidines. A recent example from the Lambert group utilises the highly basic chiral cyclopropenimine organocatalyst **6** to impart high levels of asymmetry in the Michael addition of glycine imine substrate **7** to acrylate **8**, giving amino acid derivative (*S*)-**9** in 99% yield and 98% ee (Scheme 3) *via* pre-TS assembly **10**.[8]



Scheme 3: Brønsted base-catalysed Michael addition.

1.1.1.3 Lewis Acid Catalysis

In Lewis acid activation the organocatalyst has the ability to accept a lone pair of electrons from the substrate and asymmetry can be induced *via* tight ion pairing.[9] Many organic Lewis acid catalysts operate *via* phase transfer catalysis and an example from the Maruoka group utilised axially chiral phosphonium salt **11** as catalyst for the asymmetric α-amination of β-keto ester **12** using diazodicarboxylate **13**, giving (*S*)-**14** in 99% yield and 91% ee (Scheme 4).[10]



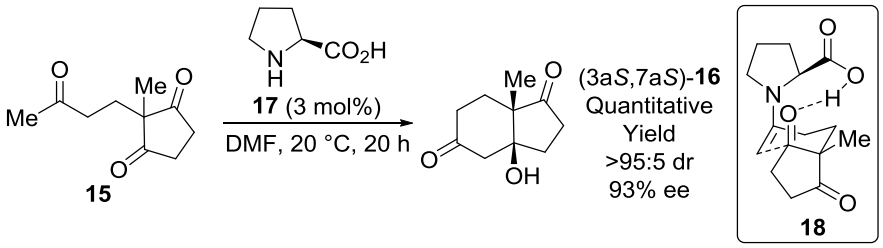
Scheme 4: Lewis Acid-catalysed asymmetric α-amination.

1.1.1.4 Lewis Base Catalysis

Lewis base activation represents the largest area of organocatalysis and can be broadly described by the ability of a catalyst to activate a substrate molecule through the donation of a lone pair of electrons.[11] The term Lewis base catalysis encompasses a range of activation modes including enamine, iminium, SOMO, ylide, acyl ammonium, ammonium enolate and carbene catalysis. Representative examples of selected reaction modes are described here with ammonium/azolium enolates described later in more detail.

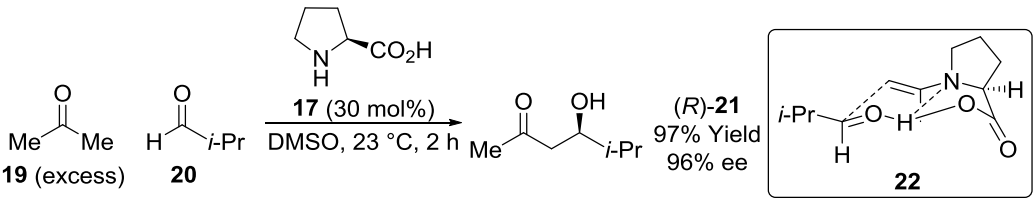
1.1.1.4.1 Enamine Catalysis

Enamine catalysis involves the condensation of a secondary amine with a carbonyl group, followed by tautomerisation of the iminium cation formed *in situ* to generate an enamine intermediate.[12] This HOMO activated, nucleophilic species can then undergo reaction with various electrophiles or can partake in pericylic reactions. The Hajos-Parrish-Eder-Sauer-Wiechert cyclisation, published in 1971, is one of the earliest and perhaps most celebrated examples of enamine catalysis and involves a proline-catalysed asymmetric intramolecular aldol reaction.[13] This reaction allows the conversion of triketone **15** to the enantiomerically enriched bicyclic diketone (3a*S*,7a*S*)-**16** in the presence of (*S*)-**17**, the amino acid proline, through proposed pre-TS assembly **18** in quantitative yield and 93% ee (Scheme 5).



Scheme 5: Hajos-Parrish-Eder-Sauer-Wiechert cyclisation.

In 2000, List and co-workers further explored the utility of (*S*)-proline in enamine organocatalysis.[14] Their work showed that the enamine intermediate could be applied to the asymmetric intermolecular aldol reaction. For example, an intermolecular aldol reaction between acetone **19** and isobutyraldehyde **20** in the presence of (*S*)-**17** generates the aldol product (*R*)-**21**, through proposed pre-TS assembly **22** in 97% yield and 96% ee (Scheme 6).

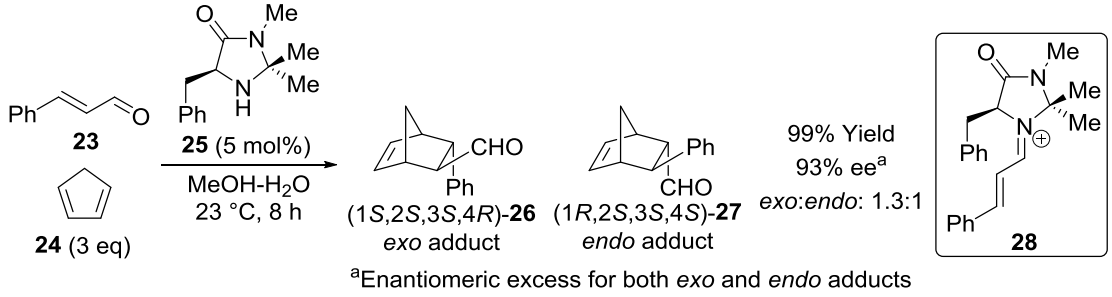


Scheme 6: (*S*)-proline-catalysed asymmetric aldol reaction.

This powerful illustration of the utility of (*S*)-proline in the asymmetric aldol reaction spurred on research into its ability to catalyse related asymmetric reactions such as the Mannich and Michael addition reactions.[15]

1.1.1.4.2 Iminium Catalysis

Iminium catalysis involves the generation of a reactive iminium ion *via* the condensation of an amine catalyst with a carbonyl substrate.[16] In 2000, Macmillan and co-workers showed how this principle could be used to catalyse a highly enantioselective organocatalytic Diels-Alder reaction.[17] Treatment of (*E*)-cinnamaldehyde **23** with cyclopentadiene **24** and imidazolidinone (*S*)-**25** affords the Diels-Alder adducts (1*S*,2*S*,3*S*,4*R*)-**26** and (1*R*,2*S*,3*S*,4*S*)-**27** as a 1.3:1 *exo*/*endo* ratio in 99% combined yield and with both isomers formed in 93% ee *via* the LUMO activated iminium ion **28** (Scheme 7).

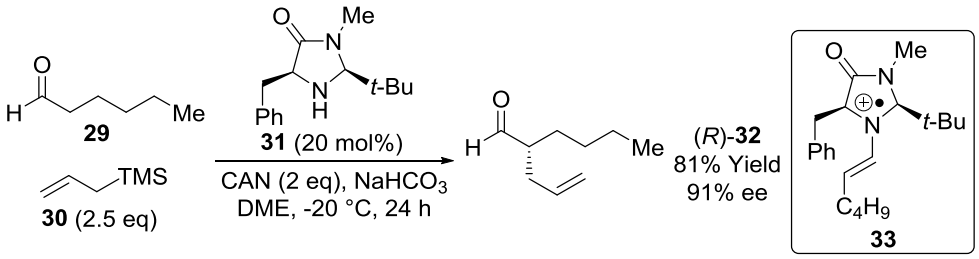


Scheme 7: Asymmetric Diels-Alder reaction.

1.1.1.4.3 SOMO Catalysis

Singly occupied molecular orbital (SOMO) catalysis involves the generation of a reactive radical cation *via* the one electron oxidation of an electron rich enamine. The resulting electrophilic species can react with carbon-based nucleophiles to produce a variety of α-functionalised products. In 2007, Macmillan and co-workers illustrated how this new mode of activation could be used to catalyse the highly enantioselective organocatalytic α-allylation of aldehydes.[18] Reaction of hexanal **29** and allyl silane **30**

with imidazolidinone (2*S*,5*S*)-**31** and 2 eq of oxidant ceric ammonium nitrate gives α-allylated aldehyde (*R*)-**32** in 81% yield and 91% ee *via* the SOMO activated radical cation **33** (Scheme 8).



Scheme 8: Asymmetric α-allylation reaction.

1.1.1.4.4 N-Heterocyclic Carbene Catalysis

Carbene catalysis involves the utilisation of a nucleophilic carbene species, often an N-heterocyclic carbene (NHC).[19] The formally electron deficient carbene centre is stabilised by two separate effects. Mesomeric stabilisation arises from π-electron donation from the adjacent nitrogen lone pairs into the vacant p_π orbital. There is also a σ-withdrawing effect due to the adjacent electronegative nitrogen substitutents (Figure 1). Introducing bulky *N*-substituents also increases the stability of NHCs by shielding the orthogonal lone pair.

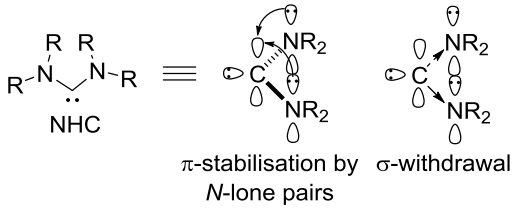
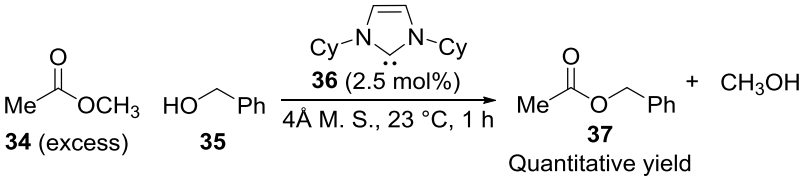


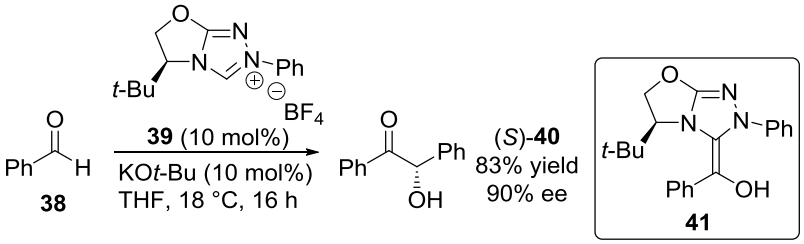
Figure 1: Stabilisation of NHCs.

In organocatalysis, NHCs are considered as versatile reactive species and have found application in a variety of different reaction types.[20] For example, in 2002 Nolan and co-workers illustrated the use of various N-heterocylic carbenes to mediate a transesterification reaction.[21,22] Treatment of methyl acetate **34** and benzyl alcohol **35** with catalytic quantities of NHC **36** furnishes ester **37** in quantitative yield (Scheme 9).



Scheme 9: NHC-catalysed transesterification reaction.

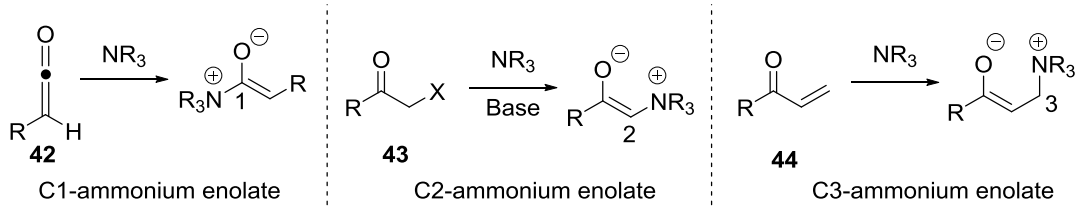
The Benzoin condensation reaction involves an acyl anion equivalent reacting with an aldehyde. In 2002, Enders and co-workers illustrated the use of a triazolium-derived triazolinylidene NHC to catalyse an asymmetric benzoin reaction.[23] Treatment of benzaldehyde **38** with catalytic amounts of NHC, formed from salt (*S*)-**39**, affords benzoin product (*S*)-**40** in 83% yield and 90% ee *via* Breslow intermediate **41** (Scheme 10).[24]



Scheme 10: NHC-catalysed asymmetric benzoin reaction.

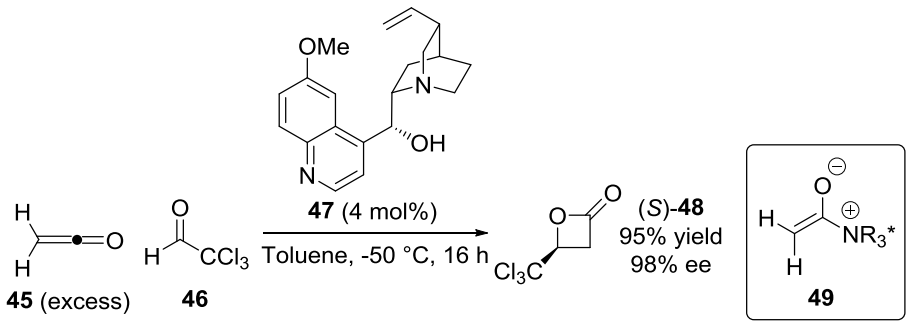
1.1.1.4.5 Ammonium Enolate Catalysis

Ammonium enolates can be considered as nucleophilic species that are generated by the action of a chiral tertiary amine catalyst.[25] Ammonium enolates can be generated by several different methods involving nucleophilic attack of the amine catalyst (NR_3) with various electrophiles (Scheme 11). For example, reaction of an amine catalyst with ketenes **42**, α-halocarbonyl compounds **43** and α,β-unsaturated carbonyl compounds **44** generates C1-, C2- and C3-ammonium enolates respectively. The ammonium enolates formed can react with various electrophiles. C1-azolium enolates are formed *via* similar methods using NHC catalysts and these will be discussed in Section 1.2.2.



Scheme 11: C1-, C2- and C3-ammonium enolates.

In 1982, Wynberg and co-workers illustrated the use of a C1-ammonium enolate to catalyse enantioselective β-lactone formation.[26] Treatment of ketene **45** with chloral **46** and catalytic amounts of cinchona alkaloid **47** furnishes β-lactone (*S*)-**48** in 95% yield and 98% ee *via* C1-ammonium enolate **49** (Scheme 12).



Scheme 12: Wynberg's β-lactone synthesis.

Ammonium enolates are considered as exceptionally versatile reactive intermediates and have been exploited for a range of asymmetric transformations. C1-ammonium enolates, commonly formed from the interaction of a nucleophilic tertiary amine such as **50** or **51** with either a preformed or *in situ* generated ketene, have found utility in many reactions, including β-lactone[27] and β-lactam[28] formation, ketene dimerisation,[29] α-halogenation[30] and formal [4+2] cycloadditions[31] (Figure 2). Alternatively, C1-ammonium enolates can be generated by the acylation of a tertiary amine followed by deprotonation by a base.[25]

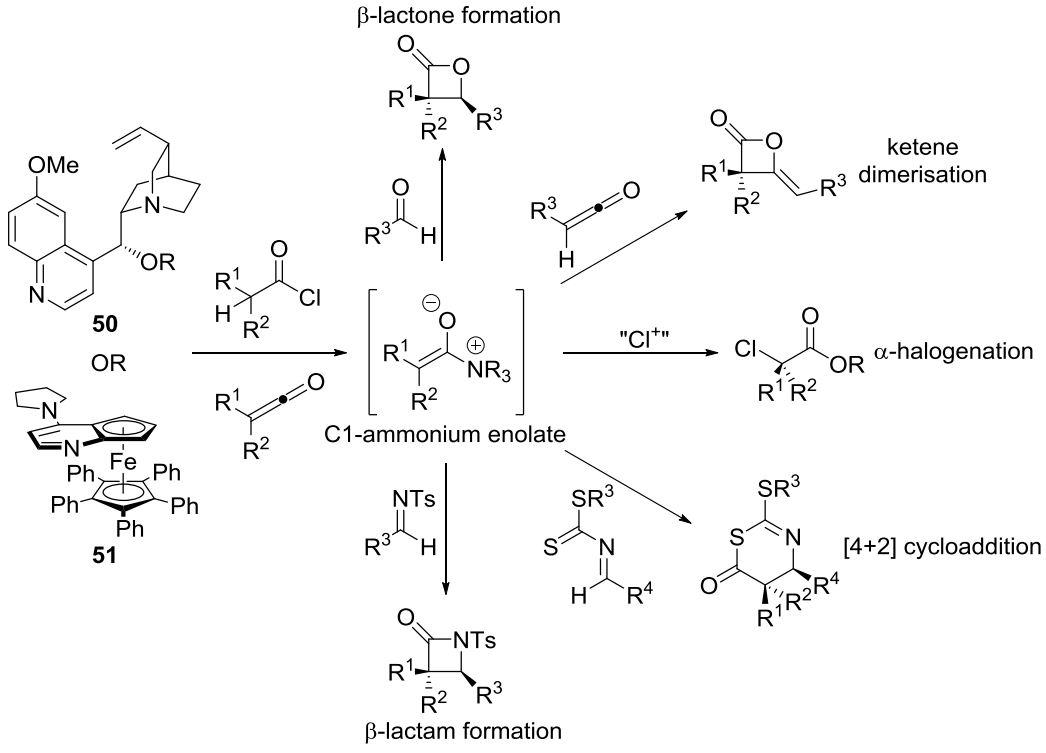
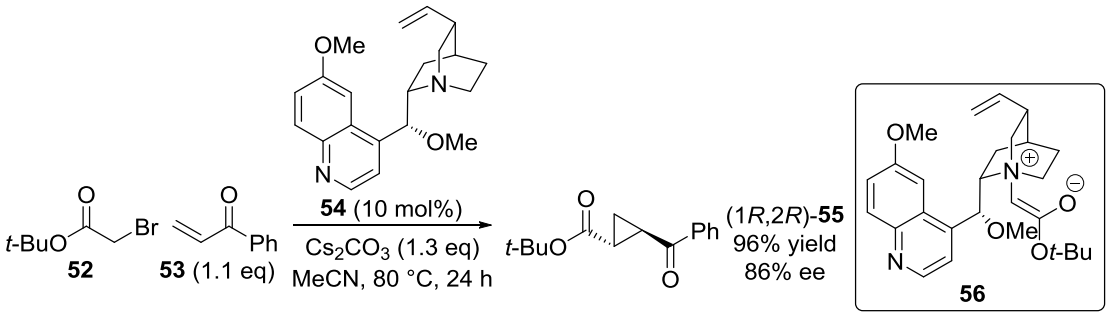


Figure 2: Selection of reactions utilising C1-ammonium enolates.

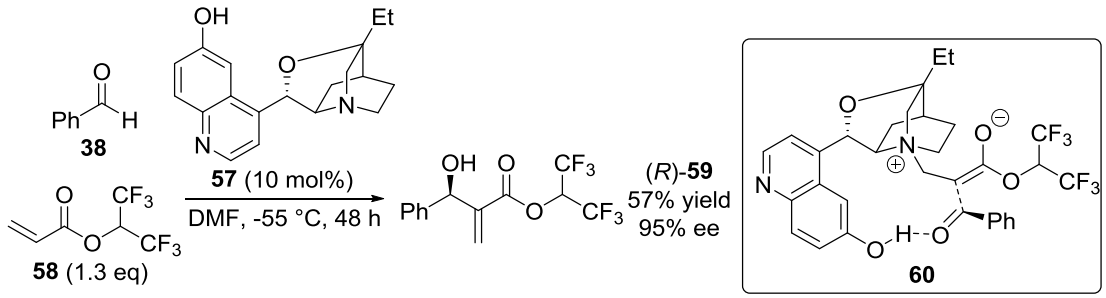
In 2003, Gaunt and co-workers illustrated the ability of C2-ammonium enolates, also known as ammonium ylides, to function as asymmetric cyclopropanating agents.[32] The catalysed reaction between α-bromo ester **52** and enone **53** by cinchona alkaloid

derivative **54** in the presence of caesium carbonate gave cyclopropane (1*R*,2*R*)-**55** in 96% yield and 86% ee *via* C2-ammonium enolate **56** (Scheme 13).



Scheme 13: Gaunt's cyclopropane synthesis.

C3-ammonium enolates have found utility in their ability to catalyse the Morita-Baylis-Hillman reaction with high enantioselectivity. In 1999, Hatakeyama and co-workers discovered that β-isocupreidine **57** catalysed the asymmetric reaction between benzaldehyde **38** and α,β-unsaturated ester **58** to furnish the coupled product (*R*)-**59** in 57% yield and 95% ee *via* C3-ammonium enolate **60** (Scheme 14).[33]



Scheme 14: Application of C3-ammonium enolates.

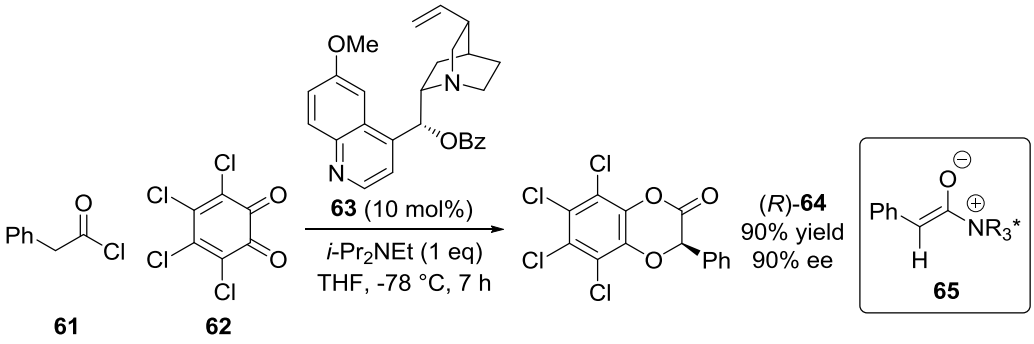
1.2 C1-Ammonium/Azolium Enolates in Formal [4+2] Cycloadditions

Both C1-ammonium and azolium enolates are reactive nucleophilic intermediates that participate in a various formal [4+2] cycloaddition reactions, many of which have been discovered over the past few years.[34] A selection of these processes will be discussed in the following sections.

1.2.1 C1-Ammonium Enolates in Formal [4+2] Cycloadditions

As described previously, C1-ammonium enolates are commonly formed from the interaction of a nucleophilic tertiary amine with either a preformed or *in situ* generated ketene and these nucleophilic species have been utilised in formal [4+2] cycloadditions.[25] In 2006 Lectka and co-workers showed that cinchona alkaloid-derived

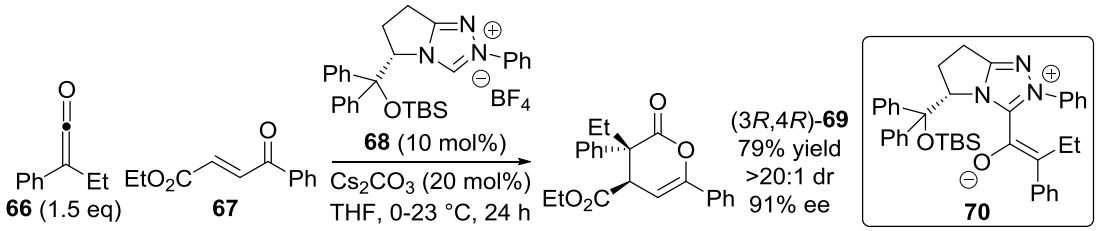
ketene enolates undergo a variety of enantioselective [4+2] cycloadditions with *o*-quinones,[35] *o*-quinone diimides[36] and quinone imides.[37] For example, reaction of acid chloride **61** with *o*-quinone **62** in the presence of catalytic cinchona alkaloid **63** gave cycloadduct (*R*)-**64** in 90% yield and 90% ee *via* C1-ammonium enolate **65** (Scheme 15).



Scheme 15: Formal [4+2] cycloaddition of C1-ammonium enolate.

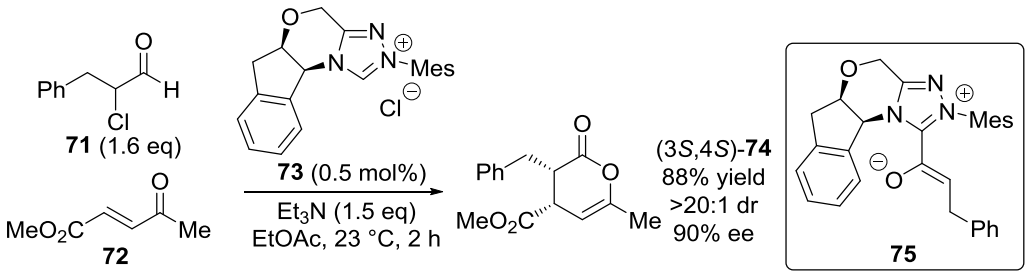
1.2.2 C1-Azolium Enolates in Formal [4+2] Cycloadditions

C1-azolium enolates also partake in a vast array of formal [4+2] cycloadditions. The enolates are formed using NHCs, with ketenes, α-functionalised aldehydes and enals the commonly employed enolate precursors.[38] For example, Ye and co-workers have shown that NHCs catalyse the [4+2] cycloaddition of isolable disubstituted ketenes with enones.[39] The catalysed reaction of ketene **66** and enone **67** by NHC precatalyst **68** in the presence of caesium carbonate gave *anti*-dihydropyranone (3*R*,4*R*)-**69** in 79% yield, >20:1 dr and 91% ee *via* azolium enolate **70** (Scheme 16).



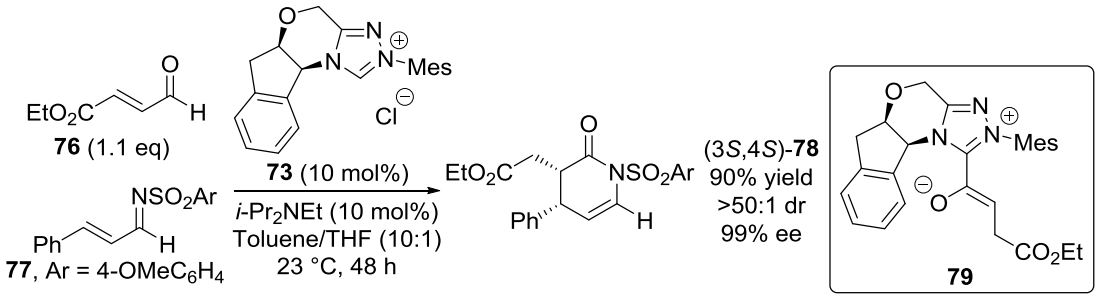
Scheme 16: NHC-catalysed formal [4+2] cycloaddition using isolable, disubstituted ketenes.

In 2006, Bode and co-workers employed NHCs to catalyse asymmetric [4+2] cycloadditions, using azolium enolates generated from α-chloroaldehydes to give *syn*-dihydropyranones with excellent enantio- and diastereocontrol.[40] Reaction of α-chloroaldehyde **71** with enone **72** in the presence of NHC precatalyst **73** and base gave *syn*-dihydropyranone (3*S*,4*S*)-**74** in 88% yield, >20:1 dr and 99% ee *via* azolium enolate **75** (Scheme 17).



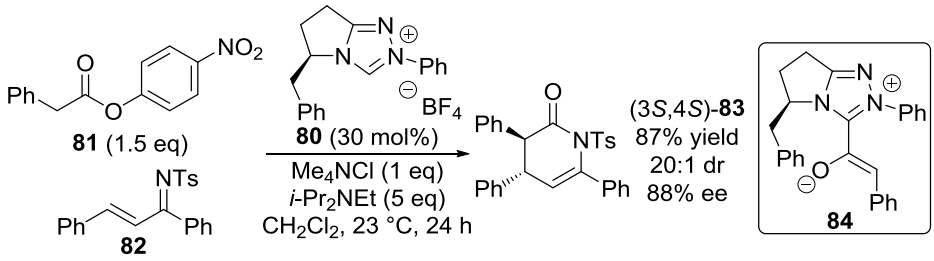
Scheme 17: Formal [4+2] cycloaddition of NHC derived azolium enolate.

The same group has also demonstrated the utility of enals as C1-azolium enolate precursors and their subsequent application towards asymmetric formal [4+2] cycloadditions.[41] In a representative example, NHC precatalyst **73** in the presence of *i*-Pr_2NEt promotes the annulation of enal **76** with ketimine **77**, giving *syn*-dihydropyridone (3*S*,4*S*)-**78** in 90% yield, >50:1 dr and 99% ee *via* azolium enolate **79** (Scheme 18).



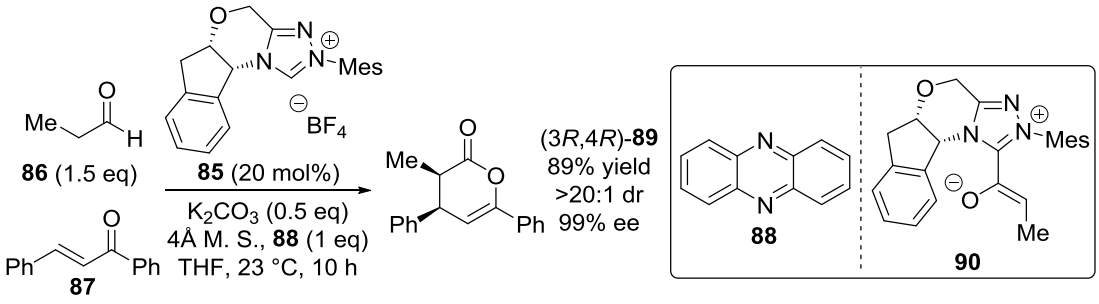
Scheme 18: Enals as C1-azolium enolate precursors.

In 2012 the Chi group showed the ability to generate C1-azolium enolates from activated carboxylate ester starting materials and demonstrated their subsequent utility in formal [4+2] cycloadditions.[42] For example, triazolium-based NHC precatalyst **80** promoted the reaction between ester **81** and ketimine **82** in the presence of Me_4NCl and excess *i*-Pr_2NEt, giving *anti*-dihydropyridone (3*S*,4*S*)-**83** in 87% yield, 20:1 dr and 88% ee *via* azolium enolate **84** (Scheme 19).



Scheme 19: Activated esters as C1-azolium enolate precursors.

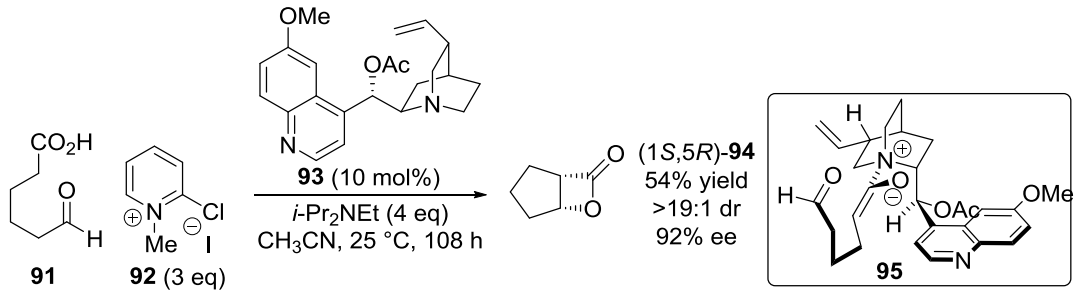
Recently, Rovis and co-workers demonstrated the use of simple aliphatic aldehydes as C1-azolium enolate precursors when a stoichiometric amount of an oxidant is used.[43] In a representative case, NHC precatalyst **85** efficiently catalyses the formal [4+2] cycloaddition between propionaldehyde **86** and chalcone **87** in the presence of K_2CO_3 as base and **88** as oxidant, giving *syn*-dihydropyranone (3*R*,4*R*)-**89** in 89% yield, 20:1 dr and 99% ee *via* azolium enolate **90** (Scheme 20).



Scheme 20: Aliphatic aldehydes as C1-azolium enolate precursors.

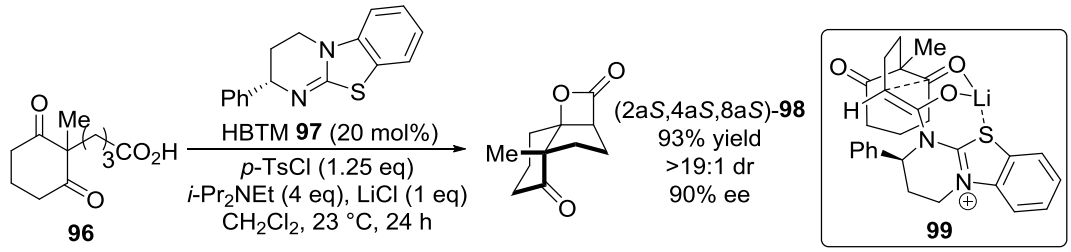
1.3 Organocatalytic Generation of Enolates from Carboxylic Acids

Many of the organocatalytic methods known to date act upon substrates at the aldehyde/ketone oxidation level. An alternative and synthetically appealing strategy for the organocatalytic generation of enolates is directly from cheap, readily available and easily handled carboxylic acids. Surprisingly, this area has received little attention to date, however Romo and co-workers have demonstrated the intramolecular cyclisation of aldehyde- and keto-acids to give β-lactones with good yields and stereoselectivities, making use of cinchona alkaloids[44] or PPY[45] as organocatalysts. For example aldehyde-acid **91** undergoes a nucleophile-catalysed aldol lactonisation (NCAL) reaction when treated with pyridinium salt **92** and cinchona alkaloid **93** in the presence of base to give bicyclic β-lactone (1*S*,5*R*)-**94** in 54% yield, >19:1 dr and 92% ee *via* C1-ammonium enolate **95** (Scheme 21).



Scheme 21: Organocatalytic β-lactone formation from aldehyde-acids.

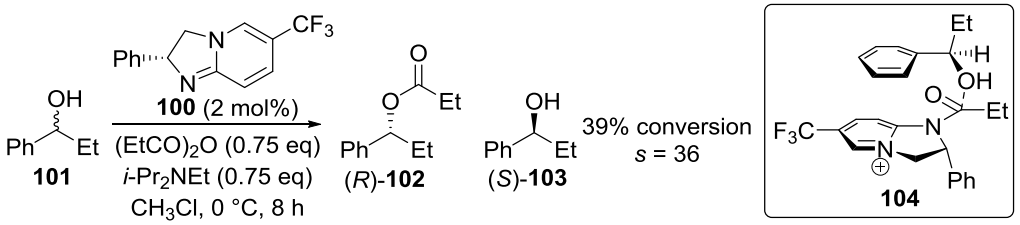
At the onset of these PhD studies no catalytic variant of this reaction had been disclosed. Subsequently Romo extended this protocol towards highly enantioselective intramolecular desymmetrising aldol-lactonisation reactions, initially using stoichiometric isothiourea tetramisole (TM)[46] and recently to substoichiometric homobenzotetramisole (HBTM),[47] first introduced by Birman who demonstrated its ability to catalyse the kinetic resolution of secondary alcohols.[48] For example, initial activation of keto-acid **96** with *p*-TsCl and *i*-Pr_2NEt, followed by reaction with catalytic homobenzotetramisole (*S*)-**97** and LiCl as a co-catalyst, gave tricyclic β-lactone (2a*S*,4a*S*,8a*S*)-**98** in 93% yield and 90% ee *via* C1-ammonium enolate **99** (Scheme 22). The organocatalytic reaction using homobenzotetramisole was published during the 1st year of this PhD.



Scheme 22: Organocatalytic activation of carboxylic acids using isothioureas.

1.4 Development of Isothioureas as Organocatalysts

Birman was the first to demonstrate the use of isothioureas in catalysis. The isothiourea catalyst architecture evolved over time beginning from the initial discovery of amidine catalyst (*R*)-**100**. The Lewis base organocatalyst could act as an acyl transfer agent and was efficient in catalysing the kinetic resolution of secondary alcohols.[49] The kinetic resolution of alcohol **101** with amidine (*R*)-**100** and propionic anhydride gave ester (*R*)-**102** and alcohol (*S*)-**103** with 39% conversion and a selectivity factor of 36 (Scheme 23). The reaction is believed to proceed through pre-TS assembly **104** in which the steric interactions between the alcohol and acyl transfer agent are minimised.



Scheme 23: Amidine-catalysed kinetic resolution of secondary alcohols.

The catalyst substructure was optimised, firstly to amidine (*R*)-**105** which was designed to provide enhanced π-stacking with benzylic and cinnamyl alcohol substrates in kinetic resolution of secondary alcohols.[50] This catalyst considerably increased reaction rates and selectivities compared with the first generation catalyst (*R*)-**100** (Figure 3). Birman then highlighted the ability of isothioureas tetramisole (*S*)-**106** and its derivative benzotetramisole (*R*)-**107** to act as acyl transfer agents.[51] These catalysts were found to be more selective than amidines (*R*)-**100** and (*R*)-**105** in the kinetic resolution of secondary alcohols.

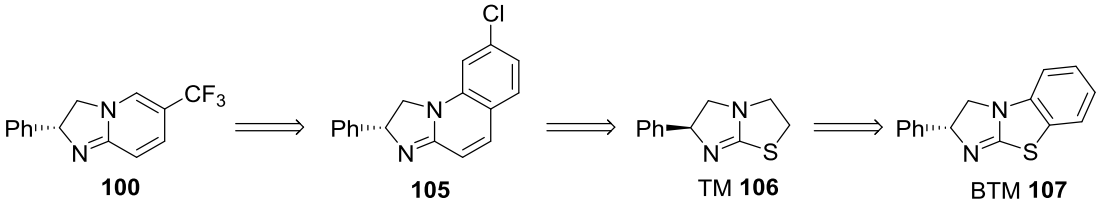


Figure 3: Amidine catalyst substructure optimisation.

The groups of Birman and Okamoto independently discovered the ability of achiral isothiourea DHPB **108** to act as a highly efficient acyl transfer catalyst.[52,53] Birman subsequently reported the higher catalytic activity of homobenzotetramisole (*S*)-**109** compared to benzotetramisole (*R*)-**107** and highlighted its ability to achieve high enantioselectivities in the kinetic resolution of secondary benzylic alcohols and in particular 2-aryl substituted cycloalkanols.[54] Independent studies by Birman[55] and Smith[56] showed that the incorporation of an alkyl substituent at the C(3) position of the homobenzotetramisole catalyst scaffold, giving isothioureas **110**, resulted in a further improvement in catalytic activity (Figure 4).

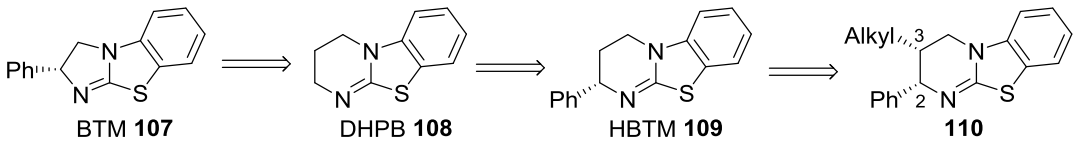


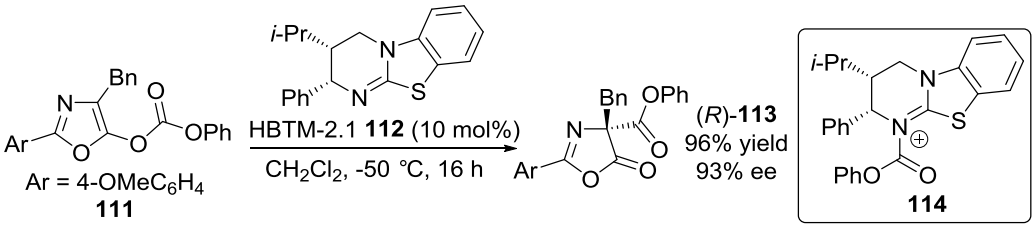
Figure 4: Further isothiourea catalyst substructure optimisation.

These isothioureas have been utilised within the Smith group as Lewis bases to catalyse numerous different reaction processes in which variation of the substituents at C(2) and C(3) have been investigated.

1.5 Previous Research in the Smith Group Using Isothioureas

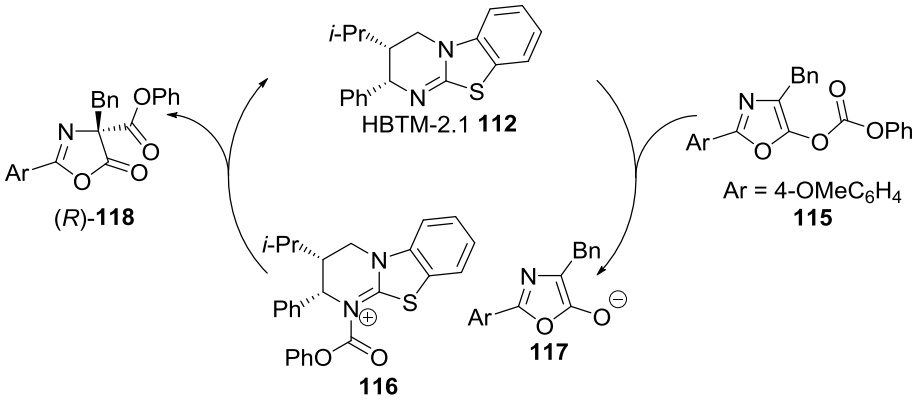
1.5.1 Asymmetric Steglich rearrangement

In 2009, Smith and co-workers reported the ability of chiral isothioureas to catalyse the asymmetric Steglich rearrangement.[56] This process utilises the ability of the isothiourea to operate as a carboxyl transfer agent. Treatment of oxazolyl carbonate **111** with HBTM-2.1 **112** undergoes rearrangement to give *C*-carboxyazlactone (*R*)-**113** in 96% yield and 93% ee *via* proposed *N*-carboxy intermediate **114** (Scheme 24).



Scheme 24: Isothiourea-catalysed Steglich rearrangement.

The proposed catalytic cycle for this reaction involves the initial nucleophilic attack of HBTM-2.1 **112** on oxazolyl carbonate **115** to generate *N*-carboxy intermediate **116** and enolate **117**. Subsequent nucleophilic attack of the enolate through C(4) to the carboxyl carbonyl group gives *C*-carboxyazlactone (*R*)-**118** and regenerates the catalyst (Scheme 25).



Scheme 25: Proposed catalytic cycle for the Steglich rearrangement.

It was proposed that upon formation of an *N*-carboxy derivative **119**, the stereodirecting C(2) substituent adopts a pseudo-axial conformation that blocks one face of the isothiourea. The enolate **120** then approaches the *N*-carboxy derivative *anti* to the stereodirecting C(2) substituent in an electrostatically complimentary orientation, assisted by C-H···O interactions, and minimising the steric interactions with the axial C(3)-H (Figure 5). These factors give rise to a highly enantioselective reaction.

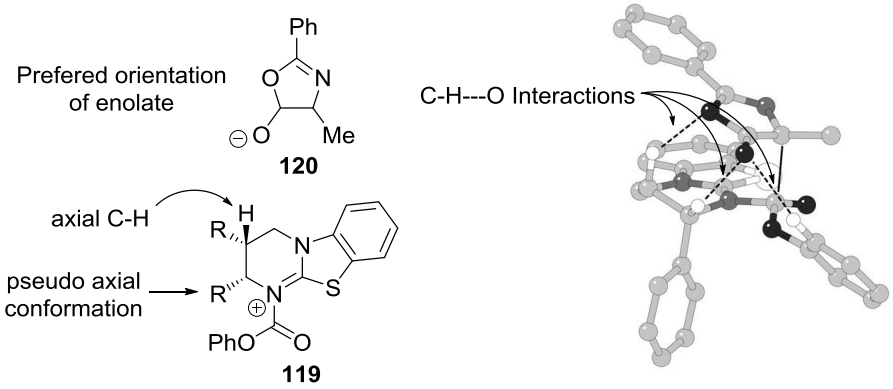
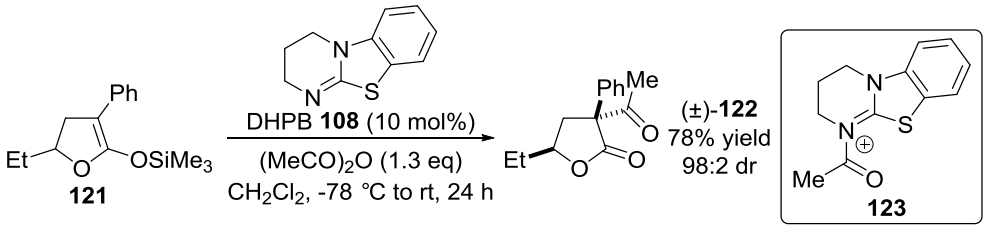


Figure 5: Proposed pre-TS assembly in Steglich rearrangement.

In this process it was found that when the phenyl stereodirecting group at C(2) was changed to an *i*-Pr substituent there was an observable decrease in catalytic activity although the product was still formed in high enantioselectivity.

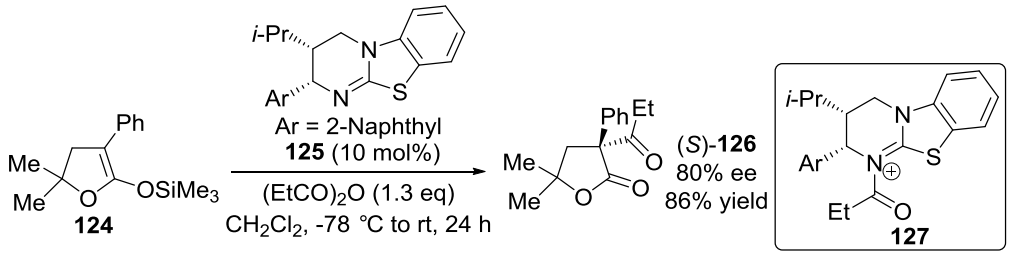
1.5.2 *C*-acylation of Silyl Ketene Acetals

In 2010, Smith and co-workers reported the isothiourea catalysed diastereoselective *C*-acylation of silyl ketene acetals.[57] In this process, the isothiourea operates as an acyl transfer agent. Treatment of silyl ketene acetal **121** with DHPB **108** in the presence of acetic anhydride gives *C*-acylated lactone (±)-**122** in 78% yield and 98:2 dr *via* proposed *N*-acyl intermediate **123** (Scheme 26).



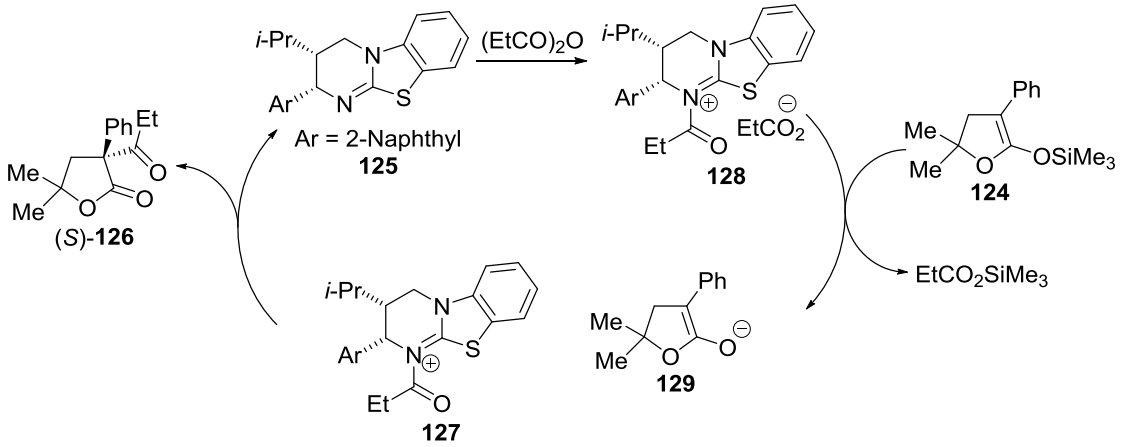
Scheme 26: Isothiourea-catalysed diastereoselective C-acylation of silyl ketene acetals.

An asymmetric variant of this methodology has been developed within the Smith group.[58] For example, treatment of silyl ketene acetal **124** with chiral isothiourea **125** in the presence of propionic anhydride gives *C*-acylated lactone (*S*)-**126** in 86% yield and 80% ee *via* proposed *N*-acyl intermediate **127** (Scheme 27).



Scheme 27: Isothiourea-catalysed asymmetric C-acylation of silyl ketene acetals.

The proposed catalytic cycle for this reaction involves the initial nucleophilic attack of **125** on propionic anhydride to generate an activated acyl-isothiouronium ion **128**, with desilyation of the silyl ketene acetal promoted by the carboxylate counterion generating enolate **129**. Subsequent nucleophilic attack of the enolate with **127** generates lactone (*S*)-**126** and regenerates the isothiourea (Scheme 28).



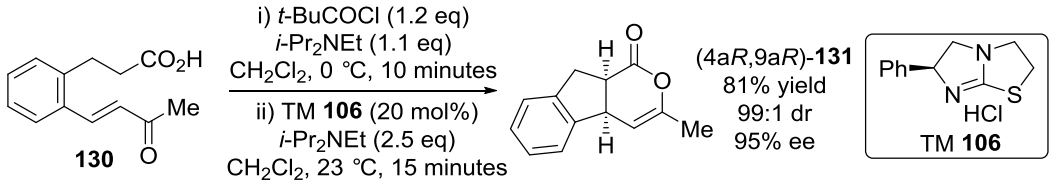
Scheme 28: Proposed catalytic cycle for the C-acylation of silyl ketene acetals.

The sense of asymmetric induction in these systems can be rationalised by direct comparison to the related *C*-carboxylation of oxazolyl carbonates discussed previously.

1.5.3 Intramolecular Michael Addition-Lactonisations

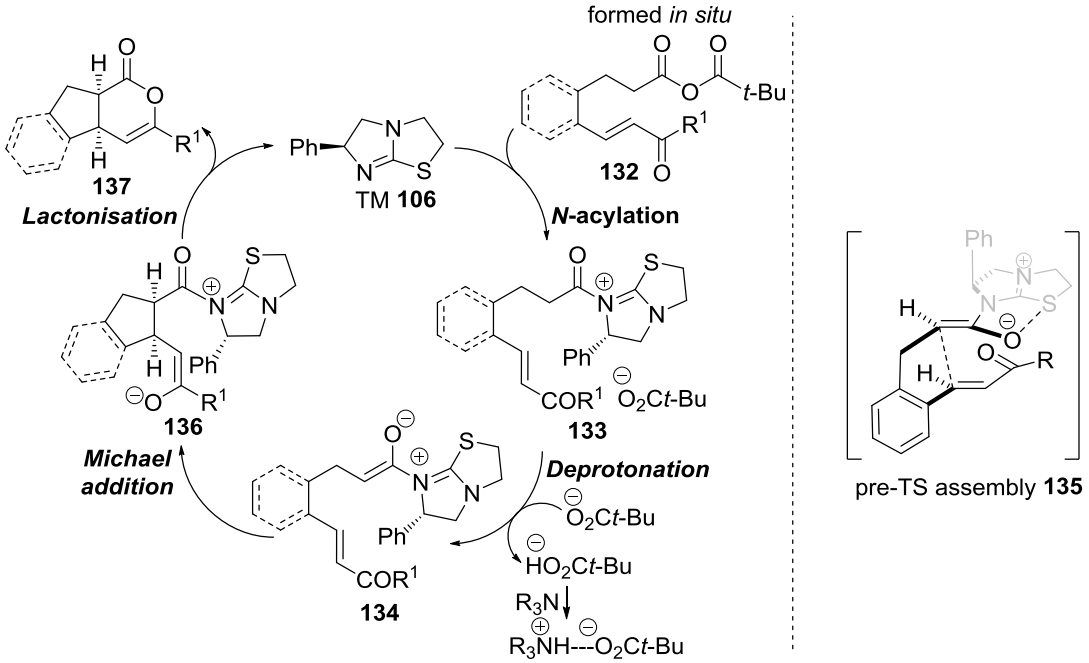
At the onset of these PhD studies no isothiourea-catalysed Michael addition-lactonisation methodologies had been reported. However, based upon the interest within the Smith group in the use of Lewis bases as organocatalysts[59] and specifically isothioureas[60] and building upon the precedents outlined by Romo and co-workers, in 2011 the Smith group reported the ability of chiral isothioureas to promote the highly enantioselective intramolecular Michael addition-lactonisation process of a range of enone acid substrates.[61] For example, commercially available chiral isothiourea

tetramisole hydrochloride (*S*)-**106** was a highly efficient precatalyst for the conversion of enone acid **130**, preactivated *in situ* to the mixed anhydride with pivaloyl chloride and *i*-Pr_2NEt, into tricycle (4a*R*,9a*R*)-**131** in 81% yield, 99:1 dr and 95% ee (Scheme 29).



Scheme 29: Isothiourea-catalysed intramolecular Michael addition-lactonisation.

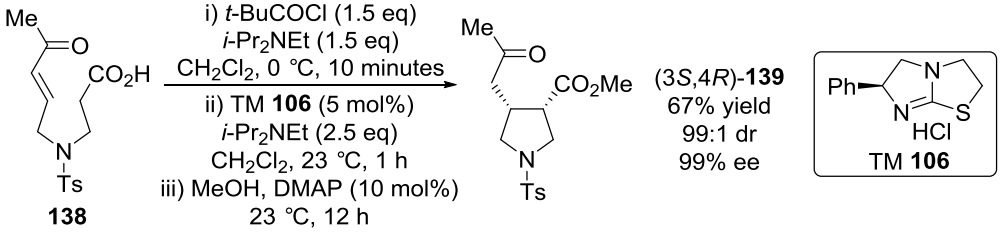
A mechanistic pathway has been proposed which firstly involves the *in situ* generation of a transient mixed anhydride **132** formed by the reaction of enone-acid and pivaloyl chloride in the presence of *i*-Pr_2NEt. Nucleophilic attack of the isothiourea catalyst on this activated species generates an acyl ammonium species **133** that, upon deprotonation, can form the key (*Z*)-ammonium enolate intermediate **134**. Intramolecular Michael addition *via* proposed pre-TS assembly **135** gives a second acyl ammonium species **136** that undergoes lactonisation to give the desired product **137** in high dr and ee, regenerating the isothiourea catalyst (Scheme 30).



Scheme 30: Proposed catalytic pathway and pre-TS assembly.

This approach was recently applied to the synthesis of disubstituted pyrrolidines.[62] In a representative case enone-acid **138** was transformed into 3,4-*syn*-disubstituted pyrrolidine (3*S*,4*R*)-**139** under similar catalytic conditions in 67% yield, 99:1 dr and 99%

ee after *in situ* ring-opening with MeOH (Scheme 31).



Scheme 31: Telescoped synthesis of stereodefined pyrrolidines.

At the time of commencing this PhD, no intermolecular variant of this Michael addition-lactonisation reaction or the aldol-lactonisation reaction shown by Romo and co-workers had been described. Furthermore, in Gaunt's review on ammonium enolate catalysis,[25] with reference to Romo's work on the *intramolecular* NCAL reaction he specifically comments on the difficulties of extending this methodology towards an *intermolecular* process: "The moderate reactivity of the zwitterionic ammonium enolates is bypassed in the intramolecular reaction because of the proximity of the aldehyde, but it cannot be avoided in the intermolecular process."

1.6 Aims and Objectives

As a consequence of the findings of both Romo and Smith regarding the ability of chiral isothioureas to organocataytically functionalise carboxylic acids towards both *intramolecular* aldol-lactonisation[47] and Michael addition-lactonisation reactions,[61,62] in addition to various communications concerning the ability of ammonium and azolium enolates to undergo intermolecular formal [4+2] cycloadditions,[35-43] the aim of this project was to investigate the ability of chiral isothiourea catalysts to catalyse the *intermolecular* formal [4+2] cycloadditions of carboxylic acids and various Michael acceptors (Figure 6). The aim was to create a robust and efficient methodology for the highly stereoselective formation of heterocyclic products from cheap and readily available carboxylic acids. It was proposed that structural variation upon both the acid and Michael acceptor components would be used to evaluate any effects on the ability of the chiral isothiourea to promote the Michael addition-cyclisation reaction. The derivatisation of stereodefined heterocycles into valuable building blocks in addition to mechanistic investigations through both computational and kinetic analysis were also significant aims of this PhD.

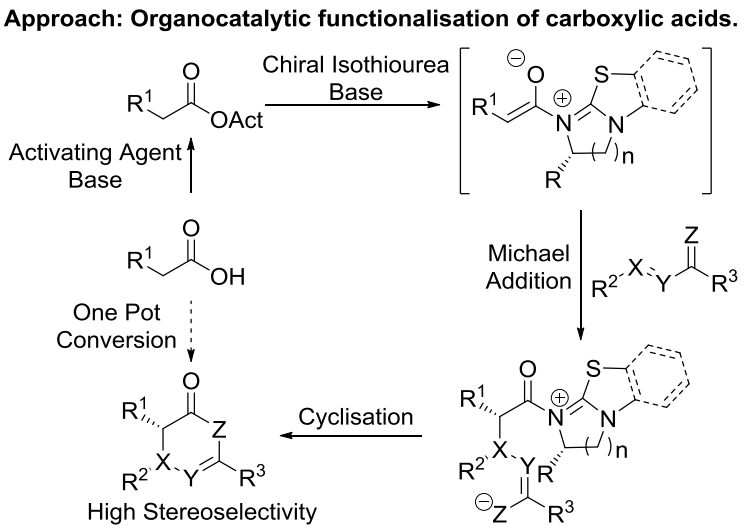


Figure 6: Proposed catalytic strategy for intermolecular Michael addition-cyclisations.

1.7 References and Notes

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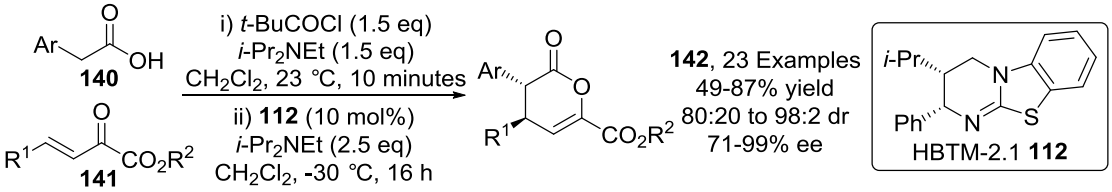
Chapter 2: Formal [4+2] Cycloadditions of α-Keto-β,γ-Unsaturated Esters

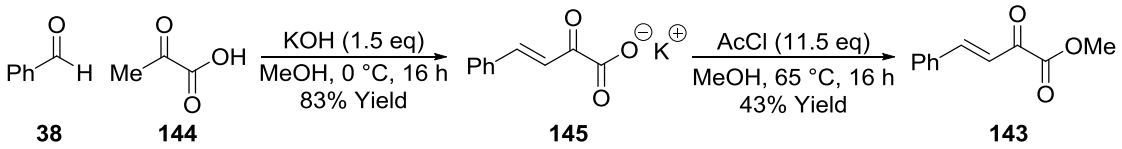
This chapter describes the discovery of reaction conditions to effect the HBTM-2.1 **112** catalysed Michael addition-lactonisation reaction between arylacetic acids **140** and α-keto-β,γ-unsaturated esters **141**, affording a variety of *anti*-dihydropyranones **142** in high yield and with excellent levels of diastereo- and enantioselectivity (Scheme 32).[61] This represents the first time that carboxylic acid derived ammonium enolates have been successfully applied towards an intermolecular reaction process.



Scheme 32: Formal [4+2] cycloaddition of α-keto-β,γ-unsaturated esters.

2.1 Synthesis and Formal [4+2] Cycloaddition of 143

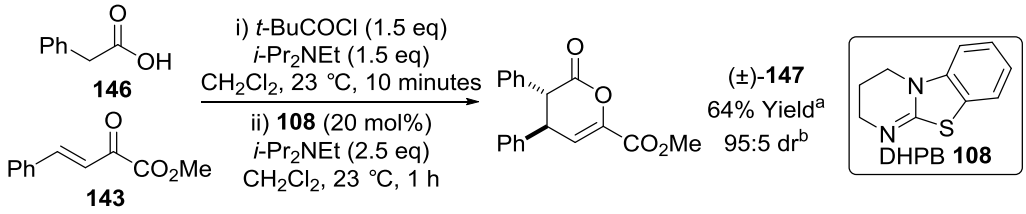
In order to evaluate the ability of isothioureas to catalyse the intermolecular Michael addition-lactonisation reaction between arylacetic acids and α-keto-β,γ-unsaturated esters a model system was selected. This Michael acceptor was chosen based upon its widespread use as an electron-deficient 4π component in various methodologies.[63] Using modified procedures to those outlined by Srivastava[64] and Zhang,[65] ketoester **143** was obtained *via* a simple two-step procedure. An aldol reaction of benzaldehyde **38** with pyruvic acid **144** and potassium hydroxide in MeOH furnished the corresponding potassium salt **145** in 83% yield. Subsequent alkylation *via* addition of **145** to a solution of methanol and acetyl chloride gave ketoester **143** in 43% yield (Scheme 33).



Scheme 33: Synthetic route towards ketoester 143.

With ketoester **143** in hand, its subsequent use in the model intermolecular Michael addition-lactonisation reaction with phenylacetic acid **140** could be investigated. The reaction conditions for the *intermolecular* reaction were chosen based upon those already optimised for the corresponding *intramolecular* reaction within the Smith group. Using pivaloyl chloride as activating agent, *i*-Pr$_2$NEt as base and achiral isothiourea

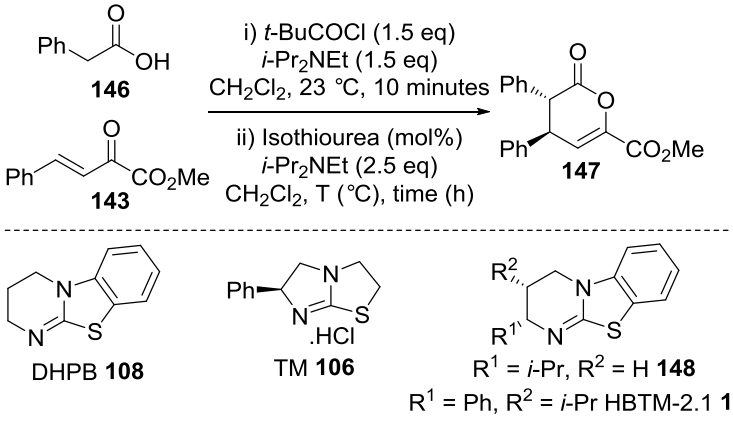
DHPB **108** as catalyst the reaction proceeded efficiently to give *anti*-dihydropyranone (±)-**147** with high diastereoselectivity (95:5 dr) in 64% yield (Scheme 34). Racemic samples needed for chiral HPLC analysis for all dihydropyranones in this chapter were made using achiral DHPB **108** as catalyst.



[a] Isolated yield of major diastereoisomer of **147** (96:4 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Scheme 34: Reaction using model system.

Based upon this promising result giving good conversion and diastereoselectivity using an achiral isothiourea catalyst, subsequent studies focused upon the development of an asymmetric protocol. Due to the work previously carried out in the group investigating the various applications of isothioureas in organocatalysis, several different isothioureas were readily available. In the asymmetric series, commercially available tetramisole hydrochloride (*S*)-**106** proved a competent enantioselective precatalyst for this transformation, giving (3*S*,4*S*)-**147** in promising diastereo- and enantioselectivity (94:6 dr, 86% ee). Variation of the isothiourea showed that HBTM-2.1 **112** offered the highest levels of enantiocontrol at 23 °C (96:4 dr, 91% ee). For optimal enantioselectivity lowering the temperature was necessary. Carrying out the reaction at −30 °C gave (3*R*,4*R*)-**147** with excellent enantiocontrol (97% ee). Subsequent variation of the catalyst loading showed that the reaction proceeds with 2 mol% of HBTM-2.1 **112** at −30 °C over 72 h without significantly compromising selectivity or yield (Table 1).



Entry	Isothiourea (mol%)	T (°C)	Time (h)	Yield (%)[a]	dr[b]	ee (%)[c]
1	**108** (20)	23	1	64	95:5	-
2	**106** (20)	23	3	60	94:6	86 (ent)
3	**148** (20)	23	3	55	96:4	83
4	**112** (20)	23	3	52	96:4	91
5	**112** (20)	–10	3	55	95:5	93
6	**112** (20)	–30	3	60	94:6	97
7	**112** (20)	–50	3	55	96:4	95
8	**112** (20)	–78	3	60	98:2	96
9	**112** (10)	–30	16	68	95:5	97
10	**112** (5)	–30	24	68	95:5	96
11	**112** (2)	–30	72	55	94:6	96

[a] Isolated yield of major diastereoisomer of **147** (≥98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Table 1: Optimisation studies for Michael addition-lactonisation protocol.

Entry 9 in Table 1 represents the optimal reaction conditions for the model system as it gives the best enantioselectivity (97% ee) at an acceptable catalyst loading (10 mol%) whilst maintaining good conversion and isolated yield (>95% conversion, 68% isolated yield). The relative and absolute configuration of (3*R*,4*R*)-**147** was assigned by analogy to a X-ray crystal structure obtained for a related compound (see Section 2.4). Chiral HPLC[66] was used to determine the enantiopurity of (3*R*,4*R*)-**147**. Comparison of the HPLC trace of the (3*R*,4*R*)-**147** with that of a racemic sample of (±)-**147** allowed for the unambiguous determination of the ee. The analysis revealed that *anti*-dihydropyranone (3*R*,4*R*)-**147** had been prepared with an enantiopurity of 97% ee (Figure 7).

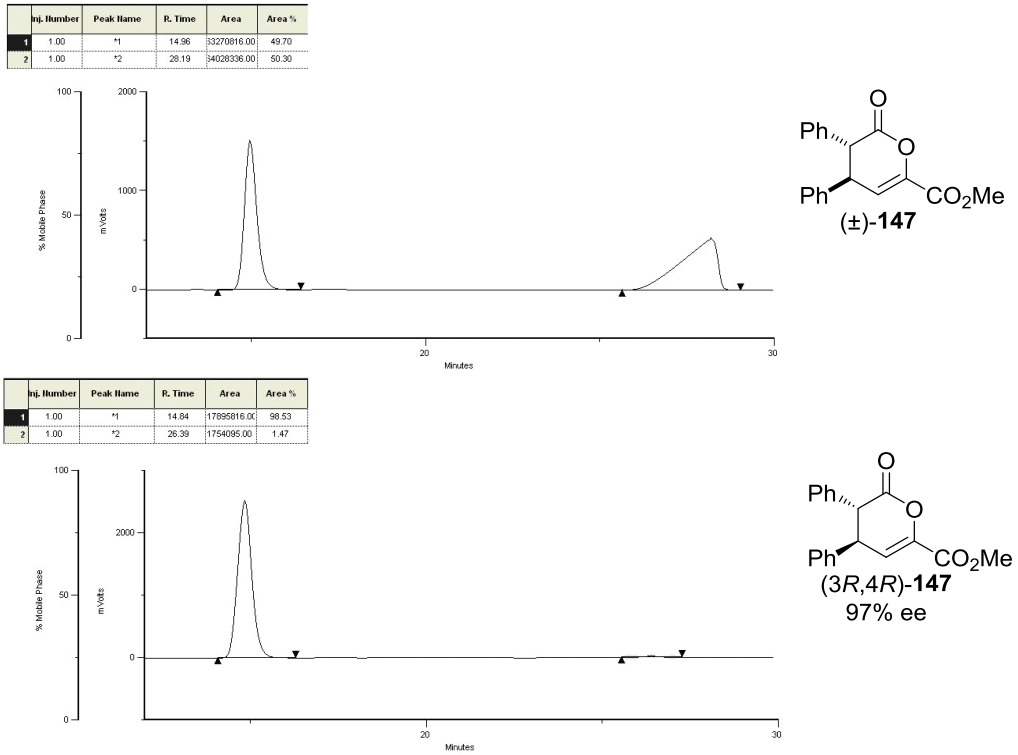
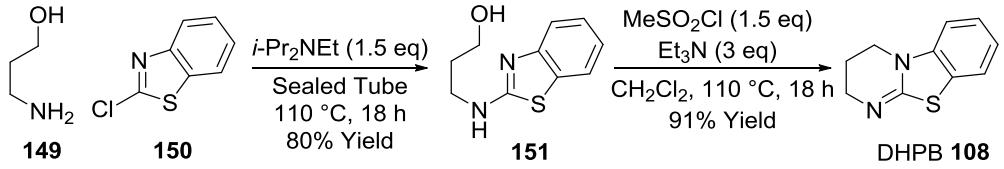


Figure 7: Chiral HPLC traces for (±)-147 and (3*R*,4*R*)-147.

Before these optimised reaction conditions could be used to assess the scope of the Michael addition-lactonisation process, isothiourea catalysts DHPB **108** and HBTM-2.1 **112** needed to be synthesised on a larger scale – DHPB **108** in order to obtain racemic products and HBTM-2.1 **112** due to its identification as the optimal chiral catalyst.

2.2 Synthesis of DHPB 108

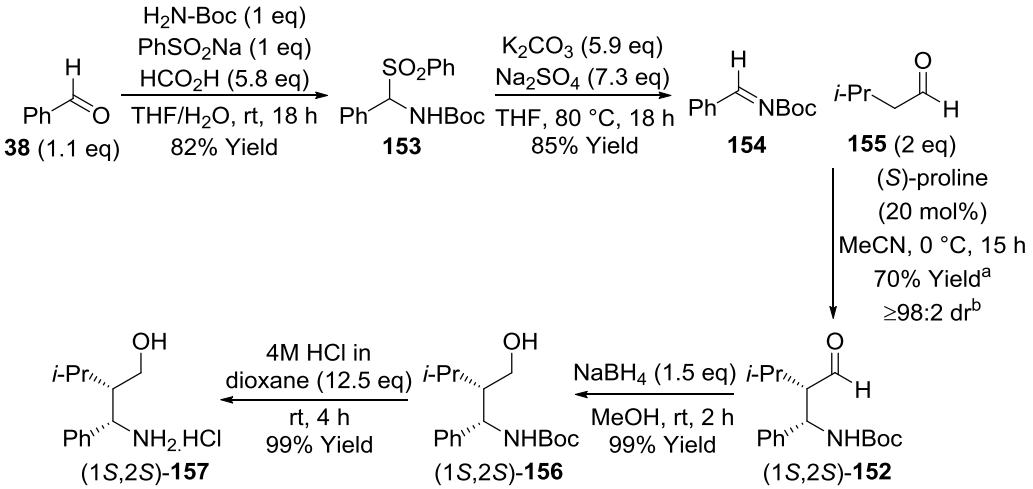
Following the methods described by Birman,[52] DHPB **108** was obtained *via* a simple two-step procedure. Reaction of 3-aminopropan-1-ol **149** with 2-chlorobenzothiazole **150** and *i*-Pr_2NEt in a sealed tube furnished alcohol **151** in 80% yield. Subsequent reaction with Et_3N and methanesulfonyl chloride in CH_2Cl_2 furnished DHPB **108** in 91% yield (4.41 g) (Scheme 35).



Scheme 35: Synthetic route towards DHPB 108

2.3 Synthesis of HBTM-2.1 112

Boc-protected amino aldehyde (1*S*,2*S*)-**152** was easily prepared from readily available starting materials following synthetic procedures outlined by List.[67] Initially, benzaldehyde **38** was converted into sulfone **153** *via* reaction with sodium benzene sulfinate and *t*-butylcarbamate in the presence of formic acid. This reaction proceeded in 97% yield to give sulfone **153** as a white solid. Formation of Boc-imine **154** was achieved by heating sulfone **153** in the presence of potassium carbonate and sodium sulphate. Reaction of Boc-imine **154** and isovaleraldehyde **155** in a (*S*)-proline-catalysed asymmetric Mannich reaction furnished Boc-amino aldehyde (1*S*,2*S*)-**152** in 70% yield. This reaction is robust and can be performed on a multi-gram (5 g) scale in addition to being both highly enantio- and diastereoselective – which is central to obtaining enantiomerically pure HBTM-2.1 **112** (>99% ee and >99:1 dr). The relative and absolute configuration within (1*S*,2*S*)-**152** was assigned by comparison to the literature. Subsequent reduction of Boc-amino aldehyde (1*S*,2*S*)-**152** with sodium borohydride in methanol proceeded in quantitative yield to afford Boc-amino alcohol (1*S*,2*S*)-**156**. Finally, removal of the Boc-protecting group with HCl in dioxane gave amino alcohol (1*S*,2*S*)-**157** in 99% yield (Scheme 36).



[a] Isolated yield of major diastereoisomer of **152** (>99:1 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Scheme 36: Synthetic route to γ-amino alcohol (1*S*,2*S*)-157.

A model explaining the enantio- and diastereoselectivity of the (*S*)-proline-catalysed Mannich reaction has been proposed by Córdova (Figure 8).[68] The model depicts the enamine – formed upon reaction of (*S*)-proline with isovaleraldehyde **155** – adopting a favourable conformation to attack Boc-imine **154**. A hydrogen bond between the

carboxylic acid of (*S*)-proline and the nitrogen atom of the imine stabilises the arrangment - this directs the facial selectivity of the enamine. The energy of the pre-TS assembly is minimised by orienting the *N*-Boc substitutent away from the pyrrolidine, which results in a highly diastereoselective reaction.

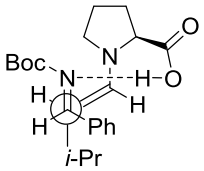
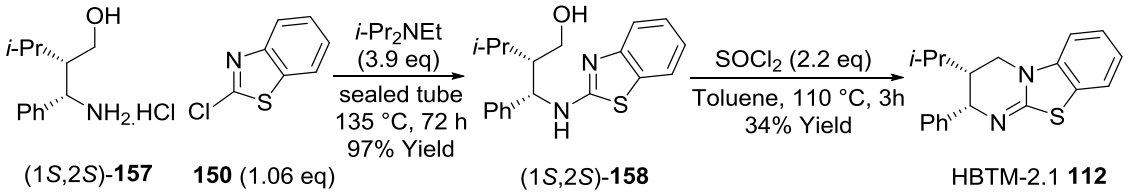


Figure 8: Proposed pre-TS assembly for the (*S*)-proline-catalysed Mannich reaction.

Conversion of amino alcohol (1*S*,2*S*)-**157** to HTBM-2.1 **112** was carried out using modified procedures described by Birman[52] and Okamoto.[53] Firstly, amino alcohol (1*S*,2*S*)-**157** was heated in a sealed tube with 2-chlorobenzothiazole **150** and *i*-Pr_2NEt to give alcohol (1*S*,2*S*)-**158** in 97% yield. Alcohol (1*S*,2*S*)-**158** was next heated with thionyl chloride in toluene to give HBTM-2.1 **112** in 34% yield (Scheme 37). This procedure yielded approximately 1.5 g of catalyst as a single diastereoisomer in >99% ee which allowed the scope of the intermolecular Michael addition-lactonisation reaction to be assessed.

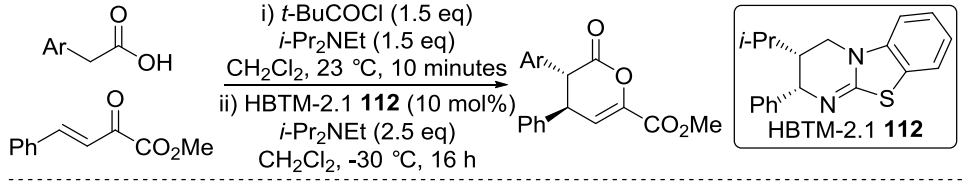


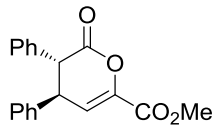
Scheme 37: Synthetic route to isothiourea catalyst HBTM-2.1 112.

In conclusion, a robust and straightforward synthesis towards HBTM-2.1 **112** was carried out. The catalyst was accessed in good yield and excellent enantioselectivity starting from cheap, commercially available starting materials. The synthesis of HBTM-2.1 **112** was subsequently improved with the help of a colleague to remove the requirement for sealed tubes and chromatographic purification, allowing for the preparation of approximately 40 g of HBTM-2.1 (2*S*,3*R*)-**112** in enantiomerically pure form.[69] A large quantity of racemic HBTM-2.1 (±)-**112** was also obtained using this improved route, using (±)-proline for the key Mannich reaction step.

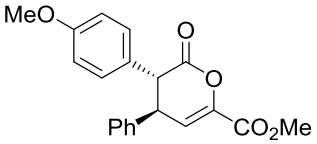
2.4 Substrate Scope – Variation of the Acid Component

With optimised reaction conditions and gram-quantities of reagents and catalysts in hand, the generality of this intermolecular Michael addition-lactonisation process catalysed by HBTM-2.1 **112** was first exemplified through variation of the arylacetic acid component (Table 2). An array of arylacetic acids are tolerated in this system, allowing the incorporation of both electron-donating and electron-withdrawing substitutents as well as 2-, 3- and 4-substitution of the aryl unit. Naphthyl and heteroaryl substituents are also accommodated within the arylacetic acid, giving the corresponding *anti*-dihydropyranones in good yield and excellent stereoselectivities (up to 96:4 dr, up to 99% ee).

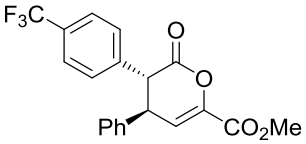




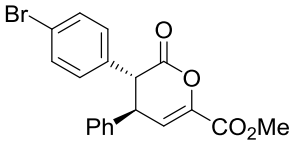
(3*R*,4*R*)-**147**
68% Yield[a]
95:5 dr[b]
97% ee[c]



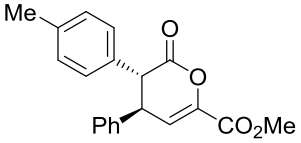
(3*R*,4*R*)-**159**
76% Yield[a]
92:8 dr[b]
98% ee[c]



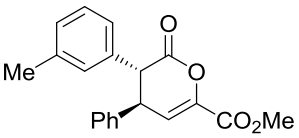
(3*R*,4*R*)-**160**
49% Yield[d]
85:15 dr[b]
71% ee[c]



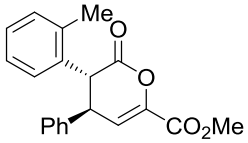
(3*R*,4*R*)-**161**
62% Yield[a]
90:10 dr[b]
93% ee[c]



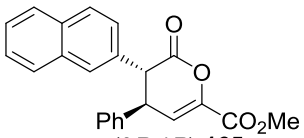
(3*R*,4*R*)-**162**
81% Yield[e]
95:5 dr[b]
99% ee[c]



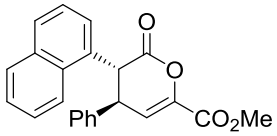
(3*R*,4*R*)-**163**
67% Yield[a]
95:5 dr[b]
97% ee[c]



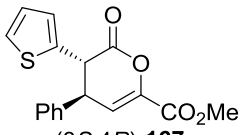
(3*R*,4*R*)-**164**
66% Yield[a]
95:5 dr[b]
87% ee[c]



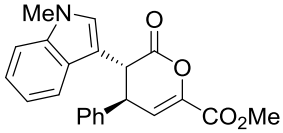
(3*R*,4*R*)-**165**
73% Yield[a]
93:7 dr[b]
97% ee[c]



(3*R*,4*R*)-**166**
72% Yield[d]
96:4 dr[b]
86% ee[c]



(3*S*,4*R*)-**167**
65% Yield[f]
80:20 dr[b]
83% ee[c]

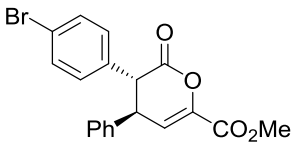


(3*R*,4*R*)-**168**
66% Yield[a]
91:9 dr[b]
97% ee[c]

[a] Isolated yield of major diastereoisomer (≥98:2 dr) unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Required a reaction time of 72 h to give approximately 80% conversion of Michael acceptor. [e] Isolated yield of product (97:3 dr). [f] Isolated yield of product (95:5 dr).

Table 2: Substrate scope - variation of arylacetic acid component.

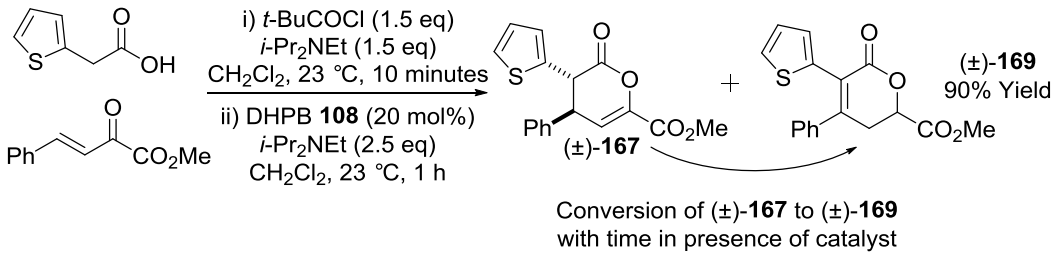
The relative and absolute configuration of dihydropyranone (3*R*,4*R*)-**161** was unambiguously confirmed by X-ray crystal structure analysis. The crystal structure shown (Figure 9) highlights the two aromatic substituents at C(3) and C(4) positions to have an *anti* relationship and confirmed the absolute configuration as (3*R*,4*R*). All other dihydropyranone derivatives were assigned by analogy. For a detailed rationale regarding the observed enantio- and diastereoselectivity of these reactions, see Section 3.7.



(3*R*,4*R*)-**161**

Figure 9: Crystal structure of (3*R*,4*R*)-161 showing relative and absolute configuration.

Within this series the stereoselectivity (80:20 dr, 83% ee) for the formation of dihydropyranone (3*R*,4*R*)-**167** was significantly lower than for other examples. It was also found that dihydropyranone (±)-**167** underwent an isomerisation process to form (±)-**169** upon extended exposure to DHPB **108** which was isolated in 90% yield (Scheme 38). Control studies showed that reaction of the isolated dihydropyranone (±)-**167** with DHPB **108** in CD_2Cl_2 in an NMR tube proceeds to give the isomerised product (±)-**169**.



Scheme 38: Observed isomerisation process of dihydropyranone (±)-167.

This allowed a possible mechanism to be proposed which involved the catalyst in a Lewis base-mediated isomerisation process (Figure 10). Although isomerisation was only observed in very few cases, generally it was found that the isomerisation pathway could be disfavoured by lowering the temperature.

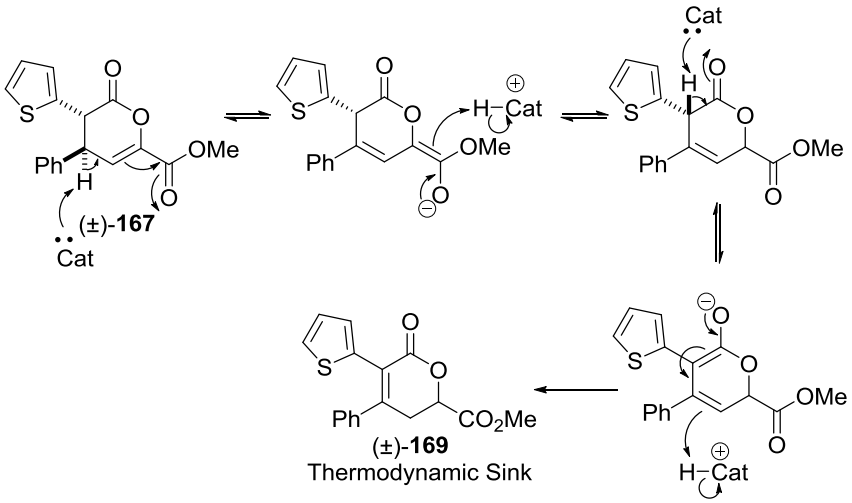
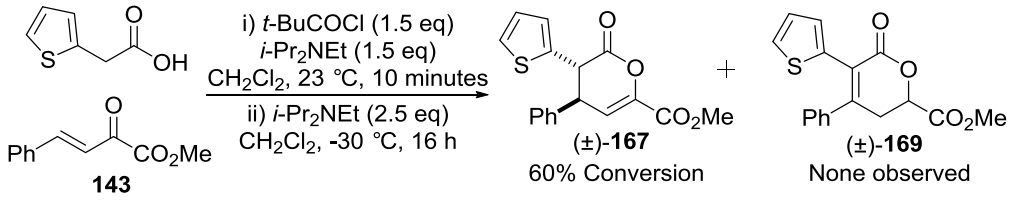


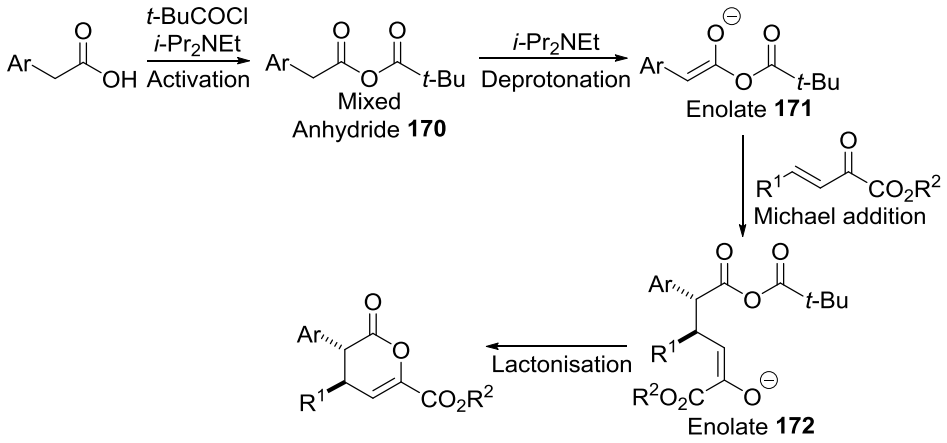
Figure 10: Possible Lewis base-mediated mechanism for observed isomerisation process.

The potential for a racemic background reaction was tested by reacting 2-(thiophen-2-yl)acetic acid with ketoester **143** under standard reaction conditions in the absence of an isothiourea catalyst. Surprisingly, this reaction proceeded to give 60% conversion of **143** to the desired dihydropyranone (±)-**167** in 80:20 dr with no observable isomerisation by-product (±)-**169** (Scheme 39). This result allowed us to draw two important conclusions: i) it is possible to carry out a racemic background reaction in the absence of the isothiourea catalyst; ii) isomerisation between (±)-**167** and (±)-**169** must be mediated by the isothiourea.



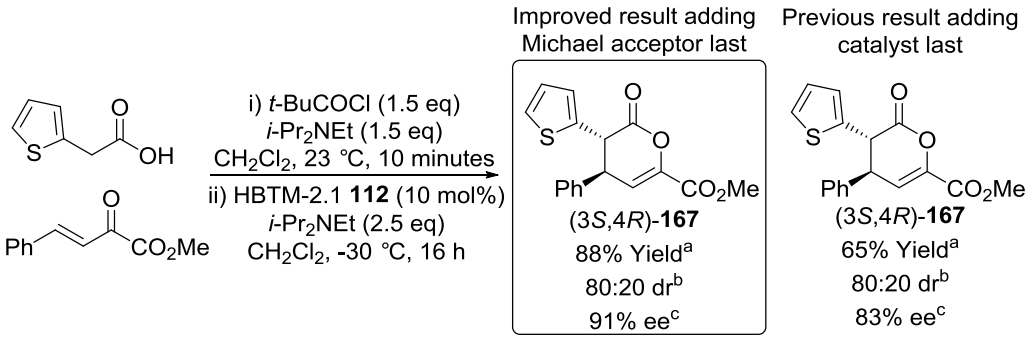
Scheme 39: Discovery of a background reaction.

A plausible mechanism for the racemic background reaction proceeds *via* initial *in situ* formation of mixed anhydride **170**, followed by deprotonation to form an enolate **171**, which can undergo intermolecular Michael addition to form a second enolate **172** followed by lactonisation to furnish racemic dihydropyranone (Scheme 40).



Scheme 40: Proposed mechanism for non-catalysed intermolecular Michael addition-lactonisation process.

In order to achieve a highly enantioselective protocol, the racemic background reaction must be minimised. Theoretically, this can be achieved by minimising the contact time of the mixed anhydride **170** and Michael acceptor in the absence of the chiral isothiourea catalyst. Practically, this can be realised by addition of the Michael acceptor last into the reaction mixture. Initially, the experimental procedure involved having all reaction components present in solution with addition of the catalyst last. This procedure allowed access to dihydropyranone (3*S*,4*R*)-**167** in 65% yield, 80:20 dr and 83% ee (Scheme 41). Utilising the new order of addition – Michael acceptor added last – dihydropyranone (3*S*,4*R*)-**167** could now be obtained in 88% yield, 80:20 dr and 91% ee indicating both a cleaner reaction profile and that the racemic background reaction has been minimised. This improved protocol is now standard for all intermolecular Michael addition-lactonisation reactions.



[a] Isolated yield of major diastereoisomer of **167** (95:5 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 41: Improved reaction protocol - minimising racemic background reaction.

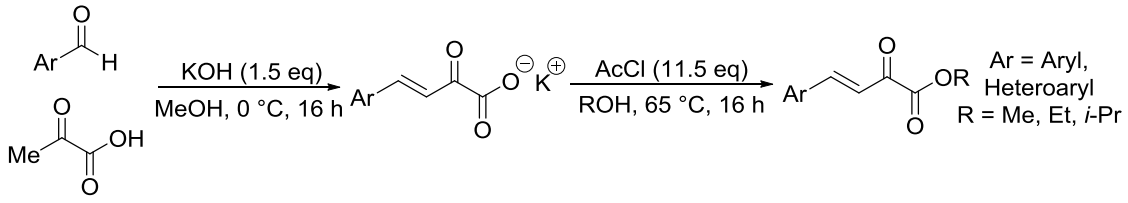
The yield (49%) and stereoselectivity (85:15 dr, 71% ee) for the formation of dihydropyranone (3*R*,4*R*)-**160** is also significantly lower than for other examples in Table 2. A possible explanation for this result is that the ammonium enolate derived from 4-(trifluoromethyl)phenylacetic acid is poorly nucleophilic and as a result the catalyst turnover is slow. This explains the extended reaction time required and lower conversion observed (80%). The slow catalyst turnover in this example could allow the racemic background reaction to become more important which would explain the decrease in stereoselectivity.

2.5 Substrate Scope – Variation of the Michael Acceptor

To further probe the generality of this protocol, the Michael-addition lactonisation procedure using phenylacetic acid and a range of synthesised γ-aryl- and γ-alkyl-substituted α-keto-β,γ-unsaturated esters was studied.

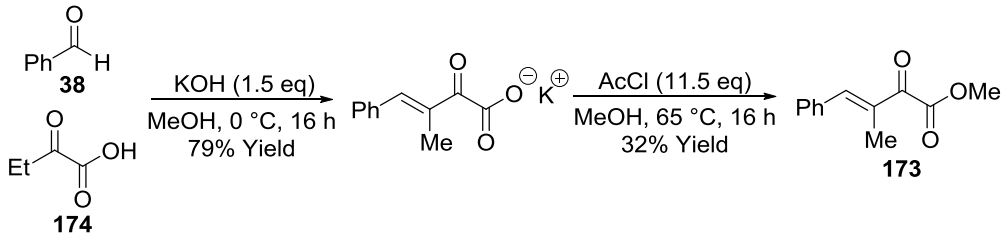
2.5.1 Synthesis of γ-Aryl-β,γ-Unsaturated α-Ketoesters

Using the same synthetic route as described previously for ketoester **143**, a variety of other γ-aryl-β,γ-unsaturated α-ketoesters were obtained through variation of the starting aryl aldehyde including 3- and 4-substituted examples and those bearing electron-donating (OMe) and electron withdrawing (NO_2) groups. γ-Heteroaryl-β,γ-unsaturated α-ketoesters were also synthesised from furfural and pyridine-3-carboxaldehyde. Additionally, the ester group could also be easily varied by selecting a different alcohol in the alkylation step (Scheme 42).



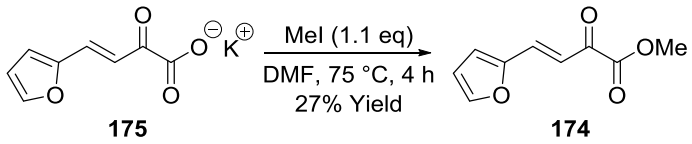
Scheme 42: Synthetic route towards ketoesters.

Ketoester **173**, substituted by a methyl group in the β-position was synthesised from benzaldehyde **38** and 2-ketobutyric acid **174** using the same procedure in 25% yield over 2 steps (Scheme 43).



Scheme 43: Synthetic route towards ketoester 173.

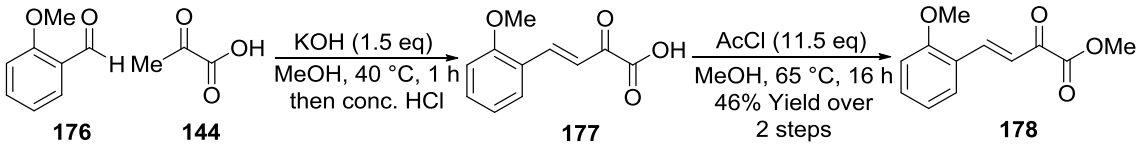
In some cases the yield for the alkylation reaction was poor and this was attributed to the limited solubility of the potassium salts in alcoholic solvents. In order to synthesise ketoester **174** an alternative alkylation procedure was required. Following the procedure outlined by Srivastava,[64] potassium salt **175** was reacted with methyl iodide in DMF to furnish **174** in 27% yield (Scheme 44).



Scheme 44: Alternative alkylation towards ketoester 174.

In order to obtain a 2-OMe substituted aromatic ring at the γ-position a modified procedure was required. It has been reported in the literature that when 2-methoxybenzaldehyde and pyruvic acid are left to react with base overnight, any aldol product formed decomposes back to the starting materials.[70] Following the procedure outlined by Reimer[70] reaction of 2-methoxybenzaldehyde **176** with pyruvic acid **144** and potassium hydroxide in MeOH at 40 °C for 1 h, followed by addition of concentrated hydrochloric acid gave β,γ-unsaturated carboxylic acid **177** which was treated with

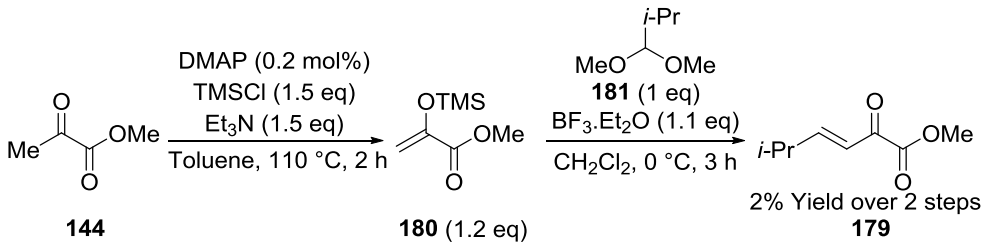
acetyl chloride in methanol to furnish ketoester **178** in 46% yield over 2 steps (Scheme 45).



Scheme 45: Modified synthetic route towards 2-substituted aromatic ketoester 178.

2.5.2 Synthesis of γ-Alkyl-β,γ-Unsaturated α-Ketoesters

Following modified procedures to those outlined by Baltas[71] and Yoshida,[72] ketoester **179** was obtained *via* a two-step procedure. Initially, reaction of methylpyruvate **144** with DMAP, TMSCl and Et_3N in toluene gave silylated enol ester **180** which was taken on crude without purification. Subsequent addition of trifluoroboron etherate to a solution of **180** and 1,1-dimethoxy-2-methylpropane **181** in CH_2Cl_2 gave ketoester **179** in a poor 2% yield over two steps (Scheme 46).

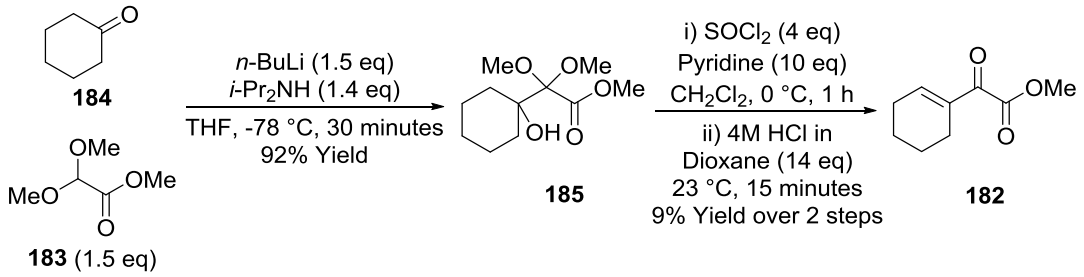


Scheme 46: Synthetic route towards ketoester 179.

The yield of this procedure was most unsatisfactory and can be partly attributed to the large amounts of triethylamine hydrochloride salt formed in the first step, resulting in difficult filtration and poor recovery of silylated enol ester **180**.

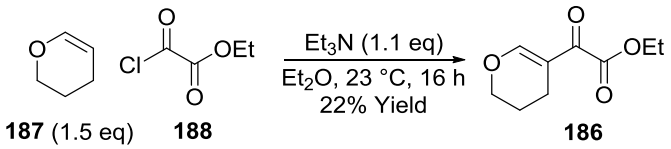
2.5.3 Synthesis of Cyclic-β,γ-Unsaturated α-Ketoesters

Following the procedure outline by Fell,[73] cyclic ketoester **182** was obtained *via* a two-step procedure. Initially, deprotonation of dimethyoxyacetate **183** with LDA in THF followed by addition of cyclohexanone **184** gave hydroxy acetal **185** in 92% yield. Subsequent treatment of **185** with thionyl chloride and pyridine in CH_2Cl_2 followed by stirring in 4M HCl in dioxane carried out both elimination and acetal deprotection steps to afford cyclic ketoester **182** in 9% yield over 2 steps (Scheme 47).



Scheme 47: Synthetic route towards cyclic ketoester 182.

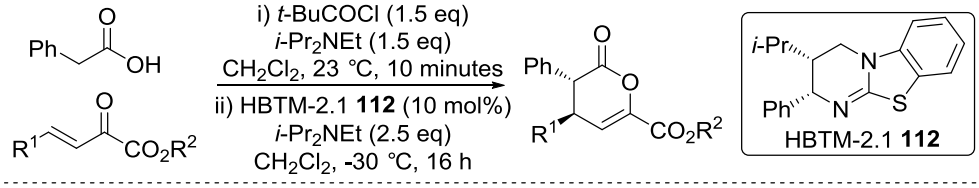
Following the procedure outline by Stetter,[74] heterocyclic ketoester **186** was obtained in 22% yield by reacting dihydropyran **187** with ethyl chlorooxoacetate **188** in the presence of Et_3N in diethyl ether (Scheme 48).

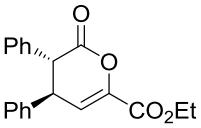


Scheme 48: Synthetic route towards heterocyclic ketoester 186.

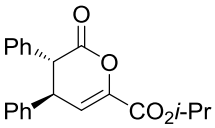
2.5.4 Intermolecular Michael Addition-Lactonisations

With a variety of γ-aryl-, γ-heteroaryl- and γ-alkyl- substituted α-keto-β,γ-unsaturated esters in hand, their subsequent use in the intermolecular Michael addition-lactonisation protocol was evaluated (Table 3). Variation of the ester group is well tolerated in this reaction to include methyl, ethyl and *i*-propyl alkyl esters. A variety of substituted γ-aryl substituents including 2-, 3- and 4-substitution, electron-withdrawing and electron-donating substituents as well as γ-heteroaryl and naphthyl substituents are all readily accommodated, furnishing *anti*-dihydropyranones **189**-**198** with high dr (up to 98:2 dr) and ee (up to 99% ee). Pleasingly, γ-alkyl substituted α-keto-β,γ-unsaturated esters are also accommodated, albeit with reduced diastereoselectivity, generating *anti*-dihydropyranones (3*R*,4*R*)-**199** and (3*R*,4*R*)-**200** with excellent enantioselectivity.

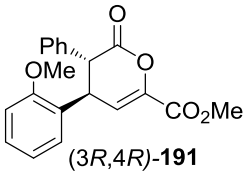




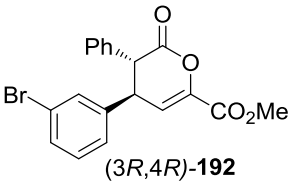
(3*R*,4*R*)-**189**
74% Yield[a]
85:5 dr[b]
98% ee[c]



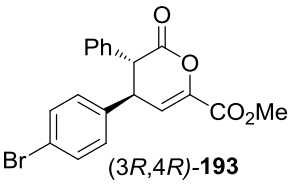
(3*R*,4*R*)-**190**
77% Yield[d]
87:13 dr[b]
99% ee[c]



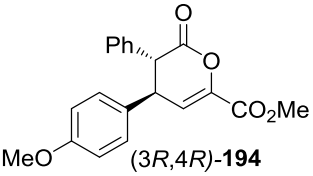
(3*R*,4*R*)-**191**
87% Yield[a]
89:11 dr[b]
99% ee[c]



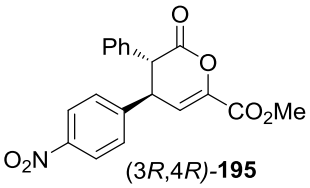
(3*R*,4*R*)-**192**
64% Yield[a]
97:3 dr[b]
97% ee[c]



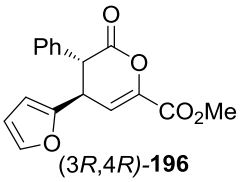
(3*R*,4*R*)-**193**
71% Yield[a]
94:6 dr[b]
98% ee[c]



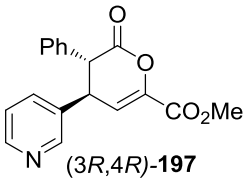
(3*R*,4*R*)-**194**
74% Yield[e,f]
92:8 dr[b]
99% ee[c]



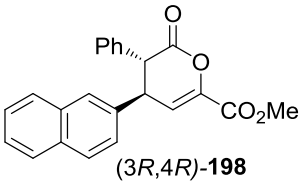
(3*R*,4*R*)-**195**
63% Yield[g,h]
91:9 dr[b]
90% ee[c]



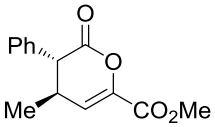
(3*R*,4*R*)-**196**
72% Yield[a]
98:2 dr[b]
98% ee[c]



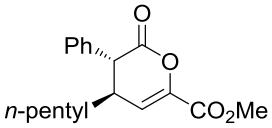
(3*R*,4*R*)-**197**
87% Yield[d]
94:6 dr[b]
97% ee[c]



(3*R*,4*R*)-**198**
82% Yield[d]
95:5 dr[b]
99% ee[c]



(3*R*,4*R*)-**199**
80% Yield[d]
88:12 dr[b]
96% ee[c]



(3*R*,4*R*)-**200**
76% Yield[i]
80:20 dr[b]
95% ee[c]

[a] Isolated yield of major diastereoisomer (≥98:2 dr) unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yield of product (97:3 dr). [e] Isolated yield of product (92:8 dr). [f] Reaction time of 40 h. [g] Isolated yield of product (91:9 dr). [h] Reaction temperature of −78 °C. [i] Isolated yield of product (90:10 dr).

Table 3 - Substrate scope - variation of α-keto-β,γ-unsaturated ester component.

The comparison of the reactions to form dihydropyranones (3*R*,4*R*)-**194** and (3*R*,4*R*)-**195** provides a useful overview of the general reactivity in these systems. The use of an electron-rich Michael acceptor to form dihydropyranone (3*R*,4*R*)-**194** requires an extended reaction time of 40 h to achieve total consumption of the Michael acceptor whereas the use of an electron-deficient Michael acceptor to form dihydropyranone (3*R*,4*R*)-**195** is rapid and is carried out at −78 °C overnight in order to minimise the formation of isomerised by-products as discussed previously for the formation of dihydropyranone (3*S*,4*R*)-**167**. The overall reactivity in this system correlates well with that observed for an inverse electron demand Diels-Alder reaction in which an electron deficient diene and an electron rich dienophile result in the fastest reaction rate (Figure 11).[75] A detailed investigation into the mechanism of this Michael addition-lactonisation process will be discussed in Chapter 3.

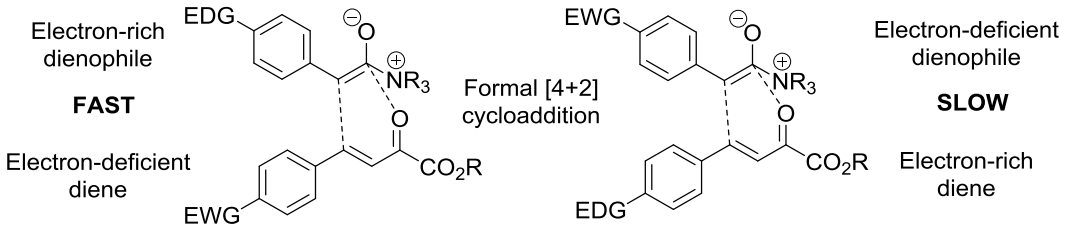
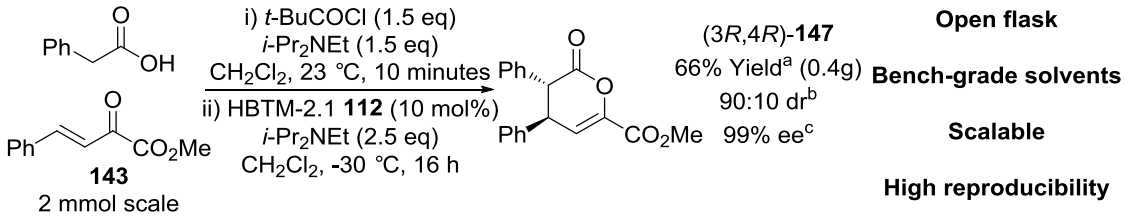


Figure 11: Similar reactivity patterns observed to inverse electron demand Diels-Alder reactions.

2.6 Scale Up and Derivatisation

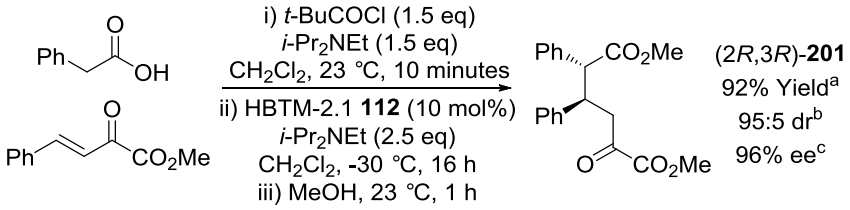
Although the intermolecular Michael addition-lactonisation reactions were routinely carried out on an analytical scale (0.2 mmol), to illustrate the applicability of this protocol towards larger-scale synthesis, the reaction between phenylacetic acid and ketoester **143** was carried out on a 2 mmol scale, giving *anti*-dihydropyranone (3*R*,4*R*)-**147** in 66% yield (0.4 g), 90:10 dr and 99% ee (Scheme 49). This reaction can also be carried out in an open flask using bench-grade solvents without degradation towards the reactivity or stereoselectivity, highlighting it as a robust and easily-reproduced protocol.



[a] Isolated yield of major diastereoisomer of **147** (91:9 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 49: Reproducible, scalable Michael addition-lactonisation protocol.

To exemplify the synthetic utility of this intermolecular reaction protocol, a domino Michael addition-lactonisation followed by *in situ* ring opening with methanol was demonstrated. Preparation of *anti*-dihydropyranone (3*R*,4*R*)-**147** using HBTM-2.1 **112** under standard reaction conditions, followed by direct addition of methanol to the crude reaction mixture gave the ring-opened product (2*R*,3*R*)-**201** in 92% isolated yield, 95:5 dr and 96% ee (Scheme 50).



[a] Isolated yield of major diastereoisomer of **201** (97:3 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 50: Tandem Michael addition-lactonisation and ring opening.

2.7 Limitations of the System

2.7.1 Acid Component

Despite the success of this Michael addition-lactonisation procedure using arylacetic acids, attempts to extend the scope of the methodology towards other carboxylic acids have been unsuccessful (Figure 12). When mono-alkyl, di-alkyl, aryl/alkyl acetic and di-arylacetic acids are used in this protocol minimal consumption of the Michael acceptor is observed. Even replacing one of the α-hydrogen atoms with fluorine has a catastrophic effect upon reactivity.

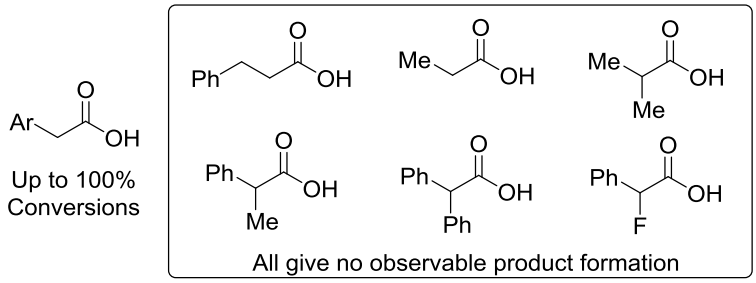
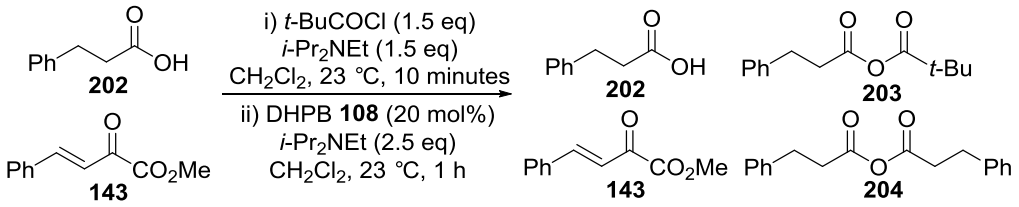


Figure 12: Various carboxylic acids tested in Michael addition-lactonisation procedure.

Analysis of the ^{1}H NMR of the crude reaction mixture (after acidic work-up) when using acid **202** revealed a complex mixture involving the presence of remaining Michael acceptor **143** and several acid-derived species. These are likely to include, among others, the parent acid **202**, mixed anhydride **203** and homoanhydride **204** although these products could not be isolated from the reaction mixture (Scheme 51).



Scheme 51: Failed reaction using acid 202.

The total amount of the acid-derived products in the crude ^{1}H NMR spectrum would appear to be significantly less than the amount of remaining unreacted Michael acceptor. A possible explanation for this observation is that the ammonium enolate derived from acid **202** may undergo competing Claisen-type self-condensation with either the mixed anhydride **203** or acyl ammonium **205** under the reaction conditions as an alternative to the desired reaction with Michael acceptor **143** (Figure 13).

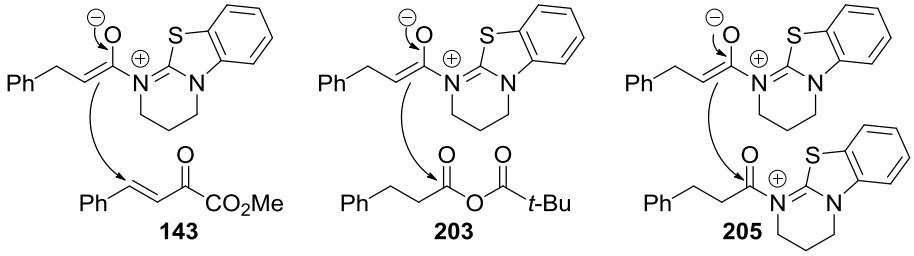


Figure 13: Possible undesired Claisen-type condensation.

Amongst others, four possible explanations for the observed drop in reactivity using alternative carboxylic acids can be suggested: i) the acyl ammonium species formed from the corresponding mixed anhydride cannot adopt a suitable conformation to deprotonate and form the ammonium enolate; ii) the acyl ammonium species formed cannot be deprotonated because the pK_a of the α-hydrogen atom is too high and requires the use of a base other than *i*-Pr$_2$NEt; iii) the ammonium enolate is formed, however it is present in very low concentration; iv) the ammonium enolate is not nucleophilic enough to react with the Michael acceptor (Figure 14). These questions are addressed in greater detail in Section 4.4 where selected acids out with arylacetic acids are successfully employed in a related system.

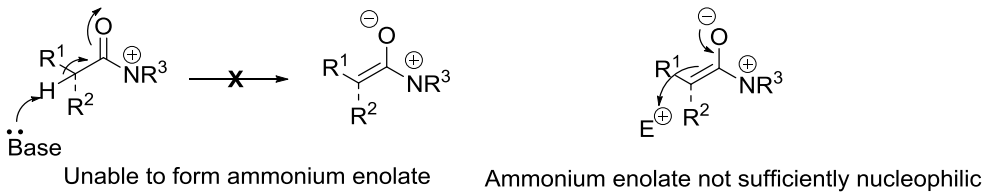


Figure 14: Possible explanations for low conversions with other carboxylic acids.

2.7.2 α-Keto-β,γ-Unsaturated Ester Component

Despite the ability of this procedure to tolerate a wide range of γ-substituted α-keto-β,γ-unsaturated esters, several Michael acceptors within this class did not lead to any observed products (Figure 15). Using the standard reaction conditions, Michael acceptors bearing α-branched γ-substituents along with cyclic and heterocyclic α-keto-β,γ-unsaturated esters were not consumed and the desired dihydropyranones were not formed. The subtle change of placing a methyl substituent on the β-position also results in <5% conversion to the desired product. As discussed in Section 2.7.1, in all cases analysis of the crude reaction mixtures by ^{1}H NMR showed remaining Michael acceptor and several acid-derived products.

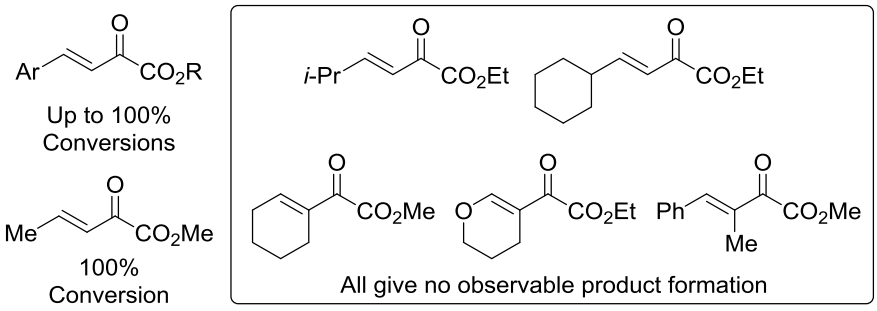


Figure 15: Various γ-substituted α-keto-β,γ-unsaturated esters tested in Michael addition-lactonisation procedure.

Several interesting comparisons can be made from these results: i) the difference in reactivity between having a γ-methyl substituent compared to a γ-isopropyl substituent as a result of increased steric hindrance; ii) the reduction in reactivity going from a γ-methyl substituent to having a 6-membered carbocycle linking β- and γ- positions; iii) the massive effect of placing a methyl substituent at the β-position compared to the parent γ-aryl substituted α-keto-β,γ-unsaturated esters.

The conclusions that can be drawn are that neither α-branched γ-substituents nor β-substitution are tolerated within the α-keto-β,γ-unsaturated esters. The reasons behind these observations remain unclear, however it would seem safe to assume that there is a very subtle relationship between the diene and dienophile within the transition state in which certain substitutions are not tolerated.

2.8 Conclusions

In conclusion, it has been shown that chiral isothiourea HBTM-2.1 **112** promotes the highly diastereo- and enantioselective intermolecular Michael addition-lactonisation of a range of arylacetic acids and α-keto-β,γ-unsaturated esters, generating *anti*-dihydropyranones with good diastereoselectivity (up to 98:2 dr) and enantioselectivity (up to 99% ee).[61] A detailed investigation of the scope and limitations of this protocol has been demonstrated. The broader applicability of this chemistry has been demonstrated *via* an efficient scale up procedure using open flasks and bench-grade solvents along with a simple derivatisation to illustrate the use of *anti*-dihydropyranones as useful synthetic building blocks.

2.9 References and Notes

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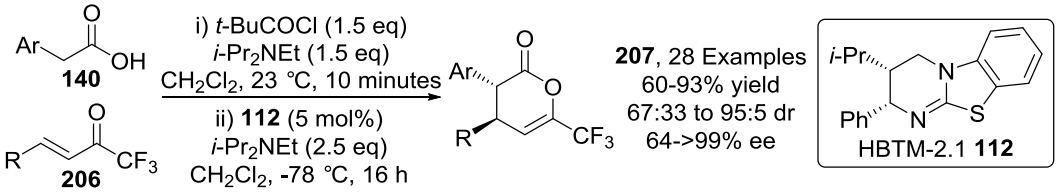
Chapter 3: Formal [4+2] Cycloadditions of Trifluoromethyl Enones

This chapter describes the discovery of trifluoromethyl enones **206** as highly useful Michael acceptors in HBTM-2.1 **112** catalysed Michael addition-lactonisation reactions with arylacetic acids **140**, forming trifluoromethyl bearing *anti*-dihydropyranones **270** in high yield and with excellent levels of diastereo- and enantioselectivity (Scheme 52).[69] Products were readily derivatised to diverse synthetic building blocks containing trifluoromethyl stereogenicity. Detailed kinetic and computational analyses were carried out, shedding light on the mechanism of these reactions.

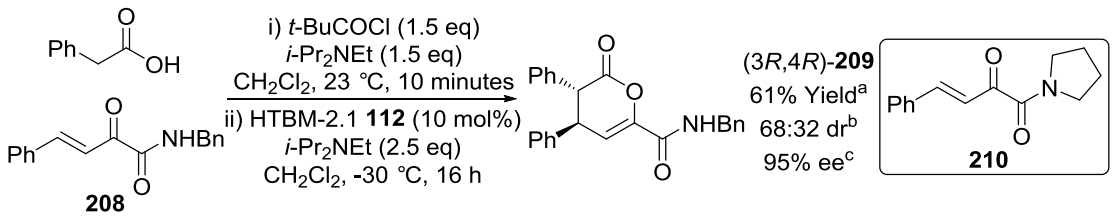


Scheme 52: Trifluoromethyl enones as Michael acceptors in formal [4+2] cycloadditions.

3.1 Synthesis and Formal [4+2] Cycloadditions

3.1.1 α-Keto-β,γ-Unsaturated Amides

Upon development of a highly diastereo- and enantioselective protocol for the Michael addition-lactonisation reaction between arylacetic acids and α-keto-β,γ-unsaturated esters (Chapter 2), interest moved towards assessing the reactivity of other Michael acceptors in this process. Several α-keto-β,γ-unsaturated amides were readily available from within the research group[76] and were tested using the standard reaction conditions. Reaction of phenylacetic acid with keto amide **208** catalysed by HBTM-2.1 **112** gave *anti*-dihydropyranone (3*R*,4*R*)-**209** in 61% yield, 68:32 dr and 95% ee. Interestingly, keto amide **210** was poorly reactive in this system, giving minimal conversion to the corresponding dihydropyranone after 16 h at 23 °C using highly reactive DHPB **108** as catalyst (Scheme 53). The limited reactivity of Michael acceptor **210** is another illustration of the subtle relationship between the ammonium enolate and the acceptor in which certain structural motifs appear to be poorly tolerated.

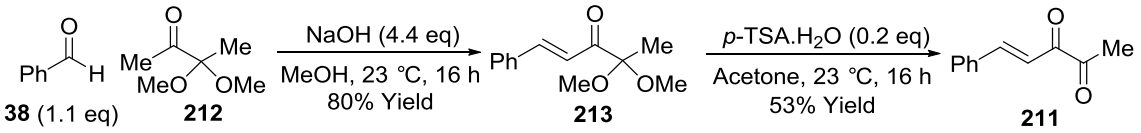


[a] Isolated yield of major diastereoisomer of **209** (97:3 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 53: Intermolecular Michael addition-lactonisation using α-keto-β,γ-unsaturated amides.

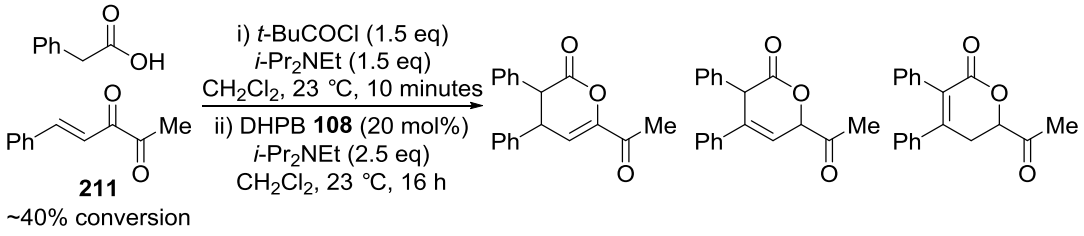
3.1.2 α-Keto-β,γ-Unsaturated Ketones

Following the procedures outlined by Muxfeldt,[77] α-keto-β,γ-unsaturated ketone **211** was synthesised in two simple steps. An aldol reaction of benzaldehyde **38** and 3,3-dimethoxybutan-2-one **212** with NaOH in MeOH gave acetal **213** in 80% yield. Subsequent deprotection using *p*-TSA in acetone gave α-keto-β,γ-unsaturated ketone **211** in 53% yield (Scheme 54).



Scheme 54: Synthetic route towards α-keto-β,γ-unsaturated ketone 211.

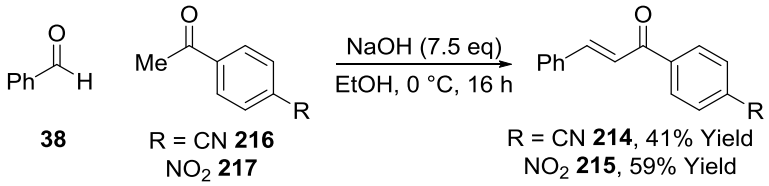
The subsequent isothiourea-catalysed Michael addition-lactonisation reaction between phenylacetic acid and α-keto-β,γ-unsaturated ketone **211** with DHPB **108** did not give full consumption of **211** after 16 h at 23 °C suggesting that the ketone appendage is not sufficiently electron withdrawing to activate the Michael acceptor (Scheme 55). Analysis of the crude reaction mixture by ^{1}H NMR showed a complex mixture including several products – likely to include the desired dihydropyranone and other isomerised products – which could not be separated and together amounted to ~40% conversion of **211**.



Scheme 55: Intermolecular Michael addition-lactonisation using α-keto-β,γ-unsaturated ketone 211.

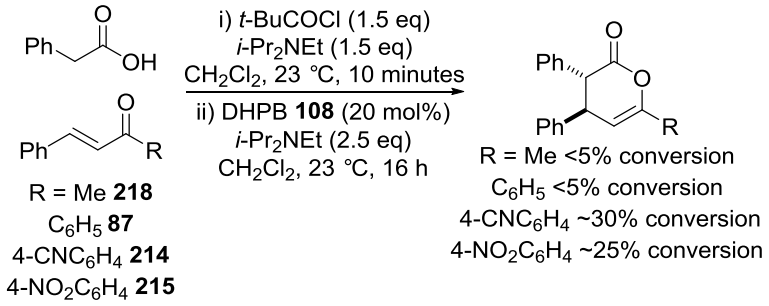
3.1.3 Enones

Enones **214** and **215** were prepared *via* the procedures described by Das and George.[78] Aldol reaction between benzaldehyde **38** and the requisite substituted acetophenone **216** or **217** with NaOH in EtOH gave enones **214** and **215** in 41% and 59% yield respectively (Scheme 56).



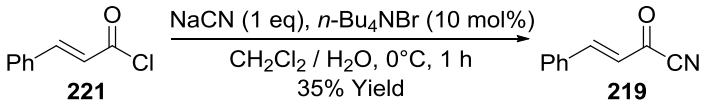
Scheme 56 - Synthetic route towards enones 214 and 215.

In addition to the commercially available (*E*)-4-phenylbut-3-en-2-one **218** and chalcone **87**, enones **214** and **215** were subjected to the standard conditions for the isothiourea-catalysed Michael addition-lactonisation reaction with DHPB **108** and phenylacetic acid for 16 h at 23 °C. Both (*E*)-4-phenylbut-3-en-2-one **218** and chalcone **87** were not consumed (<5%), whereas the more electron deficient enones **214** and **215** gave slightly improved reactivity with the crude ^{1}H NMR containing some peaks characteristic of the dihydropyranone products (Scheme 57). However, due to the poor conversion under these reaction conditions (~30% and ~25% conversion respectively) these products were not pursued.



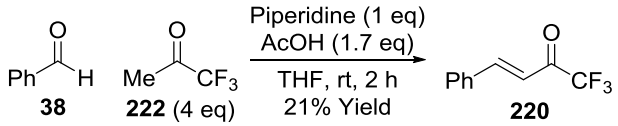
Scheme 57 - Intermolecular Michael addition-lactonisation using various enones.

Upon establishing that only very electron deficient Michael acceptors give complete conversion within the reaction protocol, enones **219** and **220** were next considered. Enone **219** was prepared following the procedure outlined by Bryce.[79] Cinnamoyl chloride **221** was reacted with *n*-Bu_4NBr and NaCN in a biphasic mixture of CH_2Cl_2 and H_2O to give enone **219** in 35% yield (Scheme 58).



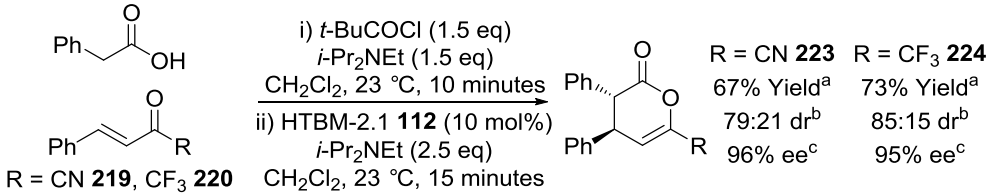
Scheme 58 - Synthetic route to enone 219.

Initially, enone **220** was prepared according to the procedure described by Liu.[80] The piperidine acid-catalysed aldol reaction between benzaldehyde **38** and trifluoroacetone **222** in THF gave enone **220** in 21% yield (Scheme 59).



Scheme 59 - Initial synthetic route towards enone 220.

The isothiourea-catalysed intermolecular Michael addition-lactonisation reactions using the electron deficient enones **219** and **220** were much more successful. Using the standard asymmetric reaction conditions with HBTM-2.1 **112**, reaction of phenylacetic acid with enone **219** gave *anti*-dihydropyranone (3*R*,4*R*)-**223** in 67% yield, 79:21 dr and 96% ee. The same reaction using enone **222** gave *anti*-dihydropyranone (3*R*,4*R*)-**224** in 73% yield, 85:15 dr and 95% ee (Scheme 60). Both reactions had reached completion after 15 minutes at 23 °C by TLC analysis.



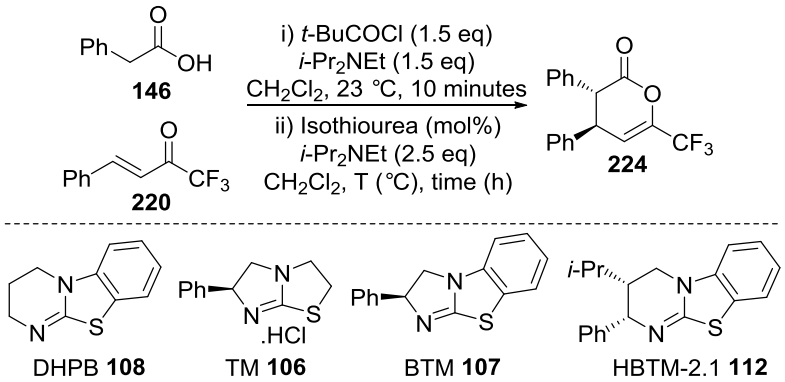
[a] Isolated yield of major diastereoisomer (>98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 60 - Intermolecular Michael addition-lactonisation using enones 219 and 220.

The trifluoromethyl unit holds a privileged position in organic chemistry. It is widely employed within both the pharmaceutical and agrochemical industries, with the incorporation of this motif strategically used to enhance binding selectivity and metabolic stability, as well as increasing lipophilicity.[81] In this context, the generation of practical and efficient methodologies capable of the selective introduction of this unit into organic molecules has developed widely, with a series of elegant strategies utilised towards these aims.[82] Bearing this in mind, along with the promising initial result using trifluoromethyl enone **220** in this reaction protocol, future work focused upon exploring the intermolecular Michael addition-lactonisation reaction of CF_3-bearing Michael acceptors.

3.2 Formal [4+2] Cycloaddition of 220

With trifluoromethyl enone **220** in hand, its subsequent use in the intermolecular Michael addition-lactonisation reaction with phenylacetic acid **146** could be investigated. The reaction conditions for the isothiourea-catalysed intermolecular Michael addition-lactonisation protocol were optimised for trifluoromethyl enone acceptor **220** in a similar manner to the α-keto-β,γ-unsaturated esters studied previously using phenylacetic acid **146** and enone **220** as the model system (Table 4). The catalysis could routinely be carried out at a lower catalyst loading and temperature presumably due to the greater reactivity of trifluoromethyl enone Michael acceptors compared to α-keto-β,γ-unsaturated esters. All reactions were carried out using bench grade solvents under air as standard.



Entry	Isothiourea (mol%)	T (°C)	Time (h)	Yield (%)[a]	dr[b]	ee (%)[c]
1	**108** (20)	23	0.5	66	86:14	-
2	**106** (10)	23	0.25	61	87:13	89 (ent)
3	**107** (10)	23	0.25	76	82:18	77 (ent)
4	**112** (10)	23	0.25	73	85:15	95
5	**112** (10)	–30	3	79	86:14	96
6	**112** (10)	–78	4	83	90:10	99
7	**112** (5)	–78	16	80	90:10	99
8	**112** (2)	–78	16	79	90:10	99
9	**112** (1)	–78	16	79	90:10	99

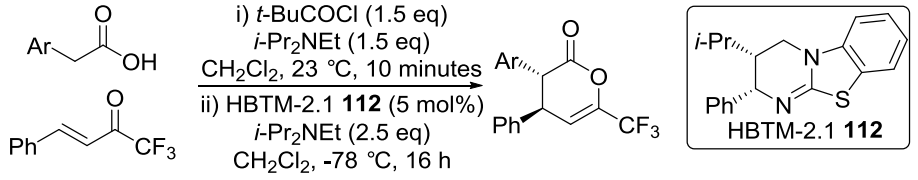
[a] Isolated yield of major diastereoisomer of **224** (≥98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

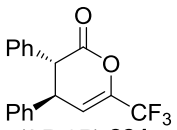
Table 4: Optimisation studies for Michael addition-lactonisation protocol.

Entry 7 in Table 4 was chosen as the optimal reaction conditions for the model system as it gives the best diastereo- and enantioselectivity (90:10 dr, 99% ee) at a low catalyst loading (5 mol%) whilst maintaining good conversion and isolated yield (>95% conversion, 80% isolated yield). Notably, in this system the catalysis remains efficient down to 1 mol% catalyst loading without any observable detriment towards stereoselectivity or yield. The optimal reactions conditions were then used to assess the scope of the Michael addition-lactonisation process. Racemic samples needed for chiral HPLC analysis for all dihydropyranones in this chapter were made using achiral DHPB **108** as catalyst.

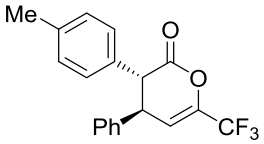
3.3 Substrate Scope – Variation of the Acid Component

With optimised reaction conditions in hand, the generality of this intermolecular Michael addition-lactonisation process catalysed by HBTM-2.1 **112** was first exemplified through variation of the arylacetic acid component (Table 5). A vast array of arylacetic acids are tolerated in this system including 3- and 4-substituted aryl rings in addition to electron-donating and electron-withdrawing substituents on the aryl unit. Naphthyl and heteroaryl substituents are also accommodated within the arylacetic acid, giving the corresponding *anti*-dihydropyranones **224-238** in good yield and excellent stereoselectivities (up to 95:5 dr, up to >99% ee)

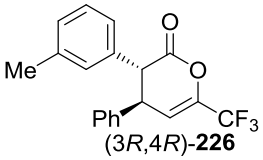




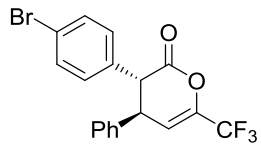
(3*R*,4*R*)-**224**
80% Yield[a]
90:10 dr[b]
99% ee[c]

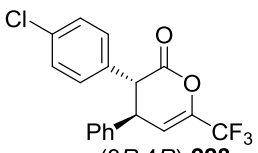


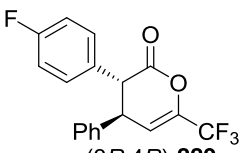
(3*R*,4*R*)-**225**
75% Yield[a]
93:7 dr[b]
98% ee

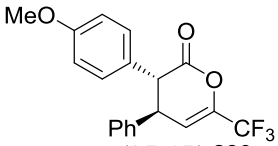


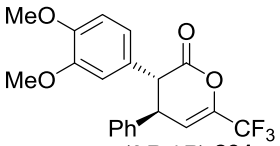
(3*R*,4*R*)-**226**
91% Yield[a]
94:6 dr[b]
>99% ee[c]

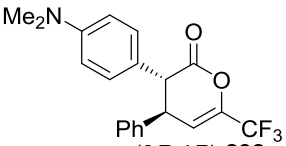

(3*R*,4*R*)-**227**
72% Yield[a]
90:10 dr[b]
95% ee[c]

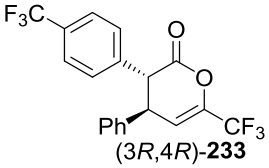

(3*R*,4*R*)-**228**
83% Yield[a]
91:9 dr[b]
96% ee[c]

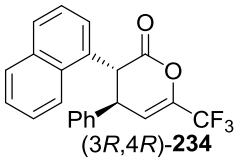

(3*R*,4*R*)-**229**
81% Yield[a]
90:10 dr[b]
99% ee[c]

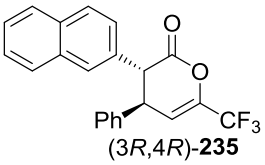

(3*R*,4*R*)-**230**
76% Yield[a]
92:8 dr[b]
98% ee

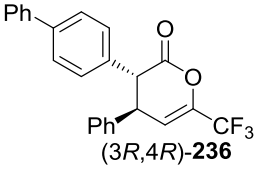

(3*R*,4*R*)-**231**
87% Yield[d]
90:10 dr[b]
98% ee[c]

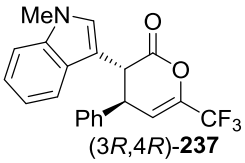

(3*R*,4*R*)-**232**
80% Yield[e]
95:5 dr[b]
99% ee[c]

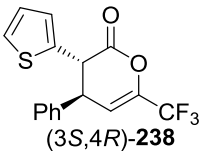

(3*R*,4*R*)-**233**
60% Yield[a]
86:14 dr[b]
64% ee[c]


(3*R*,4*R*)-**234**
88% Yield[f]
67:33 dr[b]
97% ee[c]


(3*R*,4*R*)-**235**
88% Yield[a]
94:6 dr[b]
97% ee[c]


(3*R*,4*R*)-**236**
89% Yield[a]
90:10 dr[b]
98% ee[c]


(3*R*,4*R*)-**237**
68% Yield[g]
74:26 dr[b]
96% ee[c]


(3*S*,4*R*)-**238**
75% Yield[h]
87:13 dr[b]
89% ee[c]

[a] Isolated yield of major diastereoisomer (≥98:2 dr) unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yield of product (92:8 dr). [e] Isolated yield of product (95:5 dr). [f] Isolated yield of product (71:29 dr). [g] Reaction carried out at −30 °C. [h] Isolated yield of product (96:4 dr).

Table 5: Substrate scope - variation of arylacetic acid component.

The relative and absolute configuration of dihydropyranone (3*R*,4*R*)-**227** was unambiguously confirmed by X-ray crystal structure analysis. The crystal structure shown (Figure 16) highlights the two aromatic substituents at C(3) and C(4) positions to have an *anti* relationship and confirmed the absolute configuration as (3*R*,4*R*) –

analogous to the α-keto-β,γ-unsaturated ester series. All other *anti*-dihydropyranone derivatives were assigned by analogy. For a detailed rationale regarding the observed enantio- and diastereoselectivity of these reactions, see Section 3.7

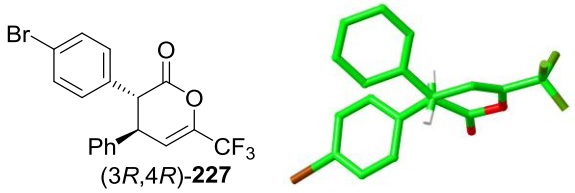


Figure 16: Crystal structure of (3*R*,4*R*)-227 showing relative and absolute configuration.

Generally, the results mirrored those found using α-keto-β,γ-unsaturated esters as Michael acceptors. However, the formation of dihydropyranones (3*R*,4*R*)-**234** and (3*R*,4*R*)-**237** occurred with reduced diastereoselectivity (67:33 *anti*:*syn* and 74:26 *anti*:*syn* respectively). The low diastereocontrol in the formation of (3*R*,4*R*)-**237** allowed isolation and characterisation of the minor (*syn*) diastereoisomer. It was found that the *syn* diastereoisomer is formed with low enantiocontrol (28% ee). The absolute configuration of the *syn* diastereoisomer is tentatively assigned as (3*S*,4*R*). Detailed investigations regarding the absolute configuration of the *syn* diastereoisomer formed in these reaction processes is discussed later in Section 3.6.3.

Within this series, and in contrast to the work in Chapter 2, no isomerisation products were observed. There are two reasonable explanations for this: i) the lower temperature used in these reactions (−78 °C compared to −30 °C when using α-keto-β,γ-unsaturated esters as Michael acceptors) retards product isomerisation; ii) conjugation into the ester functionality of dihydropyranones **239** is important in facilitating deprotonation, allowing the isothiourea catalyst to mediate the isomerisation process. As this deprotonation is not possible in dihydropyranones **240** derived from trifluoromethyl enone Michael acceptors, isomerisation products are not formed (Figure 17).

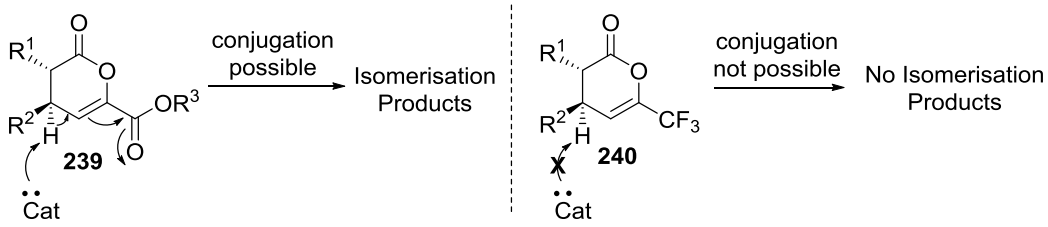
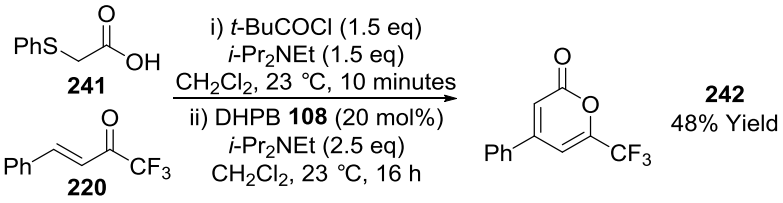


Figure 17: Possible explanation for absence of isomerisation products.

An interesting result was obtained upon employing (phenylthio)acetic acid **241** in this protocol. Under standard reaction conditions, using DHPB **108** as catalyst, full consumption of trifluoromethyl enone **220** was observed however the product obtained was pyrone **242** in 48% yield, resulting from initial Michael addition-lactonisation and subsequent elimination of PhSH (Scheme 61). This unexpected discovery was later applied to the synthesis of highly functionalised pyridines (see Chapter 7).



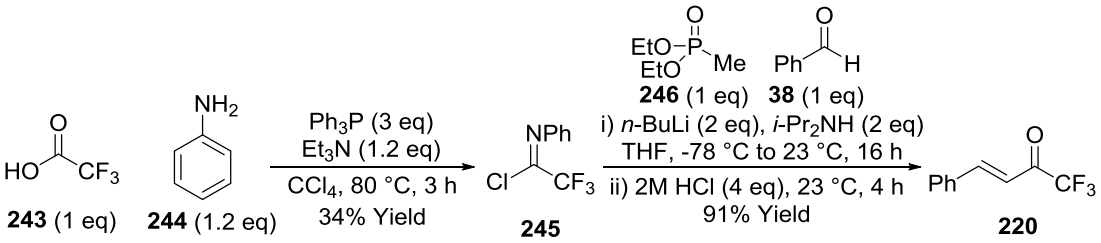
Scheme 61: Unexpected pyrone product 242 formed from functionalisation of acid 241.

3.4 Substrate Scope – Variation of the Michael Acceptor

To further probe the generality of this protocol, the Michael-addition lactonisation procedure using phenylacetic acid and a range of trifluoromethyl enones was studied.

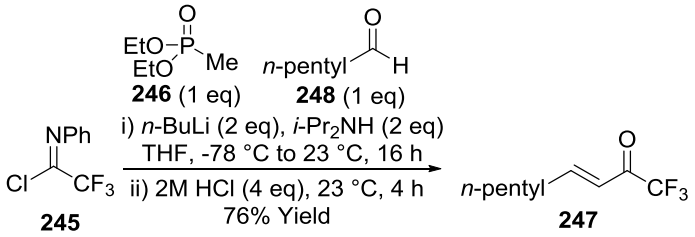
3.4.1 Synthesis of Trifluoromethyl Enones

For the preparation of a range of trifluoromethyl enones, a robust and cost-effective method was required. The generally low yielding piperidine-catalysed aldol reaction between aldehydes and the expensive and difficult to handle trifluoroacetone described by Liu was not a suitable option.[80] An alternative route towards trifluoromethyl enones was found using a two-step procedure following the methods described by Uneyama[83] and Yuan.[84] Reaction of TFA **243** with aniline **244**, PPh_3 and Et_3N in CCl_4 as solvent gave imine **245** in 68% yield. Subsequent reaction of imine **245** with LDA, diethyl methylphosphonate **246** and benzaldehyde **38** followed by acidic hydrolysis gave trifluoromethyl enone **220** in 91% yield (Scheme 62). The intermediate imine **245** is commercially available and was commonly purchased in preference to being synthesised.[85] This robust and high-yielding procedure allowed access to a variety of γ-aryl substituted trifluoromethyl enones through variation of the aldehyde including those bearing 2-, 3- and 4- substituents, electron-donating (4-OMe) and withdrawing groups (4-NO_2), in addition to naphthyl and heteroaryl substituents (2-furyl and 2-thiophenyl).



Scheme 62: Synthetic route towards trifluoromethyl enone 220.

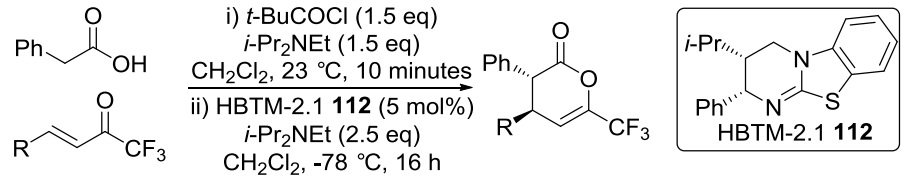
A γ-alkyl substituted trifluoromethyl enone **247** was also synthesised *via* this route employing hexanal **248** as the starting aldehyde in 76% yield (Scheme 63).

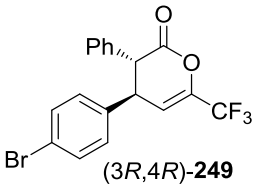


Scheme 63: Synthetic route towards γ-alkyl substituted trifluoromethyl enone 247.

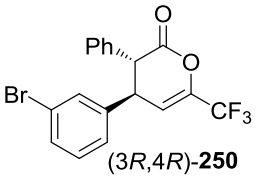
3.4.2 Intermolecular Michael Addition-Lactonisations

With a variety of trifluoromethyl enones in hand, their subsequent use in the intermolecular Michael addition-lactonisation protocol was evaluated (Table 6). A wide range of substituted γ-aryl substituents are tolerated including 2-, 3- and 4-substitution, electron-withdrawing and electron-donating substituents as well as γ-heteroaryl and naphthyl substituents, furnishing in all cases *anti*-dihydropyranones **249**-**260** with high dr (up to 95:5 dr) and ee (up to >99% ee). *Anti*-dihydropyranone **261** bearing an alkyl substituent at C(4) was also obtained in excellent ee (98%), albeit with slightly attenuated diastereoselectivity (78:22 dr).

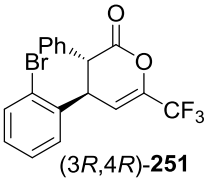




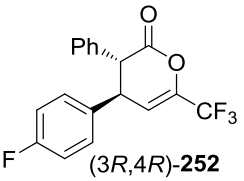
(3*R*,4*R*)-**249**
68% Yield[a]
88:12 dr[b]
98% ee[c]



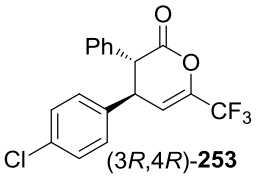
(3*R*,4*R*)-**250**
64% Yield[a]
80:20 dr[b]
97% ee[c]



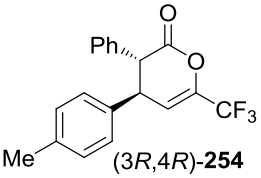
(3*R*,4*R*)-**251**
86% Yield[d]
87:13 dr[b]
97% ee[c]



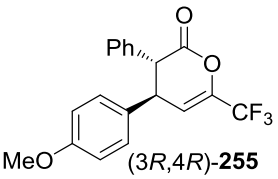
(3*R*,4*R*)-**252**
85% Yield[a]
86:14 dr[b]
98% ee[c]



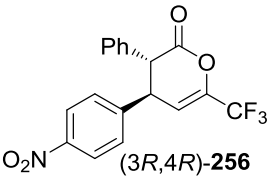
(3*R*,4*R*)-**253**
74% Yield[a]
88:12 dr[b]
>99% ee[c]



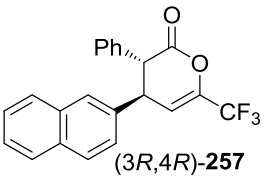
(3*R*,4*R*)-**254**
93% Yield[a]
95:5 dr[b]
97% ee[c]



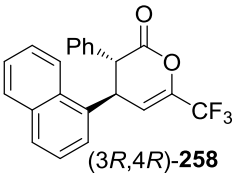
(3*R*,4*R*)-**255**
93% Yield[e]
94:6 dr[b]
98% ee[c]



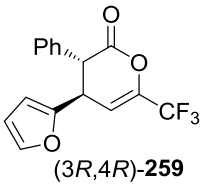
(3*R*,4*R*)-**256**
65% Yield[a]
73:27 dr[b]
86% ee[c]



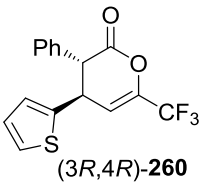
(3*R*,4*R*)-**257**
81% Yield[a]
90:10 dr[b]
>99% ee[c]



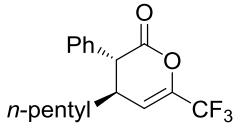
(3*R*,4*R*)-**258**
91% Yield[a]
94:6 dr[b]
98% ee[c]



(3*R*,4*R*)-**259**
77% Yield[a]
89:11 dr[b]
98% ee[c]



(3*R*,4*R*)-**260**
86% Yield[a]
88:12 dr[b]
95% ee[c]



(3*R*,4*R*)-**261**
73% Yield[a]
78:22 dr[b]
98% ee[c]

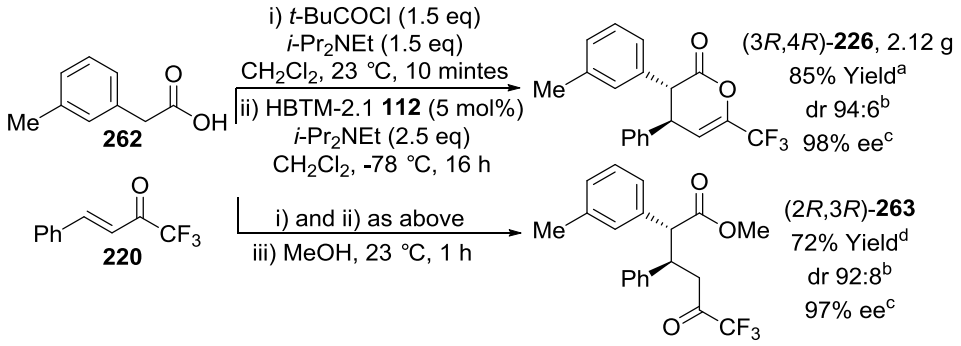
[a] Isolated yield of major diastereoisomer (≥98:2 dr) unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yield of product (95:5 dr). [e] Isolated yield of product (96:4 dr).

Table 6: Substrate scope - variation of trifluoromethyl enone component.

Although in general the system is very robust and tolerates considerable substrate variation, the stereoselectivity for the formation of dihydropyranone (3*R*,4*R*)-**256** is poorer than for other examples (73:27 dr, 86% ee). A possible explanation for the reduction in stereoselectivity is that because the Michael acceptor is very electron deficient, the non-catalysed background reaction is accelerated relative to the Lewis base-catalysed process, leading to the formation of racemic product with lower diastereocontrol (see Section 2.4 for a discussion of the background reaction in these processes).

3.5 Scale Up and Derivatisation

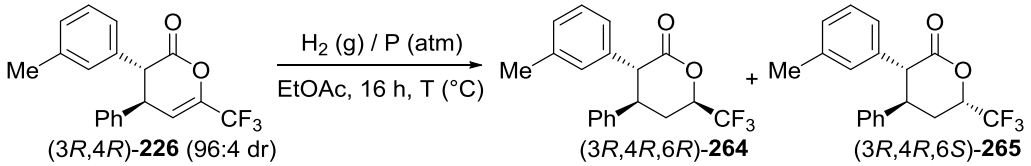
The synthetic versatility of these trifluoromethyl-substituted products was next demonstrated through a series of derivatisation processes. Firstly, this reaction sequence is readily applicable to scale up with reaction of *m*-tolylacetic acid **262** and trifluoromethyl enone **220** carried out on a multi-gram scale (7.5 mmol), generating *anti*-dihydropyranone (3*R*,4*R*)-**226** in 85% yield (2.12 g), 94:6 dr and 98% ee (Scheme 64). Notably, this reaction was carried out using 1 mol% of HBTM-2.1 **112** with no observable detriment towards the isolated yield or stereoselectivity. This reaction was performed in an open flask using bench-grade solvents, highlighting it as a robust and easily-reproduced protocol. Dihydropyranone (3*R*,4*R*)-**226** readily undergoes ring-opening with MeOH *in situ*, allowing a tandem Michael-lactonisation/ring-opening sequence to be developed, giving trifluoromethyl ketone (2*R*,3*R*)-**263** in 72% isolated yield, 92:8 dr and 97% ee directly from *m*-tolylacetic acid.



[a] Isolated yield of major diastereoisomer of **226** (96:4 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yield of major diastereoisomer of **263** (92:8 dr).

Scheme 64: Scale-up of Michael addition-lactonisation process and tandem ring-opening protocol.

One of the main goals for this project was to introduce a stereogenic centre bearing a trifluoromethyl substituent. This was achieved through the simple hydrogenation of *anti*-dihydropyranone (3*R*,4*R*)-**226** (Table 7). The use of 10 mol% Pd/C as catalyst gave low diastereoselectivity (53:47 dr) but allowed the isolation and characterisation of both diastereoisomers (3*R*,4*R*,6*R*)-**264** and (3*R*,4*R*,6*S*)-**265**. Using Wilkinson's catalyst – $(PPh_3)_3RhCl$ – gave the best diastereoselectivity (96:4 dr) using a hydrogen gas pressure of 50 bar and 80 °C reaction temperature, giving lactone (3*R*,4*R*,6*R*)-**264** in 96% yield and 98% ee in which the trifluoromethyl substituent is placed *pseudo* equatorial. Efforts to selectively access the other diastereoisomer (3*R*,4*R*,6*S*)-**265** through screening a small number of catalyst and ligand combinations were not successful.



Entry	Catalyst (mol%) / Ligand (mol%)	T (°C)	P (atm)	Conversion (%)	dr[a]	Yield (**264**:**265**) (%)[b]	ee (**264**:**265**) (%)[c]
1	Pd/C (10)	23	1	>99	53:47	51:45	98:97
2	Rh/C (10)	23	1	>99	92:8	-	-
3	$Pd(OH)_2$/C (10)	23	1	>99	56:44	-	-
4	$[Ir(COD)pyPCy_3]^+PF_6^-$ (5)	23	1	<5	-	-	-
5	$[Ir(COD)pyPCy_3]^+PF_6^-$	80	50	~10	95:5	-	-

	(5)						
6	$[Rh(COD)Cl]_2$ (5) / BINAP (15)	23	1	<5	-	-	-
7	$[Rh(COD)Cl]_2$ (5) / BINAP (15)	80	50	~40	90:10	-	-
8	$Rh(PPh_3)_3Cl$ (5)	23	1	<5	-	-	-
9	$Rh(PPh_3)_3Cl$ (5)	80	50	>99	96:4	96:-	98:-

[a] Isolated yields of **264** and **265** (>98:2 dr). [b] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Table 7: Screening for optimal hydrogenation conditions.

The relative configuration of lactones (3*R*,4*R*,6*R*)-**264** and (3*R*,4*R*,6*S*)-**265** were determined by NOE analysis. Irradiation of the hydrogen atom attached to C(6) in lactone (3*R*,4*R*,6*R*)-**264** gave a positive NOE with the hydrogen atom attached to C(4) whereas the same NOE was not present in lactone (3*R*,4*R*,6*S*)-**265** (Figures 18 and 19).

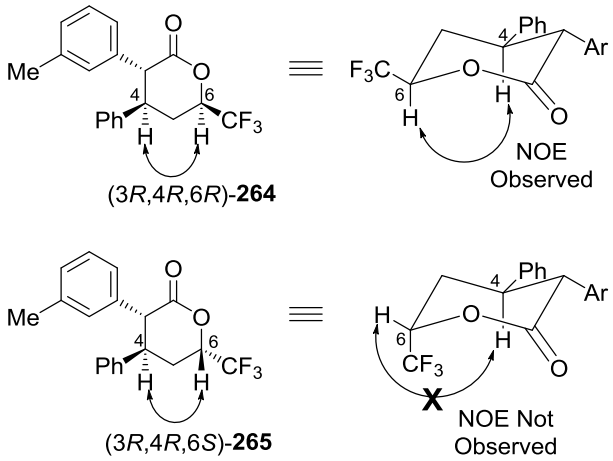
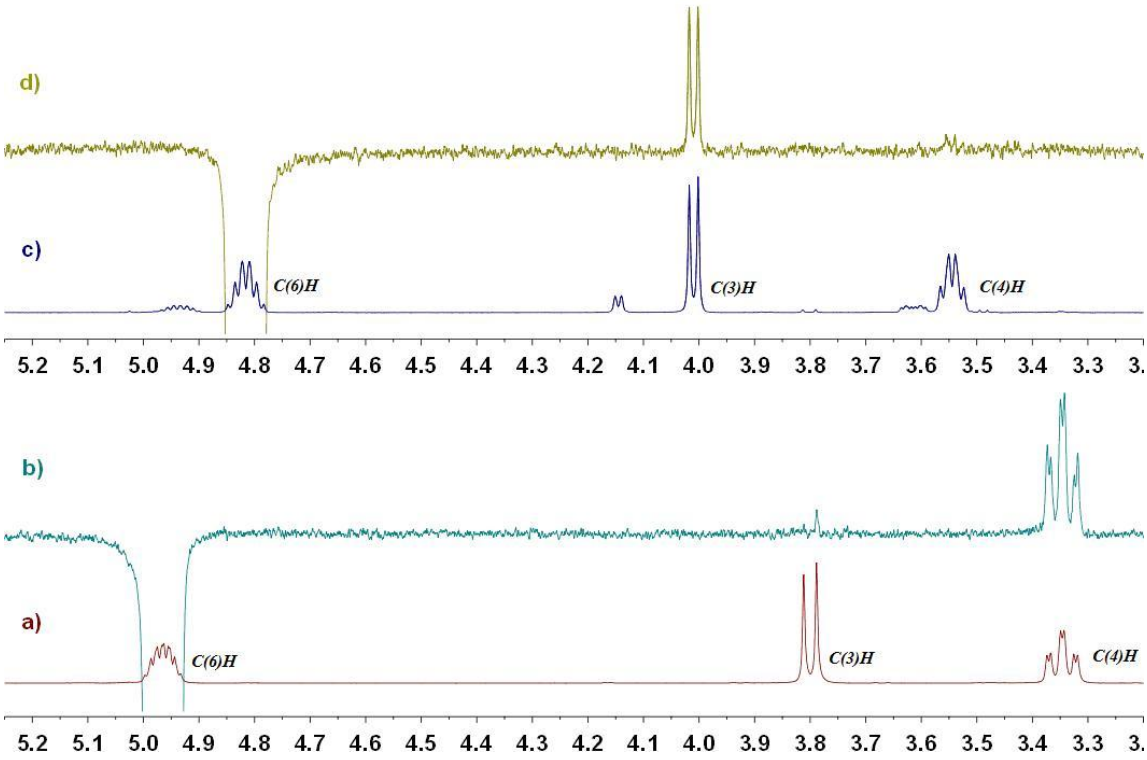


Figure 18 – NOE analysis of diastereomeric lactones 264 and 265.



a) ^{1}H NMR (300 MHz, $CDCl_3$) of (3*R*,4*R*,6*R*)-**264**. b) 1D gs-NOESY spectra of (3*R*,4*R*,6*R*)-**264**. c) ^{1}H NMR (300 MHz, $CDCl_3$) of (3*R*,4*R*,6*S*)-**265**. d) 1D gs-NOESY spectra of (3*R*,4*R*,6*S*)-**265**.

Figure 19: 1D gs-NOESY spectra for determining relative configurations.

In the case of lactone (3*R*,4*R*,6*S*)-**265**, a surprisingly strong NOE between the hydrogen atoms attached to C(3) and C(6) was observed. This can be explained by the presence of a boat conformation **266**, which according to DFT calculations at the B3LYP/6-31G** level of theory, is only 6.4 kJmol^{-1} higher in energy than the more stable chair conformation **267** and hence will be present in solution to a small extent (Figure 20). This brings the two protons at C(3) and C(6) in close enough proximity (2.319 Å) to observe an NOE.

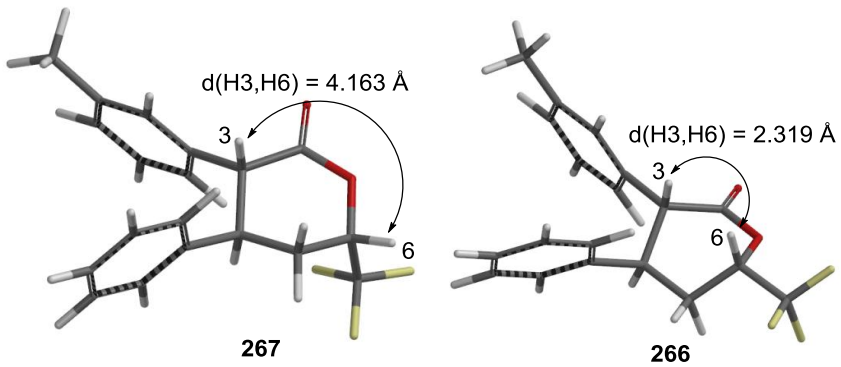


Figure 20: Geometries of both chair and boat conformations of (3*R*,4*R*,6*S*)-265.

Alternatively, the two diastereoisomers could also be distinguished by a coupling constant analysis for the C(6)*H* atom that has ddq multiplicity (Figure 21). In lactone (3*R*,4*R*,6*R*)-**264** there is an axial-axial $^{3}J_{HH}$ coupling constant of 12.2 Hz and an axial-equatorial $^{3}J_{HH}$ coupling constant of 3.2 Hz; whereas in lactone (3*R*,4*R*,6*S*)-**265** there is an equatorial-axial $^{3}J_{HH}$ coupling constant of 5.6 Hz and an equatorial-equatorial $^{3}J_{HH}$ coupling constant of 4.6 Hz.

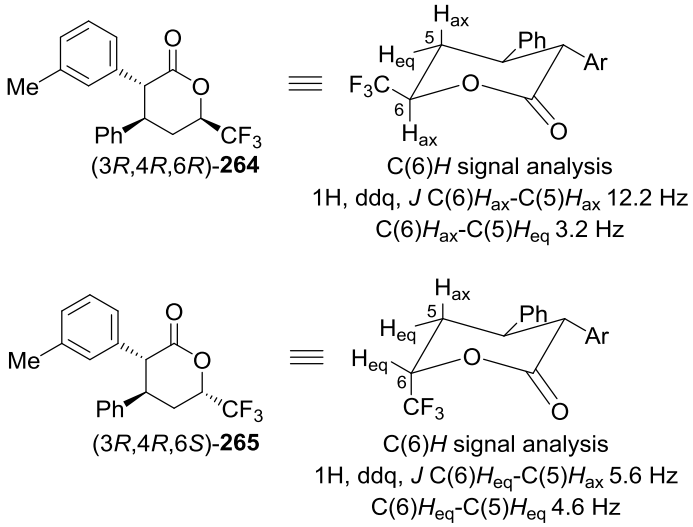
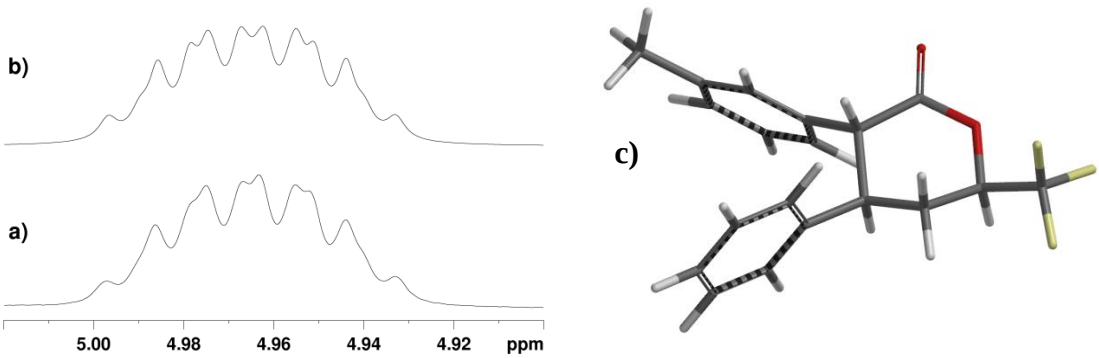


Figure 21 – Coupling constant analysis of diastereomeric lactones 264 and 265.

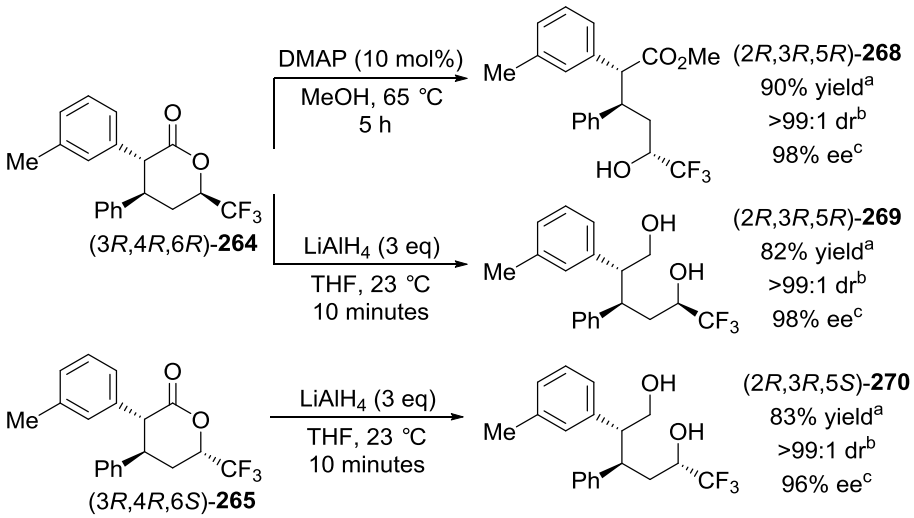
The observed coupling constants for C(6)*H* in (3*R*,4*R*,6*R*)-**264** are in agreement with a simulation of the ddq coupling pattern by Bruker Topspin DAISY module. The simulated spectrum shows a $^{3}J_{HH}$ coupling constant of 12.2 Hz which is in accordance with an axial position of C(6)*H* in the minimum energy chair conformation of (3*R*,4*R*,6*R*)-**264**. The structure of (3*R*,4*R*,6*R*)-**264**, obtained by MM conformational search and geometry optimisation at B3LYP/6-31G** level of theory is shown in Figure 22. The C(5)*H*a-C-C-C(6)*H* dihedral angle of 170.8° corresponds to coupling constant of 11.7 Hz, calculated by the Altona equation, which is in good agreement with the experimental data.



a) Experimental ddq coupling pattern of C(6)*H* in (3*R*,4*R*,6*R*)-**264**. b) Simulated ddq coupling pattern of C(6)*H* in (3*R*,4*R*,6*R*)-**264**. c) Structure of minimum energy conformation of (3*R*,4*R*,6*R*)-**264**.

Figure 22: Coupling constant analysis of (3*R*,4*R*,6*R*)-264.

Two illustrative examples for the further elaboration of these substrates have been explored. Firstly, ring opening of lactone (3*R*,4*R*,6*R*)-**264** with MeOH and catalytic amounts of DMAP gave alcohol (2*R*,3*R*,5*R*)-**268** in 90% yield, >99:1 dr and 98% ee (Scheme 65). Alternatively, treatment of lactones (3*R*,4*R*,6*R*)-**264** and (3*R*,4*R*,6*S*)-**265** with $LiAlH_4$ gave diastereomerically pure diols (2*R*,3*R*,5*R*)-**269** and (2*R*,3*R*,5*S*)-**270** in high yields and ee.

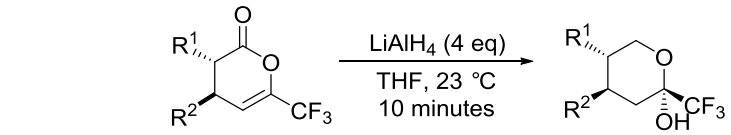


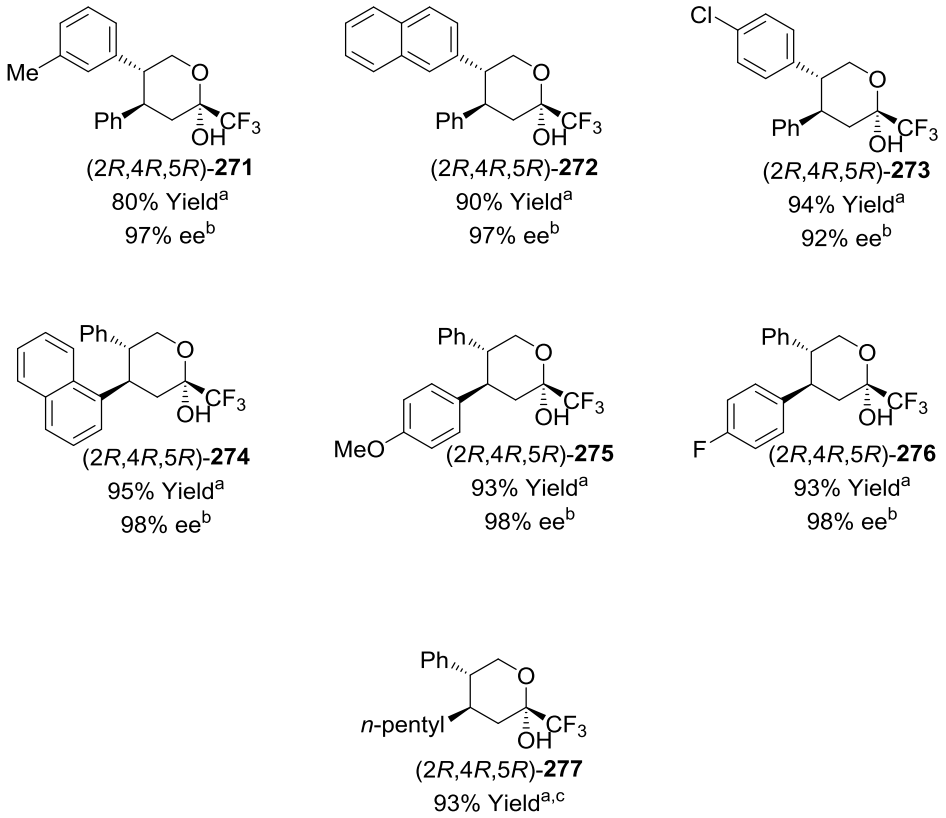
[a] Isolated yield of major diastereoisomer (>98:2 dr). [b] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 65: Lactone ring-opening procedures.

Another method for the introduction of a stereogenic centre bearing a trifluoromethyl substituent was discovered upon the treatment of dihydropyranone **226** with $LiAlH_4$, giving CF_3-lactol **271** as a single diastereoisomer in 80% yield and 97% ee after purification. This simple procedure is general and highly diastereoselective, tolerates

various substitution patterns at C(3)- and C(4)- in the dihydropyranone, and delivers CF_3-lactols **271**-**277** as single diastereoisomers in >80% yields and high ee's (Table 8).





[a] Isolated yield of major diastereoisomer (>98:2 dr). [b] Determined by chiral HPLC analysis. [c] Enantioselectivity could not be determined.

Table 8: Substrate scope for the pyran formation from dihydropyranones.

It is likely that this reaction proceeds by firstly reducing the dihydropyranone **278** to intermediate alcohol **279** which then undergoes cyclisation upon basic work-up to give the pyran **280**, placing the trifluoromethyl substituent in an equatorial position (Figure 23).

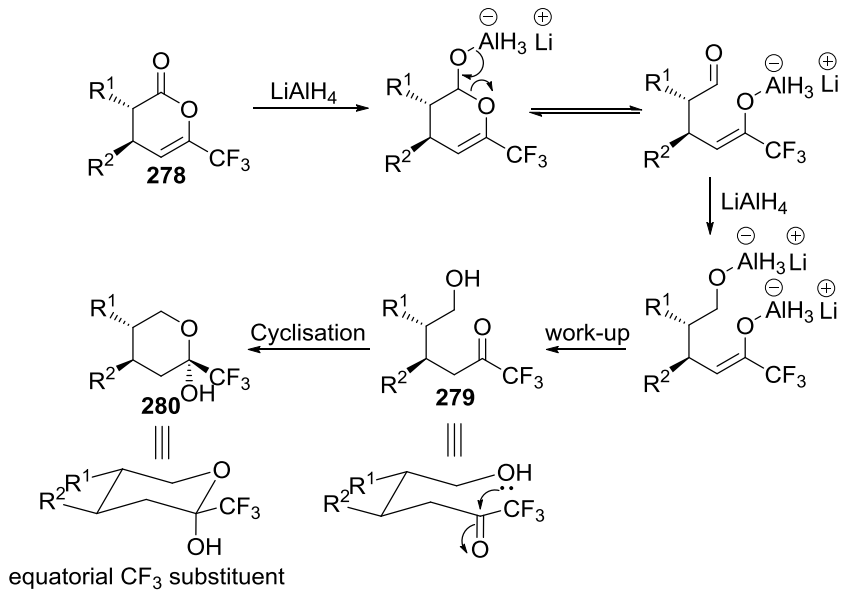


Figure 23: Possible mechanism for dihydropyranone conversion to pyran 280.

The relative configuration of pyran (2*R*,4*R*,5*R*)-**271** was determined *via* heteronuclear NOE analysis (Figures 24 and 25). Reciprocal NOE interactions were observed between the hydroxyl group and the hydrogen atoms on C(4) and C(6). These NOE interactions would only be possible for pyran (2*R*,4*R*,5*R*)-**271** in which the OH group is axial, not for pyran (2*S*,4*R*,5*R*)-**281** in which the hydroxyl group is placed equatorially as the through-space distance between the hydrogen atoms is too great (>4 Å).

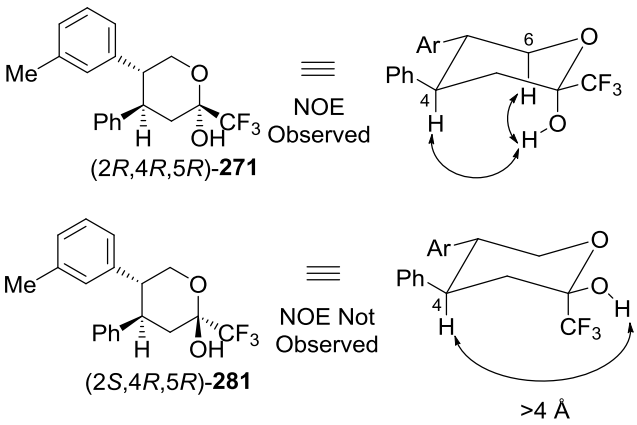
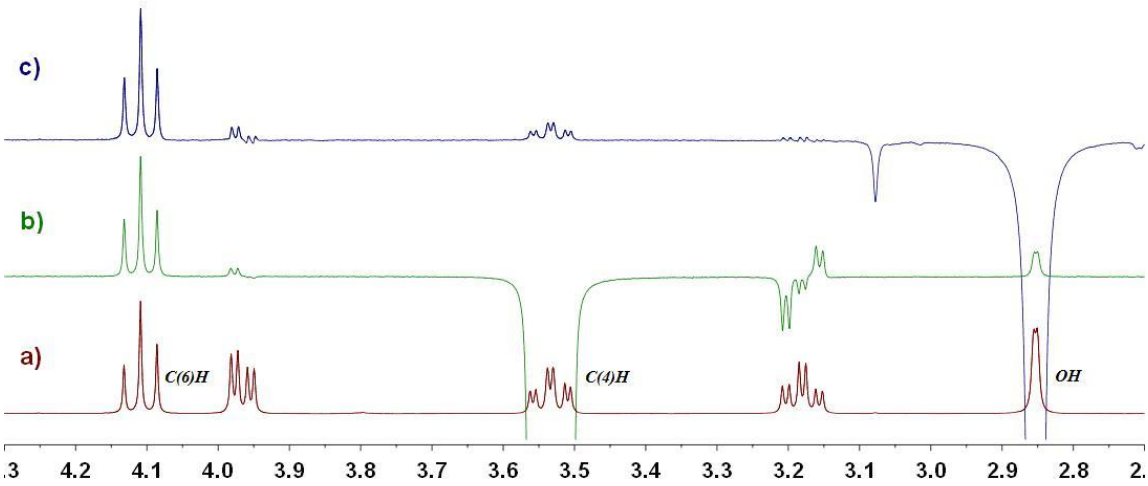


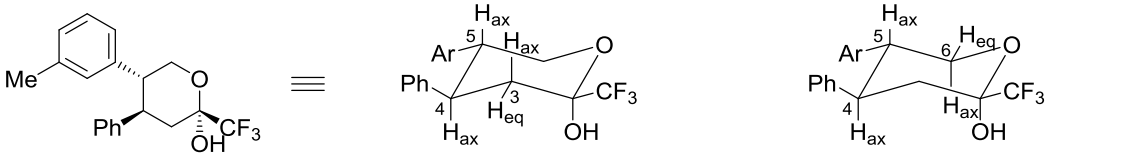
Figure 24 - NOE analysis of diastereomeric pyrans 271 and 281.



a) ^{1}H NMR (500 MHz, $CDCl_3$) of (2*R*,4*R*,5*R*)-**271**. b) 1D gs-NOESY spectra of (2*R*,4*R*,5*R*)-**271** upon selective irradiation of C(4)*H*. c) 1D gs-NOESY spectra of (2*R*,4*R*,5*R*)-**271** upon selective of O*H*.

Figure 25: 1D gs-NOESY spectra for determining relative configurations.

The *anti* relationship of the C(4) and C(5) substituents on pyran (2*R*,4*R*,5*R*)-**271** was also confirmed by analysis of the coupling constants for the hydrogen atoms on C(4) and C(5) (Figure 26). In the ^{1}H NMR, the signal for C(4)*H* appears an apparent triplet of doublets with an axial-axial $^{3}J_{HH}$ coupling constant of 12.2 Hz and an axial-equatorial $^{3}J_{HH}$ coupling constant of 3.8 Hz. The signal for C(5)*H* also appears as an apparent triplet of doublets with an axial-axial $^{3}J_{HH}$ coupling constant of 11.7 Hz and an axial-equatorial $^{3}J_{HH}$ coupling constant of 4.6 Hz. If the two aryl substituents on C(4) and C(5) had a *syn* relationship, one of the axial-axial $^{3}J_{HH}$ coupling constants for either C(4)*H* or C(5)*H* would not be present.



(2*R*,4*R*,5*R*)-**271**

C(4)*H* signal analysis
1H, td, *J* C(4)H_{ax}-C(3,5)H_{ax} 12.2 Hz
C(4)H_{ax}-C(3)H_{eq} 3.8 Hz

C(5)*H* signal analysis
1H, td, *J* C(5)H_{ax}-C(4,6)H_{ax} 11.7 Hz
C(5)H_{ax}-C(6)H_{eq} 4.6 Hz

Figure 26 – Coupling constant analysis of pyran 271.

The relative configuration of pyran (2*R*,4*R*,5*R*)-**271** was unambiguously confirmed by X-ray crystal structure analysis, with the absolute configuration derived from the known *anti*-dihydropyranone (3*R*,4*R*)-**226** (Figure 27). All other pyran derivatives were assigned by analogy.

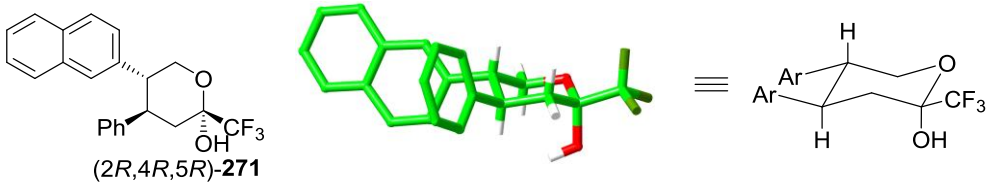
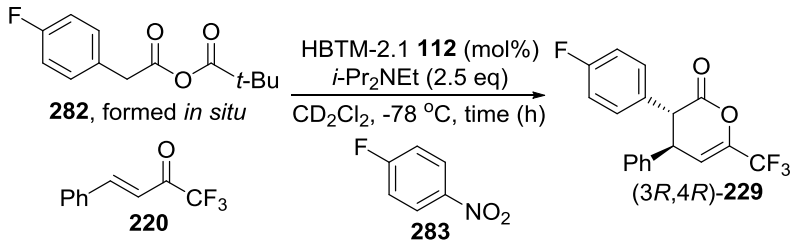


Figure 27: Crystal structure of (2*R*,4*R*,5*R*)-271 showing relative and absolute configuration.

3.6 Mechanistic and Kinetic Studies

3.6.1 Kinetic Analysis

To complement these synthetic studies, kinetic investigations aimed at establishing the catalytic cycle of the Michael addition-lactonisation process were performed. 4-Fluorophenylacetic acid (preactivated *in situ* with pivaloyl chloride and *i*-Pr_2NEt to prepare the mixed anhydride **282**) and trifluoromethylenone **220** were used as model substrates in order to measure reaction kinetics by *in situ* ^{19}F NMR spectroscopic analysis. The reactions were performed in CD_2Cl_2 at −78 °C using HBTM-2.1 **112** as catalyst and 1-fluoro-4-nitrophenol **283** as an internal standard (Scheme 66).



Scheme 66: Model system used for *in situ* ^{19}F NMR spectroscopic analysis.

Experimentally, stock solutions of known concentration of 4-fluorophenylacetic acid, 1-fluoro-4-nitrobenzene **283**, trifluoromethylenone **220** and HBTM-2.1 **112** were made using CD_2Cl_2 as solvent. Reactions were carried out by adding the required amount of 4-fluorophenylacetic acid, 1-fluoro-4-nitrobenzene **283**, *i*-Pr_2NEt, pivaloyl chloride and CD_2Cl_2 to an NMR tube. At −78 °C the required amount of HBTM-2.1 **112**, trifluoromethylenone **220** and *i*-Pr_2NEt were added, with the total volume always constant at 0.7 mL. The reaction was subsequently followed dynamically by ^{19}F NMR at −78 °C. The NMR sample was analysed using 8 scans with a relaxation delay (d1) of 25 seconds giving a total experiment time of 3 minutes 25 seconds and the sample was analysed approximately every 15 minutes. A typical ^{19}F NMR spectrum is shown below (Figure 28) in which the key species are clearly visible and highlighted, including both

diastereoisomers of the forming dihydropyranone **229** and **284**, 4-fluoronitrobenzene (internal standard) **283**, trifluoromethylenone **220** and mixed anhydride **282**.

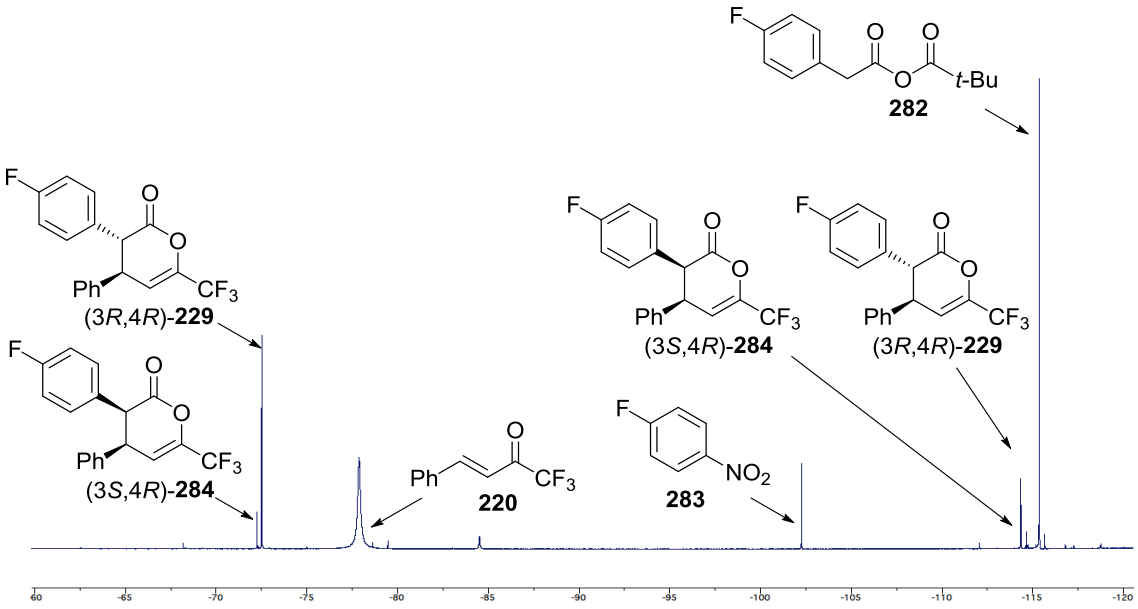
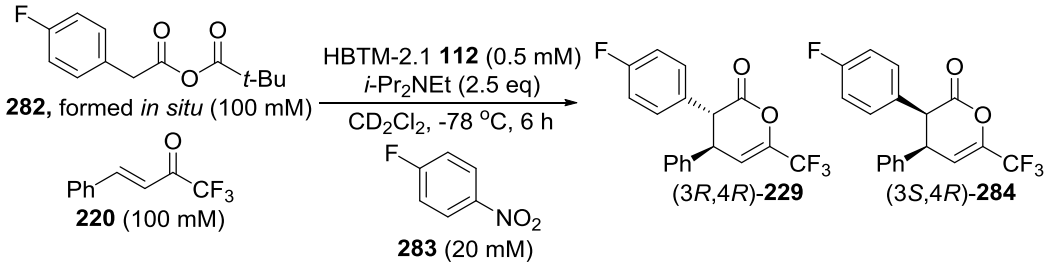


Figure 28: Typical ^{19}F NMR obtained during kinetic experiments (470 MHz, $CDCl_3$).

The initial kinetic experiment was run over approximately 6 h using the following reactant concentrations: 100 mM 4-fluorophenylacetic anhydride **282**, 100 mM trifluoromethylenone **220**, 20 mM 4-fluoro-1-nitrophenol **283**, 0.5 mM HBTM-2.1 **112** (Scheme 67).



Scheme 67: Initial kinetic experiment.

Data points were collected at approximately 15 minute intervals and the data were plotted using Excel (Figure 29). It is clearly visible that both the major and minor diastereoisomers of dihydropyranone *anti*-**229** and *syn*-**284** increase in concentration over time while the concentration of both the mixed anhydride **282** and trifluoromethyl enone **220** decrease over time. It can also be seen that the reaction was approximately 20% complete by the time of the first obtained data point and this is typically the case in most of the kinetic experiments.

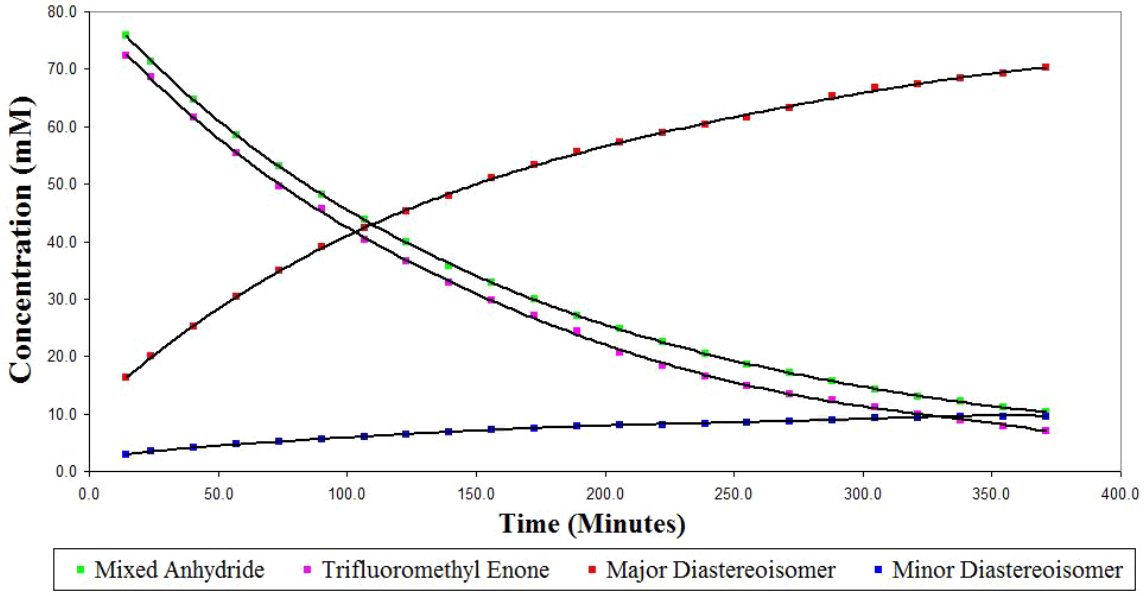


Figure 29: Excel plot of reaction course over time.

The concentration data for this experiment for both the mixed anhydride and trifluoromethyl enone over time is displayed below (Table 9).

Time (minutes)	[Mixed anhydride **282**] / mM	[Trifluoromethyl enone **220**] / mM
14.40	75.9	72.3
24.02	71.3	68.7
40.52	64.6	61.7
57.03	58.5	55.3
73.55	53.2	49.7
90.07	48.2	45.7
106.58	43.9	40.3
123.00	40.0	36.7
139.60	35.7	32.9
156.10	32.9	29.8
172.65	29.9	27.1
189.17	27.1	24.5
205.67	24.9	20.7
222.20	22.6	18.5
238.70	20.4	16.6
255.22	18.7	14.9
271.73	17.1	13.5

288.23	15.8	12.5
304.75	14.3	11.2
321.27	13.1	10.0
337.80	12.1	8.9
354.32	11.1	7.9

Table 9: Data for mixed anhydride and trifluoromethyl enone concentration over time.

Plots of the natural log of either mixed anhydride **282** or trifluoromethyl enone **220** vs. time were then constructed from this data using MATLAB® R2011a (Figure 30). Using one equivalent of enone with respect to anhydride the reaction progress could be fitted to a first-order rate expression for the concentration of the mixed anhydride **282** or the trifluoromethyl enone **220**. Plots of the natural log of the concentration of the mixed anhydride **282** vs. time are linear in all cases and these were used to obtain reaction rates. The gradient of the best fit line through the data points represents the first order rate constant k_{obs} for the reaction and is equal to 5.64±0.03 x 10^{-3}.

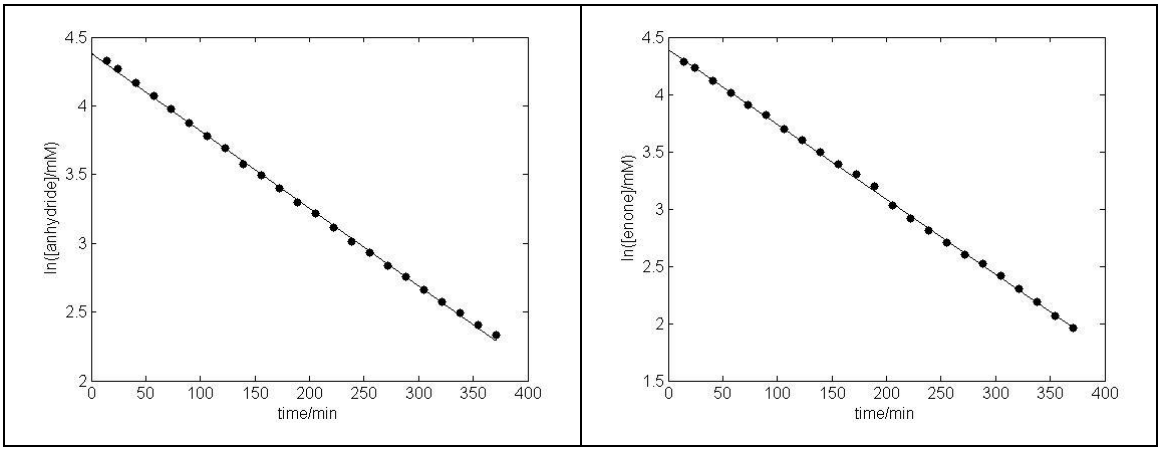


Figure 30: MATLAB plots to determine first order rate constants.

Kinetic runs for eight combinations of initial concentrations of mixed anhydride **282**, trifluoromethyl enone **220** and HBTM-2.1 **112** were performed (Table 10). Only data where either the concentration of **282** or **220** had not fallen to zero is presented and fitted. The fitted (t=0) intercept concentrations of the anhydride and observed rate constants k_{obs} are shown in the table.

Run	[Trifluoromethyl enone **220**] / mM	[Mixed Anhydride **282**] / mM	[HBTM-2.1 **112**] / mM	[Mixed Anhydride **282**]$_0$ / mM	$k_{obs} \times 10^3$ / s^{-1}
1	100	100	0.5	80.2±1	5.64±0.03
2	50	100	0.5	74.4±1	4.5±0.1
3	75	100	0.5	74.5±1	4.09±0.02
4	200	100	0.5	69.8±1	4.57±0.03
5	300	100	0.5	69.3±1	4.71±0.03
6	100	100	0.25	66.7±1	3.11±0.01
7	100	100	1.0	65.5±1	12.17±0.07
8	100	100[a] (d_2)	0.5	72.0±1	1.47±0.01

[a] 2-d^2-(4-fluorophenyl)acetic acid used.

Table 10: Kinetic data for various initial reagent concentrations.

Varying the initial concentration of trifluoromethyl enone **220** (50 mM, 75 mM, 100 mM, 200 mM and 300 mM) showed that while the reaction rate remained first order with respect to anhydride the rate was essentially independent of the concentration of the trifluoromethyl enone **220**. This result can be visualised using a plot of the natural log of the observed rate constant (k_{obs}) against the natural log of the initial concentration of the enone acceptor. The gradient of the best-fit line (roughly zero) is indicative of the order of the rate with respect to the concentration of the enone (Figure 31). Repeating the analysis, varying the initial concentration of catalyst (0.25 mM, 0.5 mM and 1.0 mM) showed a near linear first order dependence of rate on catalyst concentration (Figure 32).

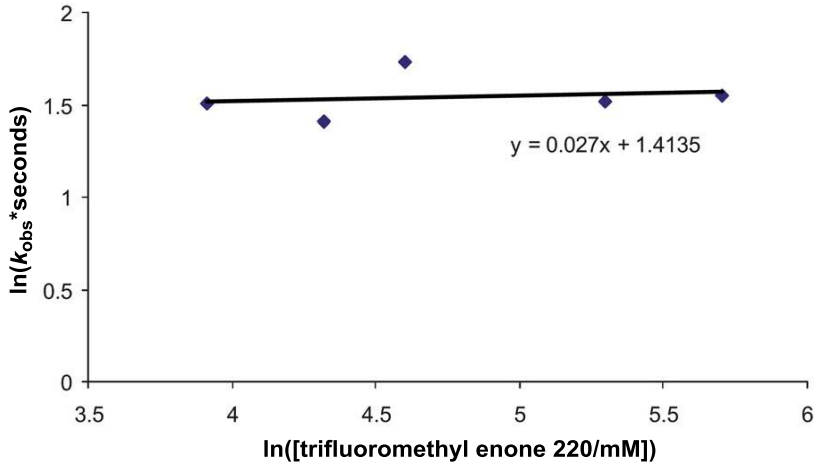


Figure 31: Plot of ln(k_{obs}) vs. ln([trifluoromethyl enone 220]).

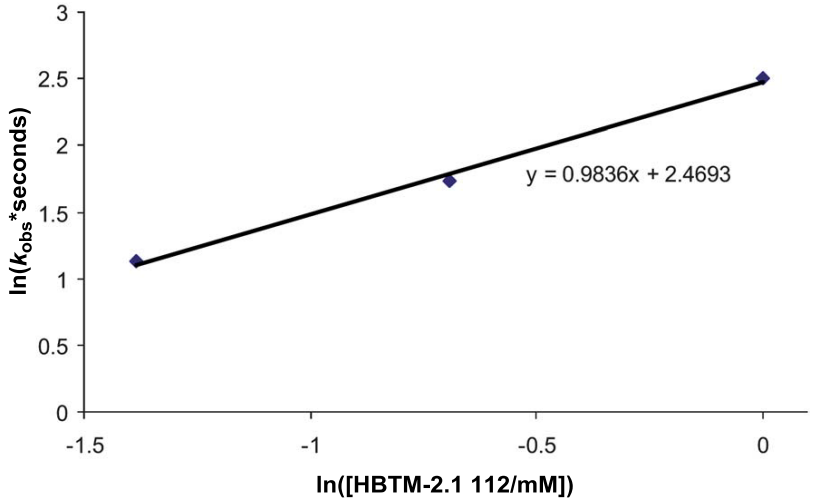
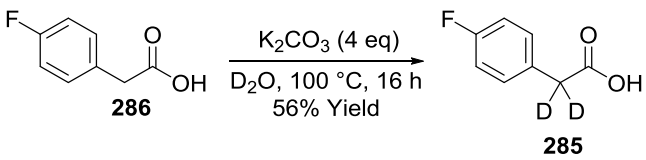


Figure 32: Plot of ln(k_{obs}) vs. ln(initial [HBTM-2.1 112]).

Further kinetic studies revealed that increasing the total equivalents of *i*-Pr_2NEt from 4 to 8 led to a minimal change in reaction rate. Notably for the acetylation of alcohols using DMAP, Zipse demonstrated kinetically that alcohol deprotonation is performed in a rate determining step by acetate instead of a trialkylamine auxiliary base in CH_2Cl_2.[86] Extrapolation of these studies to this system implicates potential deprotonation of an acyl ammonium intermediate by pivalate and the use of *i*-Pr_2NEt as a shuttle base. Shiina has reported a related process using isothioureas where pivalate has been postulated to act as a base.[87]

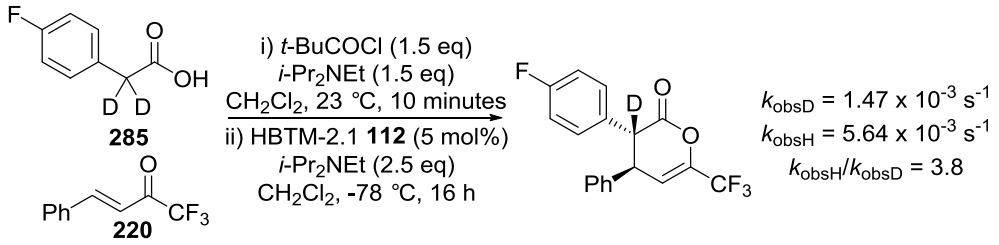
Overall these results suggest that the reaction is most likely to be first order with respect to mixed anhydride **282** and HBTM-2.1 **112** and zero order with respect to trifluoromethyl enone **220**. In order to test for kinetic isotope effects, α,α-di-deuterio 4-fluorophenylacetic acid **285** was synthesised by heating a mixture of 4-fluorophenylacetic acid **286** and K_2CO_3 in D_2O at reflux for 16 h, giving **285** in 56% yield which was >99% α,α-di-deuterated by ^1H NMR analysis (Scheme 68).



Scheme 68: Synthesis of α,α-di-deuterated acid 285.

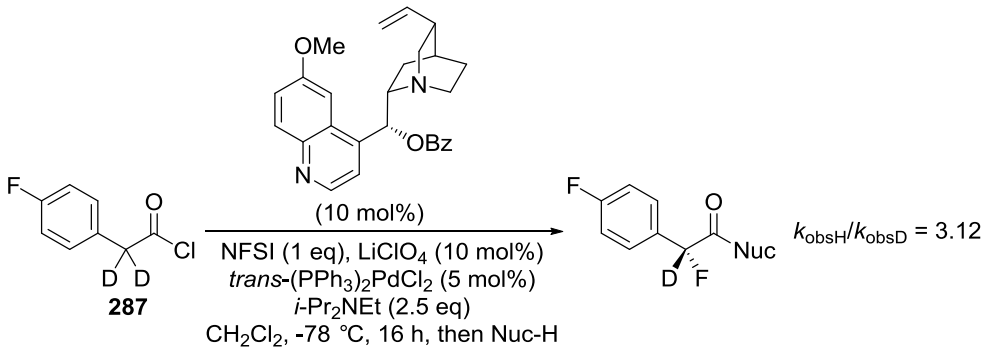
When the Michael addition-lactonisation reaction was performed using α,α-di-deuterio 4-fluorophenylacetic acid **285** (>99% d_2) the observed rate (k_{obs}) was approximately a

quarter of that for the equivalent reaction using 4-fluorophenylacetic acid (k_{obsH}/k_{obsD} = 3.8) (Scheme 69).



Scheme 69: Michael addition-lactonisation using α,α-di-deuterated acid 285.

Lectka and co-workers reported a kinetic isotope effect (k_{obsH}/k_{obsD} = 3.12) when using α,α-dideuteriophenylacetylchloride **287** in a related process involving the catalytic, enantioselective α-fluorination of acid chlorides (Scheme 70). They use this as evidence for dehydrohalogenation being the rate-determining step in this process.[88]



Scheme 70: Kinetic isotope effect observed in a related system.

Based on these kinetic studies, the catalytic cycle for this reaction likely proceeds *via* initial formation of the mixed anhydride **288**, followed by generation of the corresponding acyl ammonium ion **289**. Deprotonation will generate the (*Z*)-enolate **290**, which undergoes stereoselective Michael addition to the trifluoromethylenone **206**, followed by intramolecular cyclisation, to generate the dihydropyranone **207** and regenerate HBTM-2.1 **112** (Figure 33).

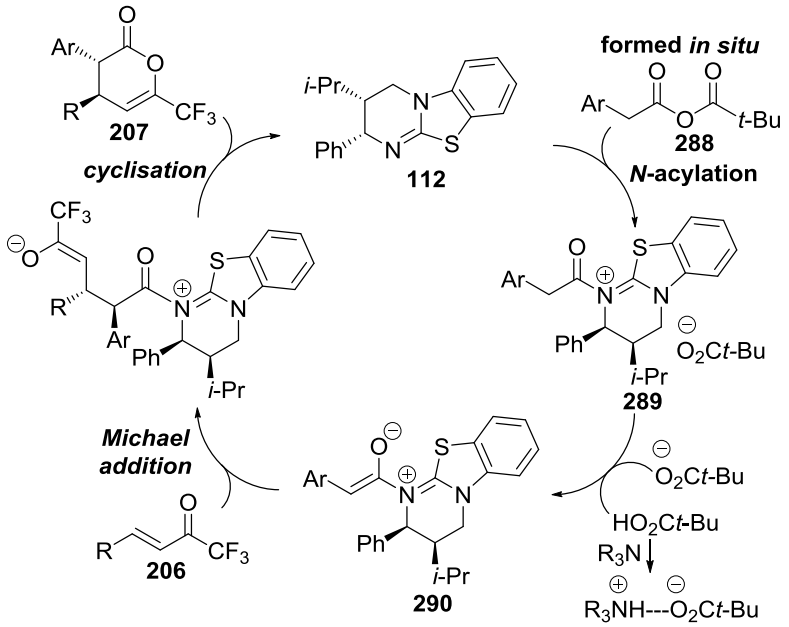
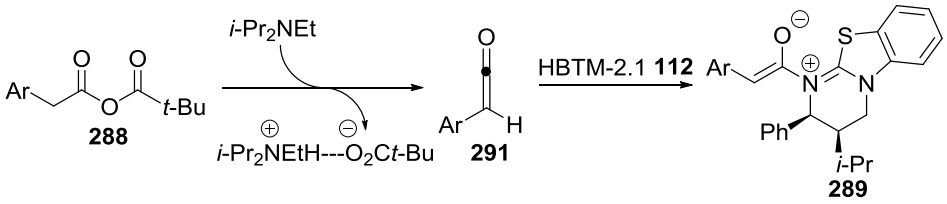


Figure 33: Proposed catalytic cycle for asymmetric Michael-lactonisation process.

An alternative reaction process, involving the *in situ* generation of a ketene **291** from the mixed anhydride **288** followed by nucleophilic addition of HBTM-2.1 **112** to generate the (*Z*)-enolate **289** can also be envisaged (Scheme 69).

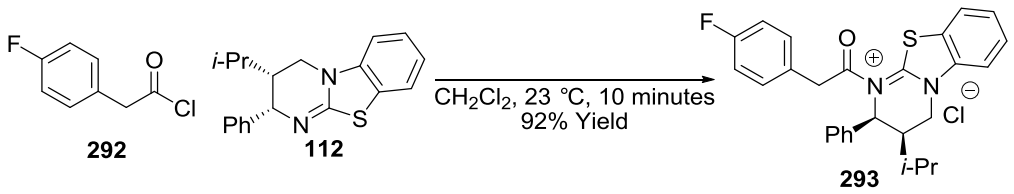


Scheme 69: Alternative ketene pathway.

The kinetic studies indicate that the rate-determining transition structure is constructed from the catalyst and the anhydride. While either the *N*-acylation or deprotonation steps are consistent with this requirement the deuterium kinetic isotope effect described above is consistent with deprotonation being rate determining. Such knowledge suggests that, within certain boundaries, the reaction rate will not be limited by the choice of enone acceptor.

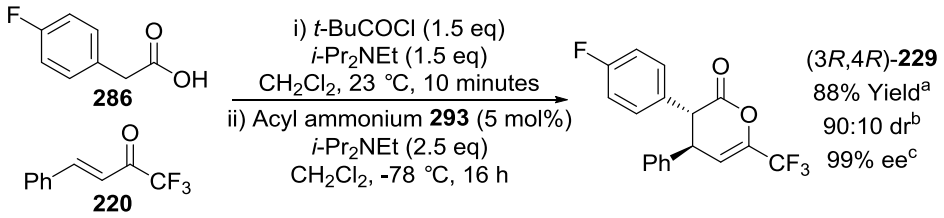
3.6.2 Reaction Intermediates

The formation of an acyl ammonium ion such as **289** is supported by the treatment of 4-fluorophenylacetyl chloride **292** with HBTM-2.1 **112** to give *N*-acyl isothiouronium chloride **293** in 92% isolated yield (Scheme 70).



Scheme 70: Acyl ammonium formation.

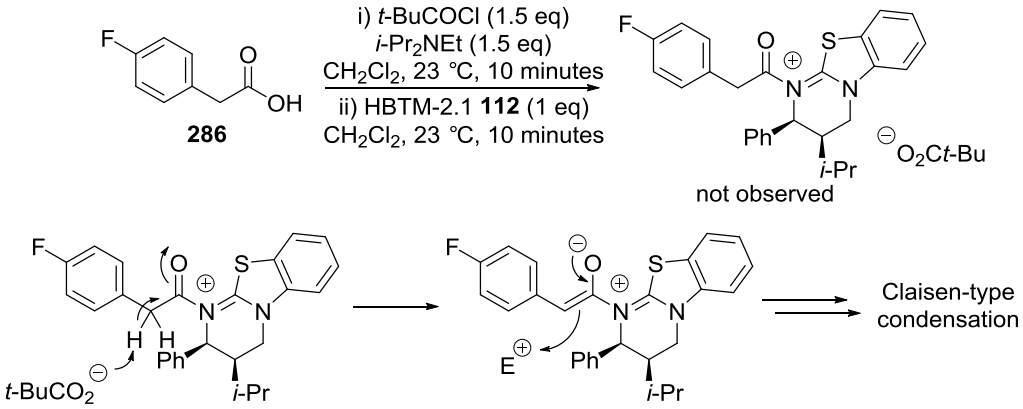
The validity of **293** as a plausible reaction intermediate was probed by its use as a precatalyst (Scheme 71). Treatment of 4-fluorophenylacetic acid **286** with pivaloyl chloride and *i*-Pr_2NEt, followed by addition of trifluoromethylenone **220** and acyl ammonium salt **293** (5 mol%) as the precatalyst gave dihydropyranone (3*R*,4*R*)-**229** in 88% isolated yield and identical diastereo- and enantioselectivity (90:10 dr and >99% ee) to that employing HBTM-2.1 **112** directly in this protocol.



[a] Isolated yield of major diastereoisomer of **229** (>98:2 dr). [b] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

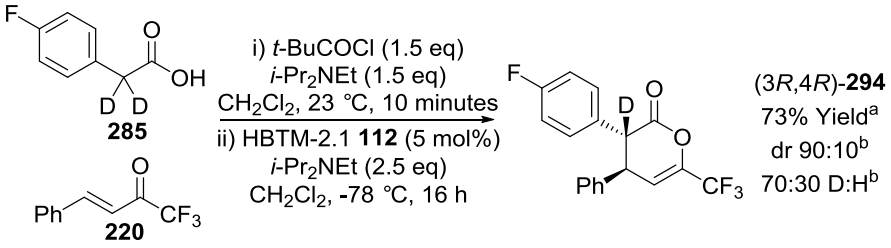
Scheme 71: Acyl ammonium used as a precatalyst.

Treatment of HBTM-2.1 **112** with the mixed anhydride derived from 4-fluorophenylacetic acid **286** without trifluoromethyl enone **220** does not produce a single acyl ammonium product, as happens with the acid chloride, but rather a complex mixture which seemingly included a significant proportion of catalyst. This result suggests that, while the reaction with the acid chloride proceeds to completion and then stops because chloride is not particularly basic, pivalate, generated in the anhydride reaction, may be basic enough to produce the enolate and further reaction such as Claisen-type condensation can occur (Scheme 72).



Scheme 72: Proposed Claisen-type condensation process.

Notably, for all cases in this kinetic analysis monitoring the product distribution with reaction progress indicated that the product diastereoselectivity increased with time, with typically an 83:17 *anti*:*syn* ratio observed after 5 minutes, and a 90:10 *anti*:*syn* ratio observed at the end of the kinetic experiments (typically 4-6 hours). Furthermore, dihydropyanone **294** derived from α,α-di-deuterio 4-fluorophenylacetic acid **285** (>99% d_2) contained around 30% proton incorporation at C(3) (Scheme 73).

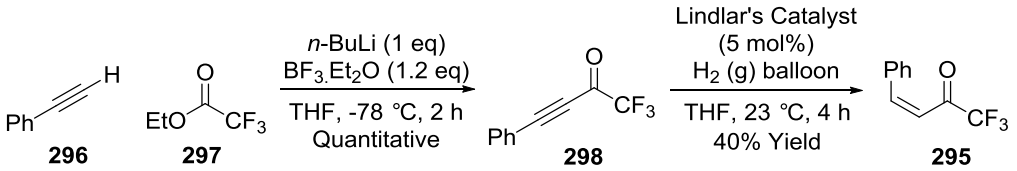


[a] Isolated yield of major diastereoisomer of **294** (>98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Scheme 73: Reaction using α,α-di-deuterio 4-fluorophenylacetic acid 285.

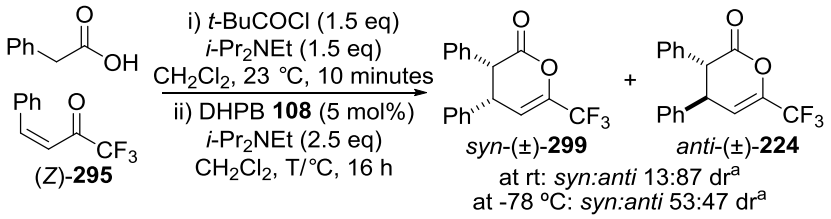
3.6.3 Stereospecificity

These observations imply *in situ* equilibration and epimerisation at C(3) during the reaction and prompted an investigation regarding the stereospecificity of this process through the employment of the (*Z*)-enone **295** as the Michael acceptor. (*Z*)-enone **295** was accessed following the procedure outline by Sasaki *via* treatment of phenylacetylene **296** with *n*-BuLi followed by quenching the resulting anion with ethyl trifluoroacetate **297**, giving alkyne **298** in quantitative yield (Scheme 74).[89] Selective reduction of **298** using Lindlar's catalyst affords the desired trifluoromethyl enone (*Z*)-**295** in 40% yield which must be used immediately to avoid isomerisation to (*E*)-enone **220**.



Scheme 74: Synthesis of trifluormethyl enone (*Z*)-95.

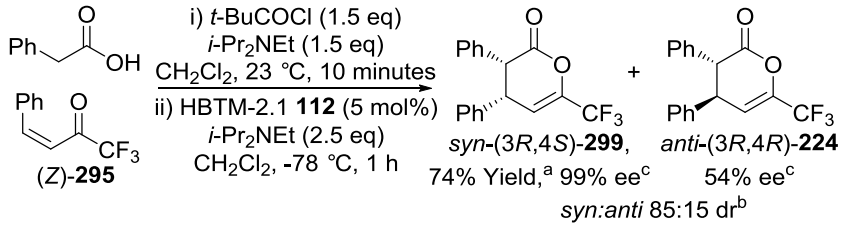
Initial studies with DHPB **108** as the isothiourea catalyst and (*Z*)-enone **295** using standard reaction conditions at 23 °C gave an 87:13 *anti*:*syn* mixture of dihydropyranones after 16 hours, essentially identical to the observed 86:14 *anti*:*syn* product ratio observed using DHPB from the (*E*)-enone (Scheme 75). At lower temperature (−78 ˚C) a 47:53 *anti*:*syn* mixture of dihydropyranones was generated, suggesting epimerisation of the initially formed *syn*-isomer to the thermodynamically preferred *anti*-isomer.



[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Scheme 75: Reaction of trifluormethyl enone (*Z*)-295 using DHPB 108.

In the asymmetric series, the use of HBTM-2.1 **112** at −78 ˚C with (*Z*)-enone **295** gave preferentially the *syn*-dihydropyranone (3*R*,4*S*)-**299** with good diastereoselectivity (85:15 dr), with purification giving a 91:9 mixture of (3*R*,4*S*)-**299** (99% ee):(3*R*,4*R*)-**224** (54% ee) in 74% yield (Scheme 76).

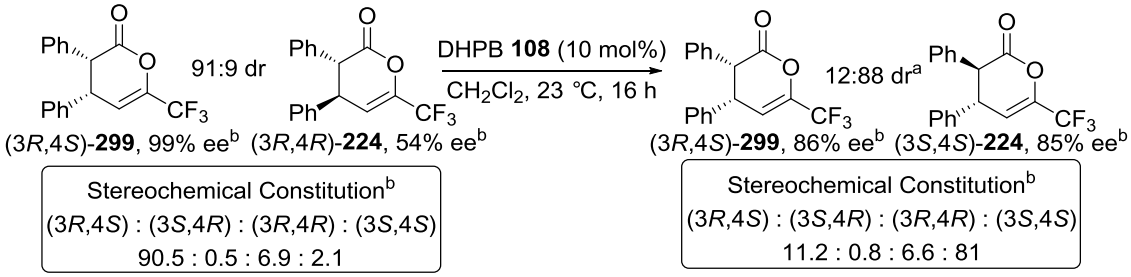


[a] Isolated yield of major diastereoisomer of **299** (91:9 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 76: Reaction of trifluoromethyl enone (*Z*)-295 using HBTM-2.1 112.

To experimentally test the hypothesis of epimerisation at C(3), treatment of the 91:9 mixture of (3*R*,4*S*)-**299** (99% ee):(3*R*,4*R*)-**224** (54% ee) with DHPB **108** (10 mol%) at

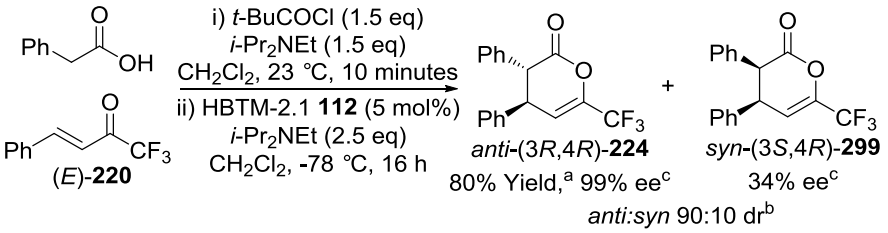
23 °C for 16 h gave a 12:88 mixture of (3*R*,4*S*)-**299** (86% ee):(3*S*,4*S*)-**224** (85% ee), consistent with epimerisation at C(3) of the *syn*-dihydropyranone (3*R*,4*S*)-**299** to the *anti*-dihydropyanone (3*S*,4*S*)-**224** (Scheme 78). This observation is in agreement with both proton/deuterium exchange at C(3) (Scheme 73) and the observed increase in product diastereoselectivity over time in the kinetic experiments. This experiment also allowed the absolute configuration of the *syn* diastereoisomer formed using (*Z*)-enone **295** assigned as (3*R*,4*S*)-**299** *via* HPLC analysis.



[a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [b] Determined by chiral HPLC analysis.

Scheme 78: Epimerisation study using DHPB 108.

The epimerisation experiment detailed above allowed for the assignment of all four stereoisomers using chiral HPLC analysis. With knowledge of the absolute configuration of *syn* diastereoisomer (3*R*,4*S*)-**299** formed using (*Z*)-enone **295**, the reaction using (*E*)-enone **220** could be re-examined to determine the absolute configuration of the minor *syn*-diastereoisomer formed (Scheme 79). Upon chiral HPLC analysis, it was found that the minor diastereoisomer **229** was formed in 34% ee and was determined to have (3*S*,4*R*) absolute configuration.

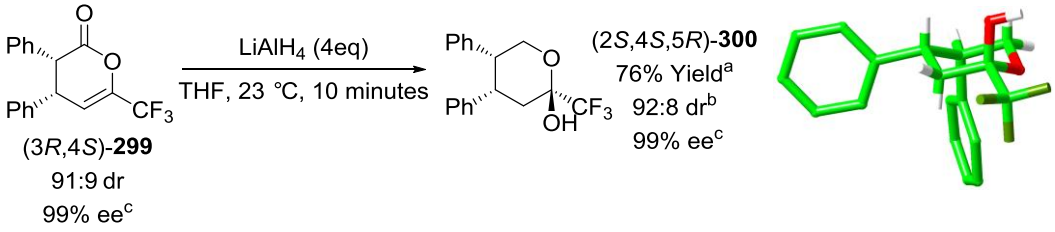


[a] Isolated yield of major diastereoisomer of **224** (98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 79: Re-examination of reaction using (*E*)-enone 220.

With *syn*-dihydropyranone (3*R*,4*S*)-**299** (dr 91:9) in hand, treatment with $LiAlH_4$ generates the CF_3-lactol (2*S*,4*S*,5*R*)-**300** (dr 91:9) in 76% isolated yield and 99% ee after purification (Scheme 80). This protocol thus allows access to stereoisomeric product

trifluoromethyl lactols by judicious choice of enone geometry. The relative configuration within (2*S*,4*S*,5*R*)-**300** was confirmed by X-ray crystal structure analysis. The known absolute configuration of the starting dihydropyranone (3*R*,4*S*)-**299** allowed the absolute configuration of (2*S*,4*S*,5*R*)-**300** to be assigned.



[a] Isolated yield of major diastereoisomer of **299** (94:6 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 80: Syn-diastereoisomer derivatisation to lactol and crystal structure.

3.7 Computational Studies

In collaboration with Dr David Fox at Warwick University, computational investigation of the proposed catalytic cycle was also undertaken. DFT calculations were performed using PC-GAMESS at the B3LYP/6-31G(d) level.[90-92] Objectives of the computational analysis included: 1) differentiating between possible Michael addition and Diels-Alder reaction mechanisms; 2) determining the lowest energy transition state for the key carbon-carbon bond forming step and use this to rationalise the observed stereochemical outcome; 3) providing further evidence to support the mechanistic findings of the kinetic analysis such as the rate-determining step of the reaction. The relative energies (in kJ mol^{-1}) for each stage of the catalytic cycle were found (Figure 34)

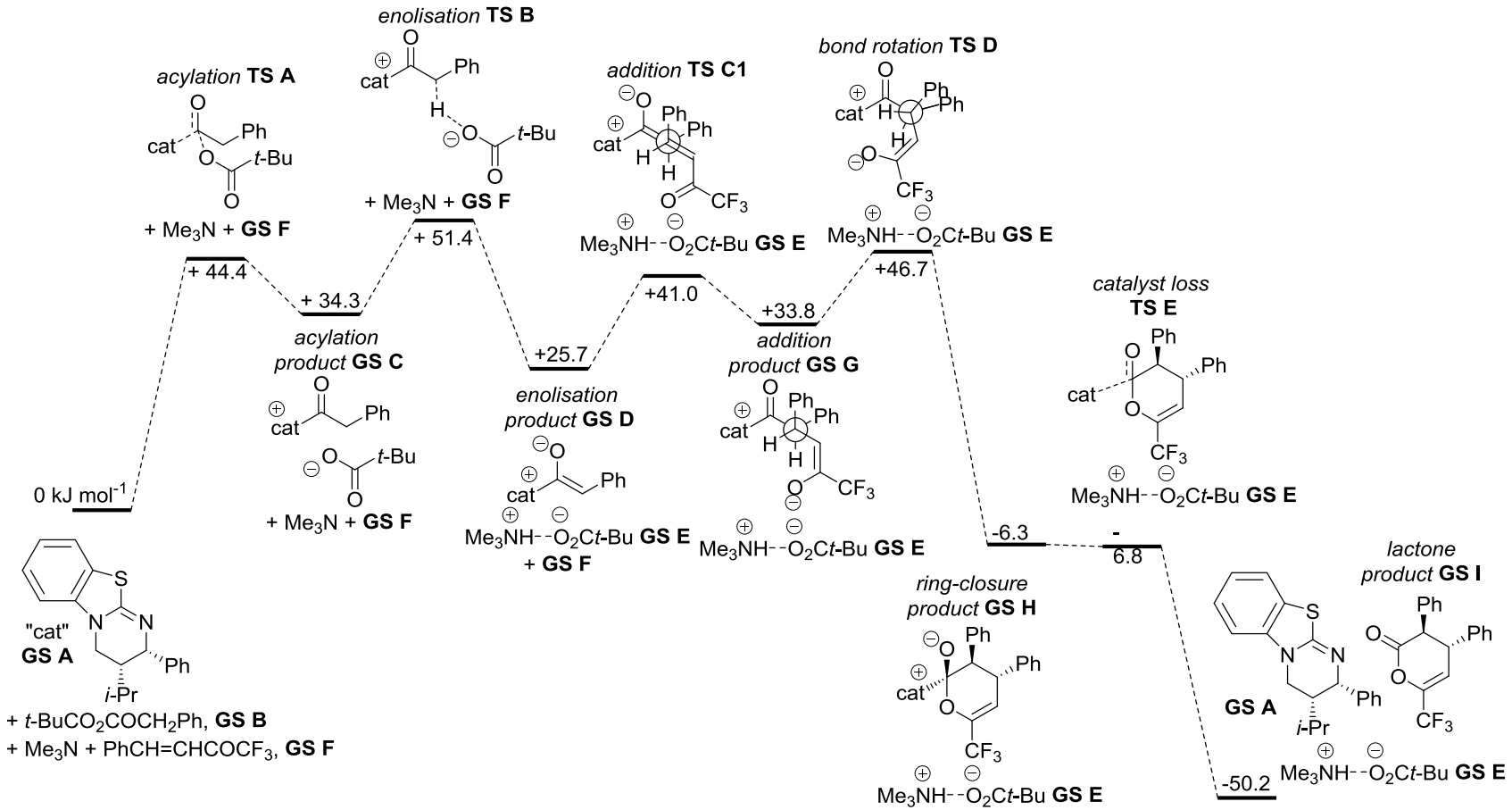


Figure 34: Catalytic cycle studied by computational modelling.

The electronic energy, ZPE and total energy of each species as well as "total energies" for each stage of the catalytic cycle (Figure 34, ground states and transition states) are given below (Table 11).

Compound	**E / Hartrees**	**ZPE / Hartrees**	**Total Energy/ Hartrees**	**Relative Energy / kJ mol^{-1}**
GS A (catalyst)	-1243.769254	0.350804	-1243.41845	
GS B (anhydride)	-730.7190804	0.266361	-730.4527194	
GS F (enone)	-760.0088765	0.148957	-759.8599195	
Me_3N	-174.4744039	0.121105	-174.3532989	
Total	**-2908.971615**	**0.887227**	**-2908.084388**	**0**
TS A (acylation)	-1974.472874	0.618616	-1973.854258	
GS F (enone)	-760.0088765	0.148957	-759.8599195	
Me_3N	-174.4744039	0.121105	-174.3532989	
Total	**-2908.956155**	**0.888678**	**-2908.067477**	**44.3921625**
GS C (acylation prod.)	-1974.477571	0.619483	-1973.858088	
GS F (enone)	-760.0088765	0.148957	-759.8599195	
Me_3N	-174.4744039	0.121105	-174.3532989	
Total	**-2908.960851**	**0.889545**	**-2908.071306**	**34.3399875**
TS B (enolisation)	-1974.466	0.614399	-1973.851601	
GS F (enone)	-760.0088765	0.148957	-759.8599195	
Me_3N	-174.4744039	0.121105	-174.3532989	
Total	**-2908.94928**	**0.884461**	**-2908.064819**	**51.3683625**
GS D (enolate)	-1627.435438	0.469951	-1626.965487	
GS E (ammonium salt)	-521.5195892	0.270399	-521.2491902	
GS F (enone)	-760.0088765	0.148957	-759.8599195	
Total	**-2908.963904**	**0.889307**	**-2908.074597**	**25.7021625**
TS C1 (addition)	-2387.441492	0.621901	-2386.819591	

GS E (ammonium salt)	-521.5195892	0.270399	-521.2491902	
Total	**-2908.961081**	**0.8923**	**-2908.068781**	**40.9681125**
GS G (addition prod.)	-2387.445938	0.6236	-2386.822338	
GS E (ammonium salt)	-521.5195892	0.270399	-521.2491902	
Total	**-2908.965527**	**0.893999**	**-2908.071528**	**33.75645**
TS D (bond rotation)	-2387.440664	0.623242	-2386.817422	
GS E (ammonium salt)	-521.5195892	0.270399	-521.2491902	
Total	**-2908.960254**	**0.893641**	**-2908.066613**	**46.66044653**
GS H (ring closed)	-2387.460795	0.623199	-2386.837596	
GS E (ammonium salt)	-521.5195892	0.270399	-521.2491902	
Total	**-2908.980384**	**0.893598**	**-2908.086786**	**-6.295274999**
TS E (cat. loss)	-2387.460427	0.622643	-2386.837784	
GS E (ammonium salt)	-521.5195892	0.270399	-521.2491902	
Total	**-2908.980016**	**0.893042**	**-2908.086974**	**-6.787725**
GS I (lactone prod.)	-1143.706165	0.270281	-1143.435884	
GS E (ammonium salt)	-521.5195892	0.270399	-521.2491902	
GS A (catalyst)	-1243.769254	0.350804	-1243.41845	
Total	**-2908.995009**	**0.891484**	**-2908.103525**	**-50.2338375**

Table 11: Relative energies for all GS and TS in catalytic cycle.

Transition states for the *N*-acylation **TS A** and deprotonation **TS B** steps were located as well as their associated intermediate ground state structures. (Figures 34 and 35).

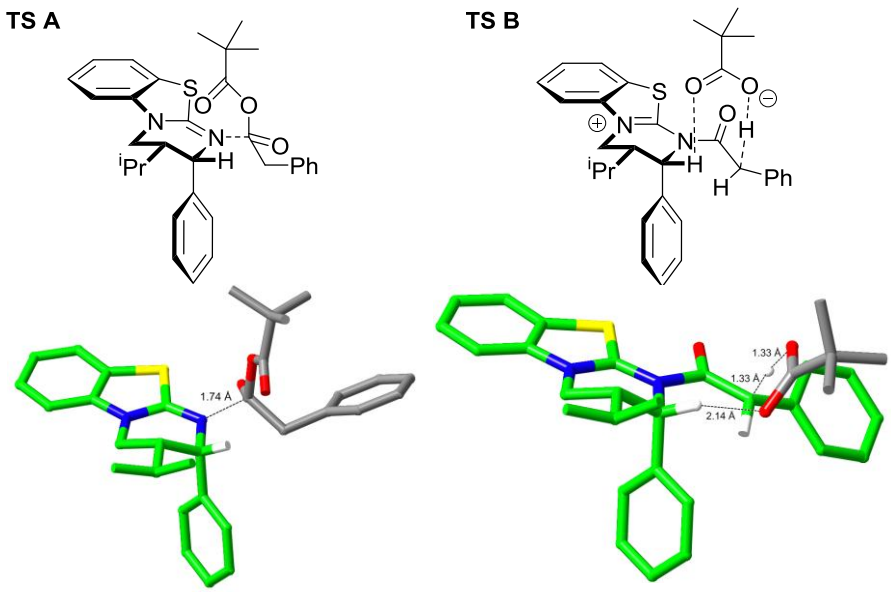


Figure 35: Calculated transition structures for the *N*-acylation (TS A) and deprotonation (TS B) steps.

The acylation of the catalyst (**GS A**) with the mixed anhydride (**GS B**) occurs in a single step to give an isothiouronium ion as its pivalate salt (**GS C**) via **TS A** (Figure 35). It is well known that acyl substitution reactions involving weak bases ($pKa_H(H_2O)$ less than 14) as nucleophiles and leaving groups can occur via concerted mechanisms, meaning there is no stable tetrahedral intermediate.[93] Examples include the reaction of aryl acetates with aryloxides[94] and the reactions of acylpyridinium ions with pyridine.[95] In these cases the strong leaving group ability of both nucleophile and leaving group renders the tetrahedral intermediate-like structure unstable with respect to instantaneous decomposition.[96] Theoretical calculations, such as for the displacement of phenolate by an amine,[97] also support a concerted displacement mechanism. Of particular note are the calculations by Zipse concerning the reaction of dimethylaminopyridine (DMAP) with acetic anhydride that indicate a concerted displacement mechanism.[86] The similar reacting atoms and basicities of DMAP (sp^2 nitrogen, $pKa_H(H_2O)$ = 9.87[98]) and isothiourea catalyst (**GS A**) (sp^2 nitrogen, $pKa_H(H_2O)$ = 9.8 for a related isothiourea[99]) suggest that the acylation mechanism of HBTM-2.1 **112** may be very similar to that of DMAP. Our calculations suggest that after acylation of HBTM-2.1 **112**, the carboxylate deprotonates the cationic intermediate to give the ammonium enolate (**GS D**) (Figure 34). Zipse has also demonstrated kinetically that deprotonation, in their case of an alcohol, is performed in a rate determining step by acetate instead of a trialkylamine auxiliary base in dichloromethane, which was supported with DFT calculations.[86]

Transition states for the conjugate addition **TS C** (a number of diastereoisomers) were located as well as the associated intermediate ground state structures (Figures 34 and 36).

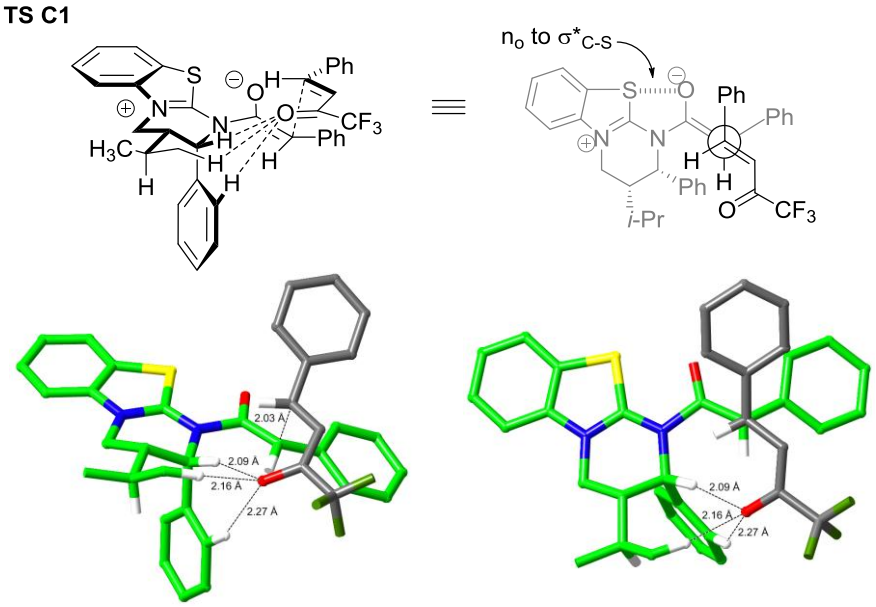


Figure 36: Calculated transition structures for the conjugate addition (TS C1) step.

The structure of the enolate **GS D** highlights the preference for the isothiouronium heterocycle to adopt a half-chair type conformation with the C(2)-phenyl unit pseudoaxial to minimise 1,2 steric interactions and the C(3)-*i*-Pr unit pseudoequatorial. Previous modelling studies within the group showed that upon *N*-carboxylation of HBTM-2.1 **112**, the C(2)-phenyl substituent preferentially adopts a pseudoaxial orientation to minimise 1,2 steric interactions.[56] A similar conformational preference in the key (*Z*)-ammonium enolate intermediate is expected due to sp^2 hybridisation at the adjacent centre. The groups of Birman and Houk have recently disclosed two reports including DFT calculations to investigate the origin of enantioselectivity in benzotetramisole (BTM)-catalysed dynamic kinetic resolutions. The computational analysis carried out also highlights the preference of the C(2)-phenyl substituent in BTM to adopt a pseudoaxial orientation upon *N*-carboxylation.[100] The enolate oxygen preferentially lies approximately coplanar and *syn* to the S atom within the isothiouronium ion, allowing a potentially stabilising n_o to σ^*_{C-S} interaction.[101] Notably, the 1,5-S---O distance calculated within the enolate (2.40 Å) is the shortest of all TS or products within this proposed catalytic cycle, with a general trend indicating the 1,5-S---O distance is inversely proportional to charge on the oxygen atom (Figure 37).

Structure	S-O distance / Å	Lowdin charge on enolate oxygen
GS C	2.478	-0.224856
TS B	2.43	-0.284809
GS D	2.401	-0.37678
TS C1	2.42	-0.282726
GS G	2.447	-0.238161

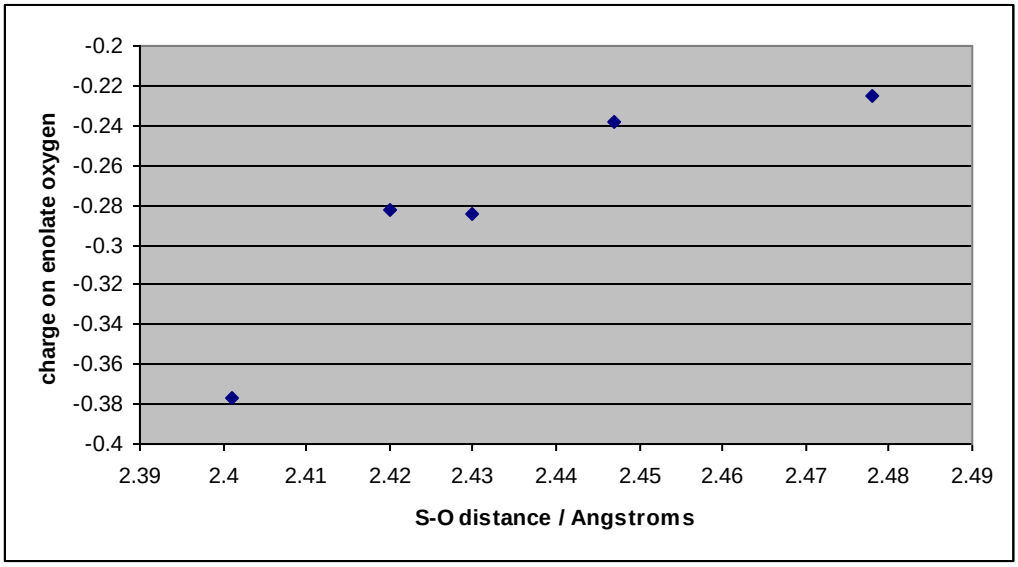


Figure 37: Computational analysis of 1,5-S---O bond distance.

This interaction is stabilising as can be clearly seen by comparison of the energy corresponding to the "anti"-enolate rotamer ground-state structure (Figure 38). This structure is roughly 17 kJ/mol higher in energy (including ZPE) than the "syn"-enolate structure **GS D**.

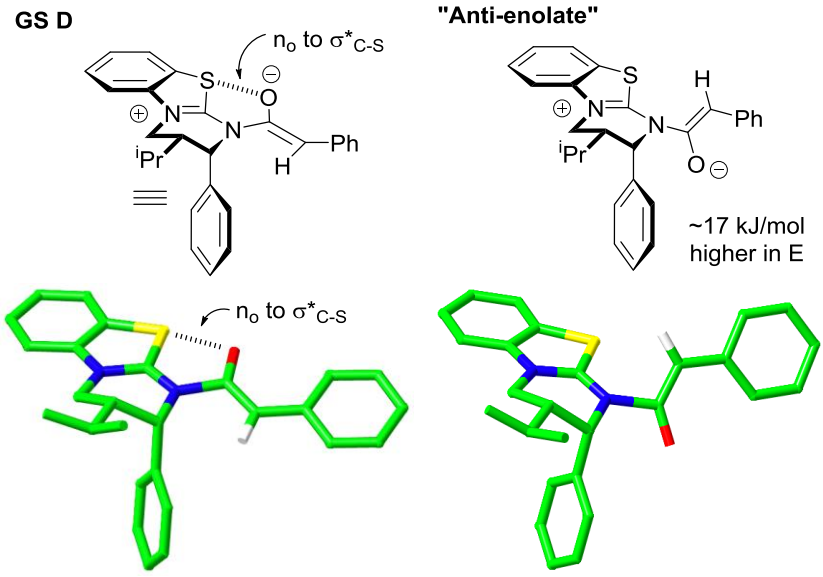


Figure 38: Calculated ground-state structures for GS D and the "anti-enolate".

A number of diastereoisomeric transition states were found for the reaction of the enolate **GS D** with the (*E*)-enone **220** giving both the observed and different stereoisomers of the product (Table 12). See Section 9.3.3 for all calculated structures (TS C1-9).

TS	Product stereochemistry	Energy / Hartrees	ZPE / Hartrees	Total Energy / Hartrees	Relative energy / kJ/mol
TS C1	(3*R*,4*R*)	-2387.441492	0.621901	-2386.819591	0
TS C2	(3*R*,4*R*)	-2387.435291	0.621401	-2386.81389	14.9659125
TS C3	(3*R*,4*R*)	-2387.428468	0.621535	-2386.806933	33.227775
TS C4	(3*R*,4*R*)	-2387.431979	0.621095	-2386.810884	22.85535
TS C5	(3*R*,4*S*)	-2387.434845	0.621491	-2386.813354	16.372125
TS C6	(3*R*,4*S*)	-2387.434845	0.621491	-2386.813354	16.372125
TS C7	(3*S*,4*S*)	-2387.436265	0.621812	-2386.814453	13.48725
TS C8	(3*S*,4*R*)	-2387.431979	0.621395	-2386.810584	23.6431125
TS C9	(3*S*,4*R*)	-2387.43197	0.621252	-2386.810718	23.2918875

Table 12: Relative energies for various TS C structures.

Transition state **TS C1** is significantly lower in energy than others (more stable by over 13 kJmol^{-1}). This energy difference corresponds to a selectivity of over 1000-to-1 in favour of the major product stereoisomer compared to others and these calculations are consistent with the high level of enantiomeric excess observed for the major diastereoisomer. We postulate that the structure of **TS C1** is stabilised by the relatively short distances between the forming oxy-anion of the acceptor and three C-H hydrogens of the positively charged isothiouronium catalyst (NCH-O 2.09 Å, PhH-O 2.27 Å and *i*-PrH-O 2.16 Å). While not particularly strong individually these stabilising contacts may be enough to impart the high selectivity for the observed stereoisomer of product (3*R*,4*R*)-**224**. The transition state **TS C1** and the associated stereochemical rational detailed here can be applied to all HBTM-2.1 **112** catalysed reactions detailed in this thesis.

The enolate product **GS G** of this major reaction pathway was established as a ground-state structure. Transition states for the bond rotation (**TS D**) and ring closure steps (**TS**

E) were located as well as the associated intermediate ground state structures (Figures 34 and 39).

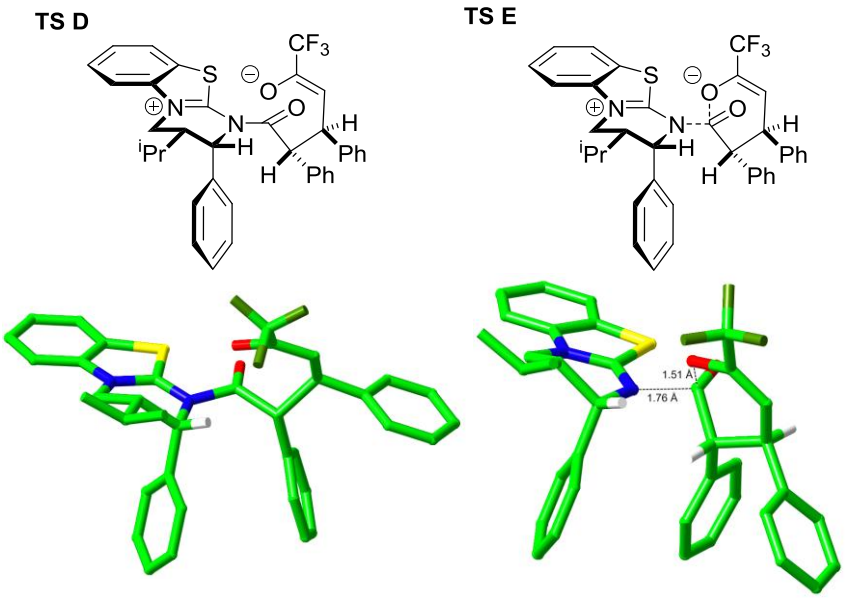


Figure 39: Calculated transition structures for the bond rotation (TS D) and ring closure (TS E) steps.

The **GS G** intermediate must rearrange *via* a transition state structure such as eclipsed structure **TS D** (Figure 39) in order to allow the formation of the C-O bond and the six-membered ring "tetrahedral-intermediate" **GS H**. **GS H** then decomposes to free catalyst (**GS A**) and lactone product (**GS I**) via **TS E**. Despite exhaustive searching a true ground state structure for the product of this rotation could not be found as all such structures minimise to the ring-closed structure **GS H**. These studies imply that once the carbon-carbon bond formation is complete to give **GS G**, only bond rotation around this new bond is a barrier to formation of the six-membered ring. Interestingly, while the electronic energy of the tetrahedral intermediate **GS H** is lower in energy than the subsequent transition state **TS E** involving regeneration of the free catalyst, if zero-point energies are included in overall energies then the relative order of stability is reversed i.e. **GS H** is higher in energy than the subsequent transition state **TS E** and would seem to decompose to give free catalyst and lactone product in a barrier-less exergonic process. Intrinsic reaction coordinate calculations support **GS H** to be the ground state starting material for **TS E**, but it would seem that **GS H** is not a true ground state on the reaction path. Instead, it is possible that after bond rotation, the six-membered ring is formed with concerted, but highly asynchronous expulsion of the catalyst.

Another addition transition state (**TS C4**) leading to product (3*R*,4*R*)-**224** is roughly 23 kJ/mol higher in energy (inc. ZPE) than **TS C1** (Figures 40 and 41). Intrinsic reaction coordinate calculations on **TS C4** indicate that this higher energy transition state is much closer to that of a concerted Diels-Alder type reaction. This type of mechanism has been suggested by Bode for the reaction of acrolein and a carbene-catalyst-derived enolate.[102]

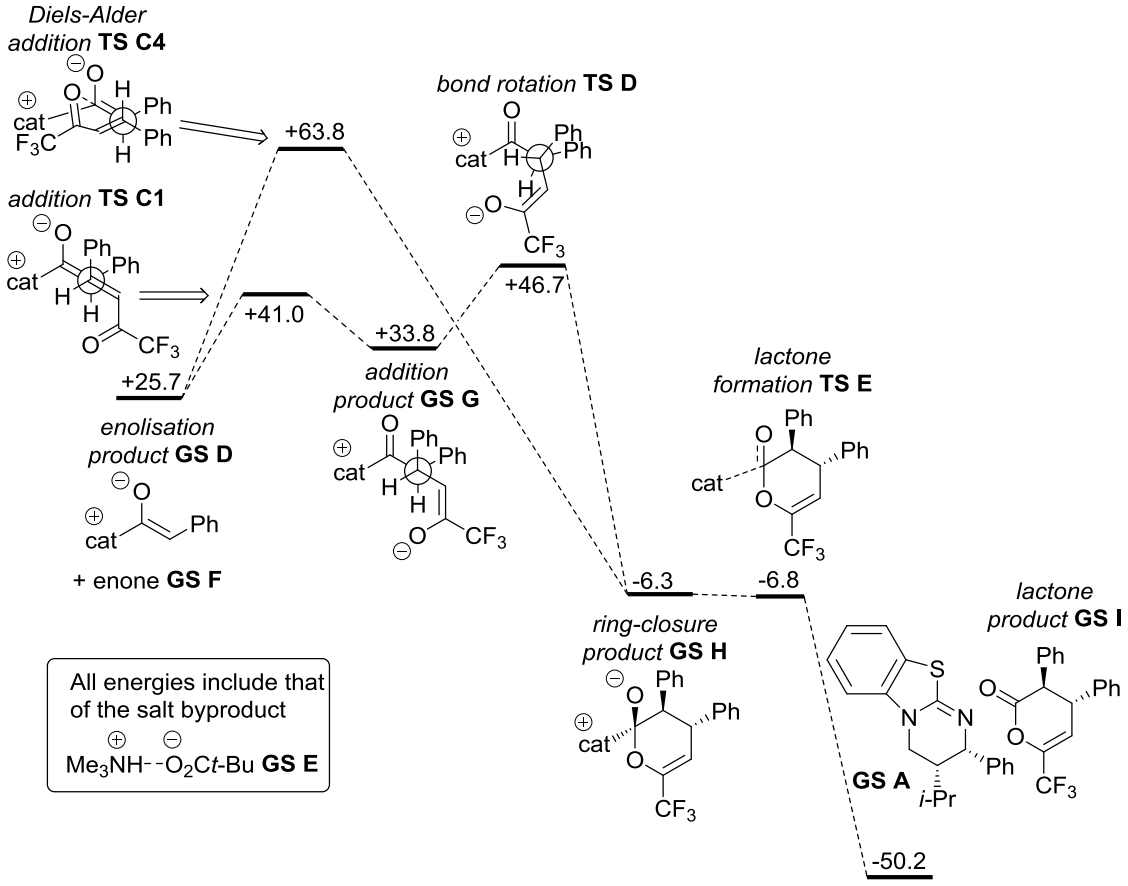


Figure 40: Comparison of calculated transition structures for the conjugate addition (TS C1) and Diels-Alder-like (TS C4) steps.

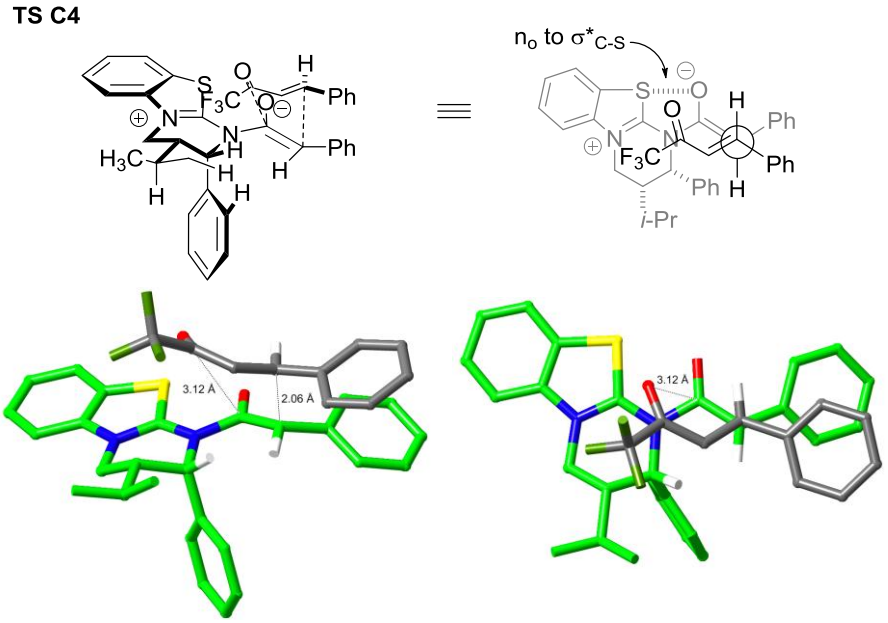


Figure 41: Calculated transition structures for the Diels-Alder type-like transition state (TS C4).

The reaction coordinate shows that the reaction is highly asynchronous with two phases: i) C-C bond formation giving a non-ground state enolate structure, and ii) C-O bond formation giving a "tetrahedral-intermediate" structure similar to **GS H**. As discussed above it is unlikely that this **GS H**-like structure is a true ground-state and so a third phase, that of catalyst expulsion, is probably part of this concerted addition process. Despite involving concerted C-C and C-O bond formations this reaction pathway is so asynchronous that the expected transition-state stabilisation for a normal pericyclic processes is not seen, and the seemingly more unusual stepwise reaction path via **TS C1** and the zwitterionic intermediate **GS G** is lower in energy and therefore a more significant conduit of reaction flux.

The energies in Figures 34 and 40 are relative to the sum of the energies of the free catalyst (**GS A**), the mixed anhydride (**GS B**), Et_3N (a surrogate for *i*-Pr_2NEt) and the enone (**GS F**), and are electronic energies including zero point energy (ZPE). We were particularly interested in supporting the proposal that the rate-determining step of the reaction is the enolisation step and considered the relative energies from these calculations to predict the highest energy transition state in the reaction sequence. The deprotonation step **TS B** has a higher energy than the isomeric acylation transition step **TS A**. The reactions are performed in the presence of an excess of amine base so it is assumed that the pivalic acid forms a hydrogen-bond complex with an amine after

enolisation. The full proton transfer between pivalic acid and Et_3N is not seen on the gas phase, but rather an arrangement consistent with a strong hydrogen bond. As the reaction solvent is relatively non-polar compared to water it is not certain as to the degree of salt formation seen in the reaction. It is however probable that a strong association of the pivalic acid and excess amine occurs. The subsequent conjugate addition and cyclisation steps have a lower energy, suggesting that the deprotonation step may be rate determining. The kinetic analysis suggests a first order dependence of the reaction rate on the concentration of the anhydride, and the computational modelling suggests that the initial acylation is endergonic. Together these results suggest that the resting state of the reaction is the free catalyst, and that the initial acylation of the catalyst is reversible, i.e. the isothiouronium pivalate (**GS C**) reverts to catalyst (**GS A**) and mixed anhydride (**GS B**) faster than the enolisation. It must be noted that the computational analysis does not include effects due to the changing concentration of the enone **220**. Overall, the computational analysis suggests that the acylation is reversible, the rate determining step is the enolisation and, given the highly exergonic nature of the cyclisation step, that the reaction rate should be first order in catalyst and mixed anhydride, and zero order in enone, in agreement with the kinetic analysis.

The transition state structure for this Michael addition reaction using (*Z*)-enone **295** that leads to the observed product configuration (3*R*,4*S*)-**299** (calculated using the method as described earlier) is shown in Figure 42 in which the important stabilising CH-O interactions are highlighted (NCH-O 2.17 Å, PhH-O 2.38 Å and *i*-PrH-O 2.17 Å).

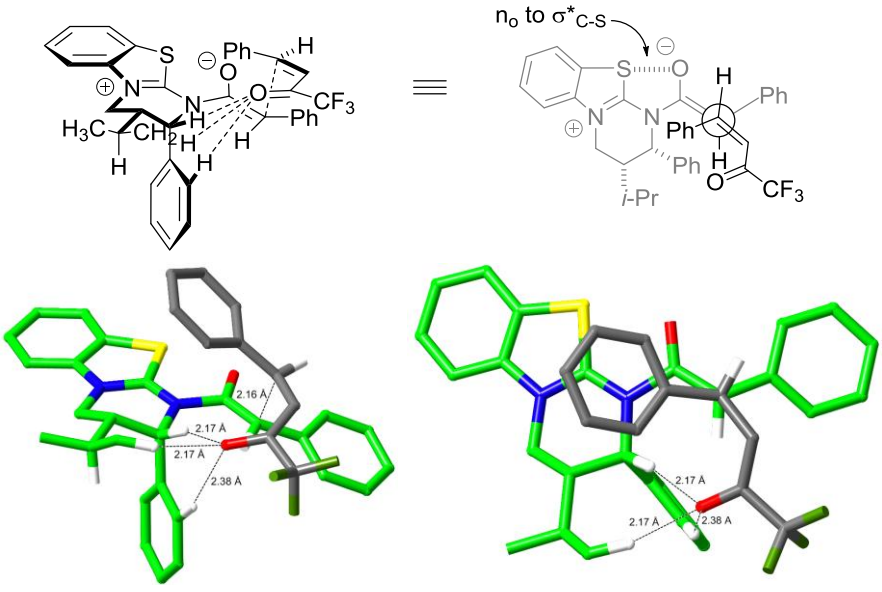


Figure 42: Calculated transition structures for the conjugate addition to (*Z*)-enone 295.

3.8 Rational Catalyst Design

Upon identification of stabilising CH-O interactions between the catalyst backbone and incoming Michael acceptor (Figures 41 and 42), the development of novel isothioureas capable of enhancing these interactions and potentially giving higher reaction efficiencies and stereoselectivities was investigated. It was proposed that an elaborated isothiourea, incorporating a 3,5-$(CF_3)_2C_6H_3$ aryl ring at C(2) would increase the acidity of neighboring protons and enhance the attractive PhH-O interaction with the developing negative charge on the enone oxygen atom (Figure 43). Isothiourea **301** was selected as a suitable catalyst to test this hypothesis.

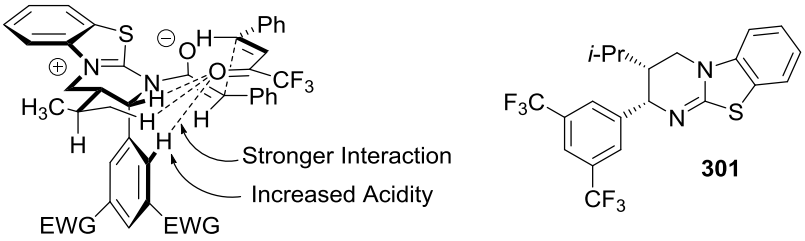
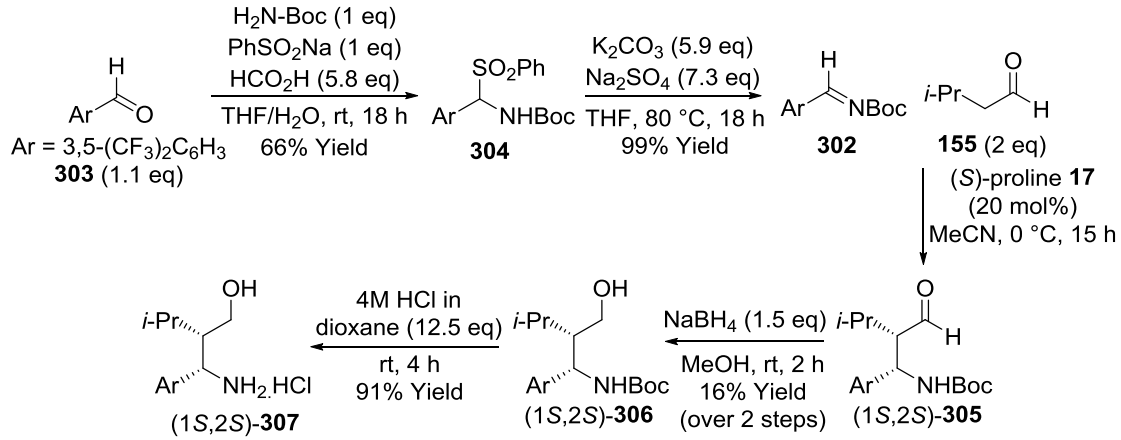


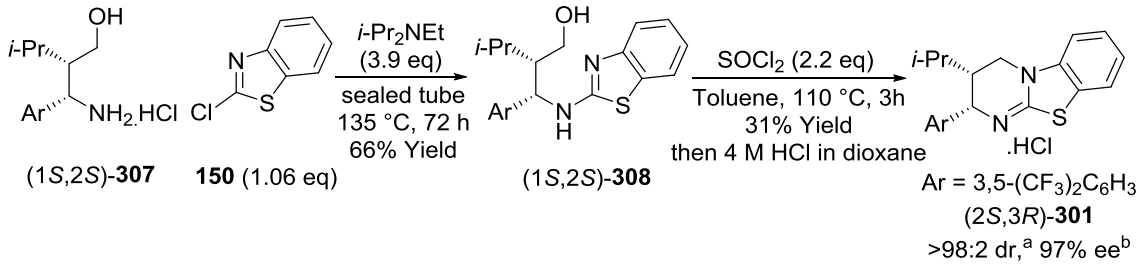
Figure 43: Proposed catalyst modification to increase indentified stabilising interactions.

Isothiourea **301** was synthesised *via* the route described for HBTM-2.1 **112** in Section 2.3. Boc-imine **302** was prepared in 2 simple steps from the corresponding aldehyde **303**, *via* sulfone **304**. However, the subsequent (*S*)-proline-catalysed Mannich reaction using **302** is not as clean as when using the benzaldehyde derived imine (as for the synthesis of HBTM-2.1) and the product is taken on crude at this stage. Reduction of the resulting aldehyde (1*S*,2*S*)-**305** with $NaBH_4$ allowed isolation of the product alcohol (1*S*,2*S*)-**306** in 16% yield over 2 steps. Removal of the Boc-protecting group with HCl in dioxane gave amino alcohol (1*S*,2*S*)-**307** in 91% yield (Scheme 81).



Scheme 81: Synthetic route to γ-amino alcohol (1*S*,2*S*)-307.

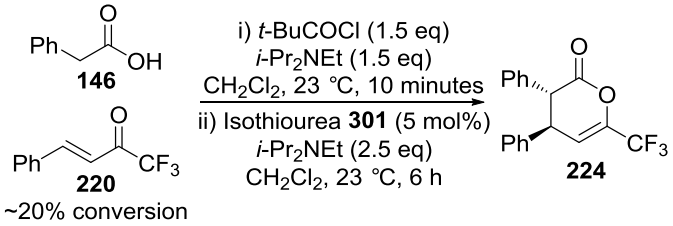
Amino alcohol (1*S*,2*S*)-**307** was converted into the isothiourea catalyst (2*S*,3*R*)-**301** in 20% yield over 2 steps using the same procedures as described for the synthesis of HBTM-2.1 **112** (Scheme 82). One exception was that the final isothiourea catalyst was treated with 4M HCl in dioxane in order to isolate the HCl salt of **301** which could be purified by recrystallisation. The unoptimised synthesis afforded (2*S*,3*R*)-**301** in 2% yield over 7 steps, as one diastereoisomer in 97% ee.



[a] Determined by ^{1}H NMR spectroscopic analysis. [b] Determined by chiral HPLC analysis.

Scheme 82: Synthetic route to isothiourea catalyst 301.

Isothiourea **301** was then tested as a catalyst for the model reaction between phenylacetic acid **146** and trifluoromethyl enone **220** in the presence of pivaloyl chloride and *i*-PrNEt$_2$ (Scheme 83). Unfortunately, the reaction towards dihydropyranone **224** only proceeded to approximately 20% conversion of **220** to **224** after 6 h at 23 °C and hence the yield and ee of this transformation were not determined. Comparatively, HBTM-2.1 **112** gives full conversion to **220** after only 15 minutes at 23 °C. This decrease in catalytic efficiency could be attributed towards a reduction in the nucleophilicity of isothiourea **301** due to the electron-withdrawing groups added to the C(2)-aryl ring.



Scheme 83: Isothiourea 301 as catalyst for Michael addition-lactonisation reaction.

3.9 Conclusions

In conclusion, after testing several electron deficient Michael acceptors, it was found that trifluoromethyl enones are highly compatible in the HBTM-2.1 catalysed Michael

addition-lactonisation protocol, forming a range of C(6)-trifluoromethyl *anti*-dihydropyranones with good diastereoselectivity (up to 95:5 dr) and enantioselectivity (up to >99% ee).[69] Furthermore, this process is stereospecific, with the diastereoisomer of product formed dependent upon the configuration of trifluoromethyl enone used. A variety of product derivatisations were demonstrated including those that introduce an additional trifluoromethyl-bearing stereogenic centre with high diastereoselectivity. Kinetic studies indicate this process is first order with respect to both *in situ* formed anhydride and catalyst concentration, with a primary kinetic isotope effect observed using α,α-di-deuterio 4-fluorophenylacetic acid. DFT computational studies support a rate-determining formation of a reactive ammonium enolate prior to a stereochemistry-determining enone conjugate-addition step. Attempts to make use of attractive CH-O interactions identified during the computational studies to design more efficient and selective isothiourea catalysts have not proved successful.

3.10 References and Notes

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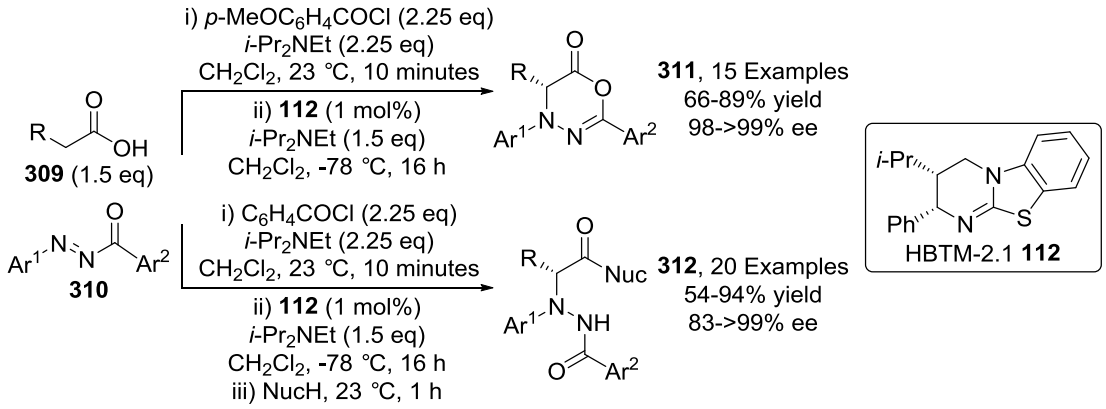
Chapter 4: Formal [4+2] Cycloadditions of *N*-Aryl-*N*-Aroyldiazenes

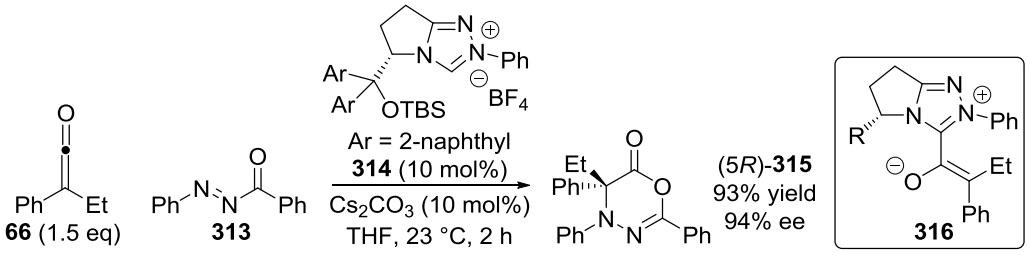
This chapter describes the ability of HBTM-2.1 **112** to catalyse the α-amination of carboxylic acids **309** through the use of *N*-aryl-*N*-aroyldiazene Michael acceptors **310**. Either 1,3,4-oxadiazin-6-ones **311** or *N*-protected α-substituted amino acid derivatives **312** (upon ring opening) are formed in high yields and excellent enantioselectivity (Scheme 84).[103] For the first time, carboxylic acids other than arylacetic acids have been successfully applied to this protocol.



Scheme 84: Formal [4+2] cycloaddition of *N*-aryl-*N*-aroyldiazenes.

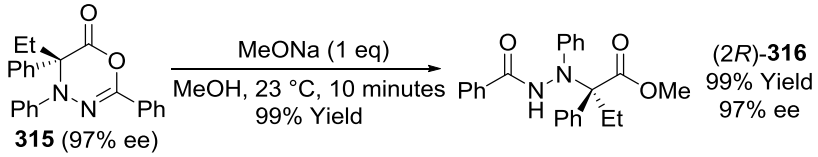
4.1 Introduction

The development of new methodologies which allow access to amino acid derivatives is an area of great importance in organic chemistry.[104] In particular, catalytic, asymmetric methodologies which allow amino acid derivatives to be accessed in high enantiomeric excess are extremely valuable.[105] Within the arena of formal [4+2] cycloadditions the group of Ye have shown that NHCs catalyse the asymmetric α-amination of ketene-derived enolates using *N*-aryl-*N*-aroyl diazenes as Michael acceptors.[106] For example, reaction of ketene **66** and diazene **313** in the presence of NHC precatalyst **314** and caesium carbonate afforded 1,3,4-oxadiazin-6-one (5*R*)-**316** in 93% yield and 94% ee *via* azolium enolate **316** (Scheme 85).



Scheme 85: α-amination of ketene-derived enolates using diazenes.

The utility of 1,3,4-oxadiazin-6-one (5*R*)-**315** was then demonstrated *via* the simple ring-opening with sodium methoxide, giving α,α-disubstituted amino acid derivative (2*R*)-**316** in 99% yield and 97% ee (Scheme 86).

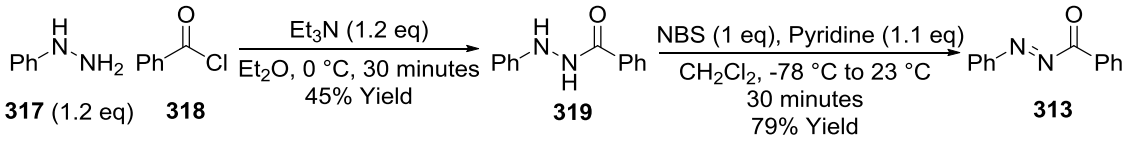


Scheme 86: Derivatisation to α,α-disubstituted amino acid derivative 316.

Based upon this precedent, it was proposed that *N*-aryl-*N*-aroyl diazenes could be useful Michael acceptors for the isothiourea-catalysed α-amination of acetic acids. Interestingly, this methodology would allow access to mono α-substituted amino acid derivatives and care would be needed to avoid epimerisation of the acid labile α-stereocentre in these enantioenriched products.

4.2 Synthesis and Formal [4+2] Cycloaddition of 313

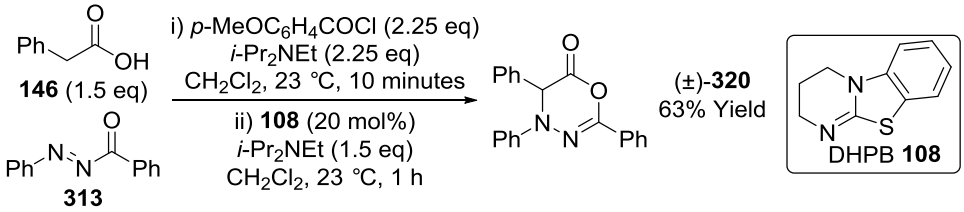
In order to evaluate the ability of isothioureas to catalyse the α-amination of carboxylic acids, *N*-aryl-*N*-aroyldiazene **313** was synthesised *via* a two-step procedure outlined by Bowman.[107] Acylation of phenyl hydrazine **317** with benzoyl chloride **318** in the presence of Et_3N in Et_2O gave hydrazide **319** in 45% yield. Subsequent oxidation using NBS and pyridine afforded diazene **313** in 79% yield after chromatographic purification (Scheme 87).



Scheme 87: Synthetic route towards diazene 313.

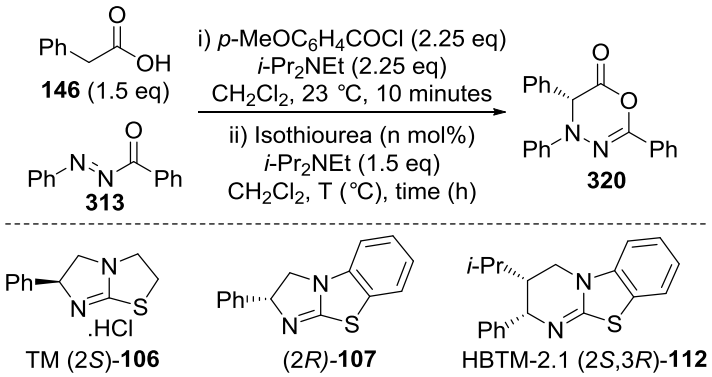
With diazene **313** in hand, its subsequent use in the model intermolecular Michael addition-lactonisation reaction with phenylacetic acid **146** could be investigated. Initially, using DHPB **108** as catalyst and 1 eq of acid **146**, the diazene acceptor was 78% consumed after 1 h at 23 °C but consumption did not increase beyond this time. Diazene **313** was fully consumed if 1.5 eq of carboxylic acid was used and the amounts of activating agent and *i*-Pr_2NEt were scaled up accordingly to 2.25 eq. However, it proved difficult to purify the highly non-polar 1,3,4-oxadiazin-6-one **320** *via*

chromatography due to the presence of pivalic anhydride – a by-product from the carboxylic acid activation step – which co-elutes with the product. To overcome this problem, *p*-methoxybenzoyl chloride was employed as the activating agent; the more polar *p*-methoxybenzoic anhydride contaminant is easily separated from the 1,3,4-oxadiazin-6-one **320**. Further studies showed that the amount of base used in the second (Michael addition) step could be reduced from 2.5 to 1.5 eq with no detriment towards product conversion. Using these modified conditions, (±)-**320** could be isolated pure in 63% yield (Scheme 88). Racemic samples needed for chiral HPLC analysis for all products in this chapter were made using achiral DHPB **108** as catalyst.



Scheme 88: Modified reaction conditions towards 1,3,4-oxadiazin-6-one 320.

Focus next shifted towards identifying an asymmetric protocol. Using the optimised reaction conditions for DHPB, tetramisole hydrochloride (2*S*)-**106** (10 mol%) and benzotetramisole (2*R*)-**107** (10 mol%) gave approximately 65% and 20% conversion respectively towards the product while HBTM-2.1 (2*S*,3*R*)-**112** (10 mol%) again proved the most efficient catalyst, giving full conversion of diazene **313** after 1 h at 23 °C, affording (5*R*)-**320** in 66% yield and 95% ee. Lowering the temperature to –78 °C allowed the product to be obtained in >99% ee and the catalyst loading could be lowered to 1 mol% without detriment towards product yield (Table 13). All reactions were carried out using bench grade solvents under air as standard.



Entry	Isothiourea (mol%)	T (°C)	Time (h)	Conversion (%)	Yield (%)	ee (%)[a]
1	**106** (10)	23	1	65	-	-

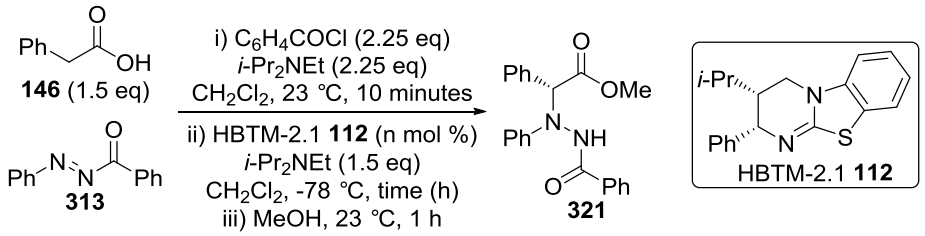
2	**107** (10)	23	1	20	-	-
3	**112** (10)	23	1	100	66	95
4	**112** (10)	0	2	100	65	98
5	**112** (10)	–30	16	100	61	99
6	**112** (10)	–78	16	100	81	99
7	**112** (5)	–78	16	100	83	>99
8	**112** (1)	–78	16	100	89	>99

[a] Determined by chiral HPLC analysis.

Table 13: Optimisation studies for Michael addition-lactonisation protocol.

Entry 8 in Table 13 represents the optimal reaction conditions for the model system and these conditions were used for testing the scope of this reaction (see Section 4.3.1).

It should be noted that heterocyclic products such as **320** are susceptible towards decomposition (presumably due to ring-opening) during chromatographic purification on silica meaning that these products had to be routinely purified *via* a rapid and short "silica plug". With this limitation in mind, a one-pot Michael addition ring-opening protocol was also optimised, allowing access to hydrazide products that show much improved stability towards chromatographic purification (Table 14). In this system benzoyl chloride was used as activating agent, again to allow for easy chromatographic purification of the more polar hydrazide product from the less polar benzoic anhydride by-product derived from the activation step. Using the previously optimised reaction conditions, the 1,3,4-oxadiazin-6-one **320** intermediate could be directly ring opened by treatment with MeOH *in situ*, giving hydrazide (2*R*)-**321** in 94% yield and 99% ee. In this process the catalyst loading could be lowered further to 0.25 mol%, giving (2*R*)-**321** in 83% yield and >99% ee. The enantioselectivity is maintained upon lowering to 0.1 mol% catalyst loading (40 h reaction time) although the isolated yield drops to 60%.



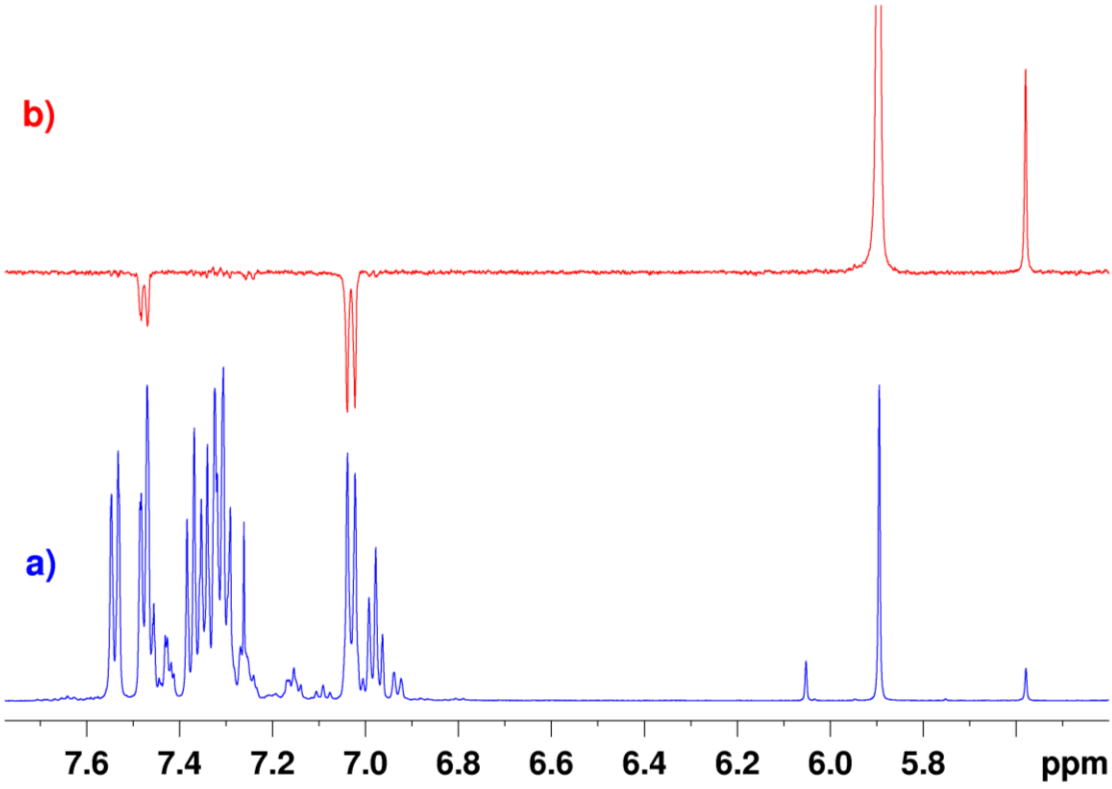
Entry	HBTM-2.1 **112** (mol%)	Time (h)	Conversion (%)	Yield (%)	ee (%)[a]
1	1	16	100	94	99
2	0.5	16	100	85	>99
3	0.25	16	100	83	>99
4	0.1	40	65	60	99

[a] Determined by chiral HPLC analysis.

Table 14: Optimisation studies for Michael addition-lactonisation/ring-opening protocol.

The conditions outlined in Entry 1 were used to assess the scope of this reaction (see Section 4.3.2).

All hydrazides such as **321** exist as a mixture of rotamers (typically a 90:10 mixture) by ^{1}H NMR. The rotameric nature of these compounds was proven through 1D gs-NOSEY/EXSY NMR analysis in which exchange between the two rotamers was observed (Figure 44). In the figure below a) is the expansion of ^{1}H NMR spectrum of compound (2*R*)-**321** and b) is the 1D gs-NOESY/EXSY spectrum acquired upon selective irradiation of aliphatic C(2)*H* resonance at 5.89 ppm. The positive phased peak at 5.58 ppm indicates that hydrazide (2*R*)-**321** exists in solution in the form of two fast exchanging species, likely rotamers. The negative phased doublets at 7.03 and 7.48 ppm appear in the spectrum due to NOE between the aliphatic C(2)*H* resonance and adjacent C(2)-Ar(2,6)*H* for both major and minor rotamer.

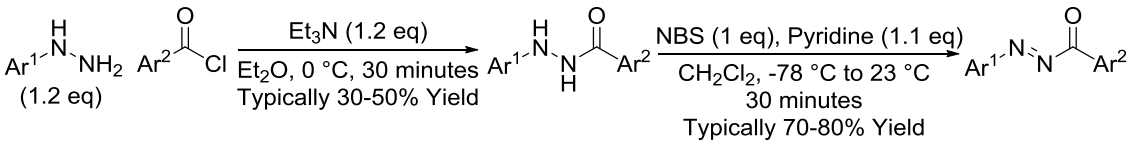


a) Expansion of ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound (2*R*)-**321**. b) 1D gs-NOESY/EXSY spectrum acquired upon selective irradiation of aliphatic C(2)*H* resonance at 5.89 ppm.

Figure 44: NMR evidence for rotameric hydrazides.

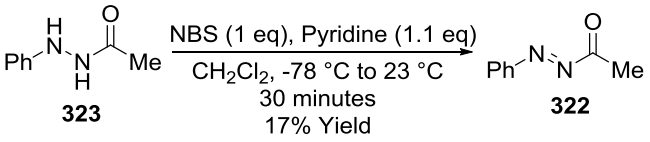
4.3 Synthesis of *N*-Aryl-*N*-Aroyl Diazenes

Using the same synthetic route as described previously for diazene **313**, a variety of *N*-aryl-*N*-aroyl diazenes were obtained *via* variation of the starting aryl hydrazine and aroyl chloride components (Scheme 89). The aryl hydrazine was varied to include aryl substitutents bearing electron-donating (4-OMe), electron-withdrawing (4-F, 4-CF_3, 4-CN) and 2,4,6-substitution (mesityl). The aroyl chloride was varied to include 2-, 3- and 4-aryl substitution including electron-donating (4-OMe) and electron-withdrawing groups (4-NO_2 and 4-CF_3). Heteroaryl (2-furyl) and naphthyl aroyl chlorides were also used in the synthesis of diazene Michael acceptors.



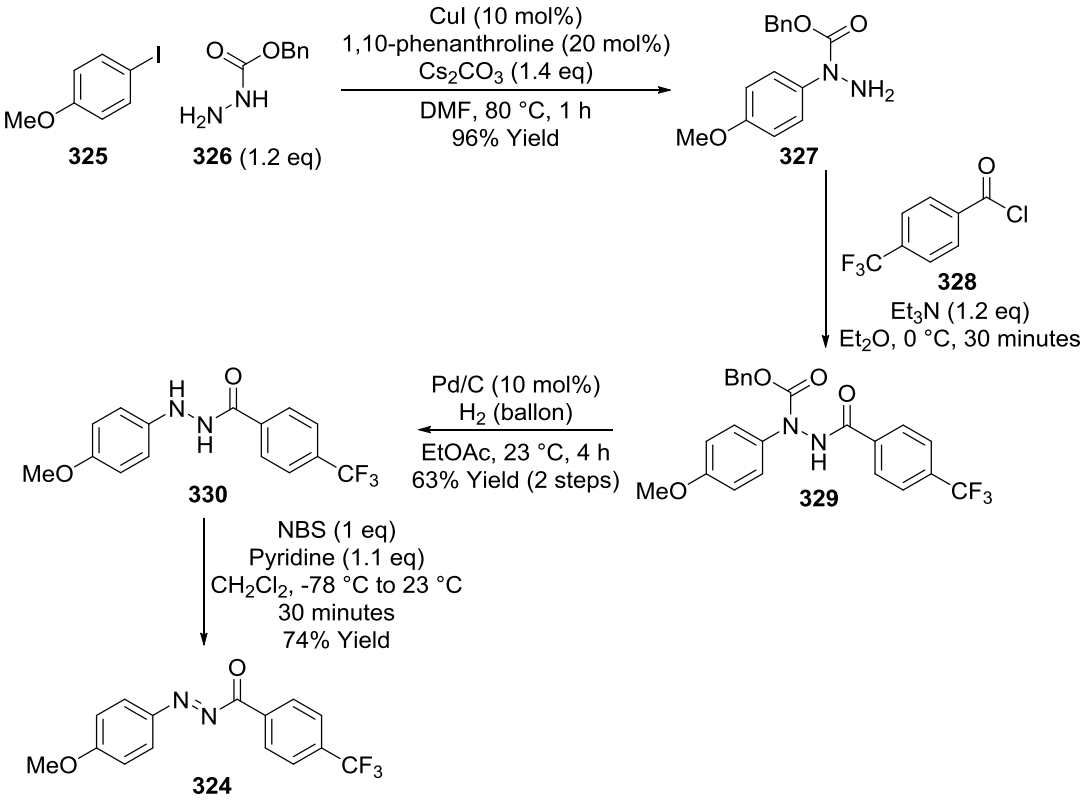
Scheme 89: Synthetic route towards diazene Michael acceptors.

A diazene in which the *N*-aroyl substituent was replaced by an *N*-acetyl group **322** was also synthesised by oxidation of commercially available 1-acetyl-2-phenyl hydrazine **323** in a poor 17% yield (Scheme 90).



Scheme 90: Synthetic route towards diazene 322.

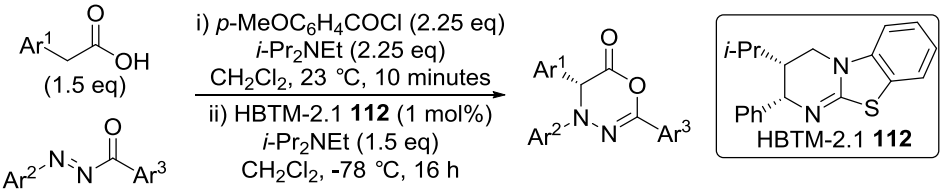
As can be seen from Scheme 89, the initial acylation of hydrazines with aroyl chlorides to form hydrazides often proceeded in modest isolated yields (30-50%). Despite this, in most cases this was acceptable to provide sufficient quantities of the final diazene Michael acceptors to study their use in the Michael addition lactamisation protocol. However, for the more expensive hydrazine starting materials this low yield was undesirable and an alternative synthetic route was designed for diazene **324** as an illustration of a more scalable and practical synthesis of this Michael acceptor class. Following the procedure outlined by Buchwald,[108] the copper-catalysed cross coupling between 4-iodoanisole **325** and benzyl carbazate **326** in DMF gave **327** in 96% yield (Scheme 91). Subsequent acylation with 4-trifluoromethylbenzoyl chloride **328** following the procedure outlined by Bowman[107] gave Cbz-protected hydrazide **329** that was taken on crude and deprotected using Pd/C (10 mol%) under at atmosphere of H_2 (g), giving hydrazide **330** in 63% yield over 2 steps. Subsequent oxidation as outlined previously proceeded in 74% yield allowing access to multigram quantities of diazene **324**.

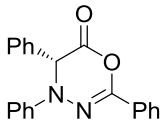


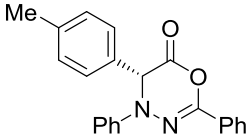
Scheme 91: Practical and scalable route to diazene 324.

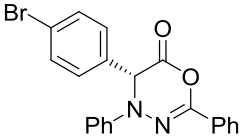
4.3.1 Substrate Scope – 1,3,4-Oxadiazin-6(5*H*)-ones

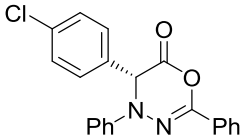
Subsequent studies probed the generality of this process through variation of the arylacetic acid and diazene components to form a variety of 1,3,4-oxadiazin-6(5*H*)-ones (Table 15). Using 1 mol% of HBTM-2.1 **112**, this protocol readily tolerates a wide range of 4- and 3- substituted arylacetic acids, containing electron withdrawing and donating groups in addition to extended aromatic systems (products **320** and **331**-**337**). Diazenes containing electron withdrawing *N*-aryl substitution (product **338**), and extensive *N*-aroyl substituent variation (products **339**-**344**) are also accommodated, in all cases giving the corresponding 1,3,4-oxadiazin-6(5*H*)-ones in high yield and enantioselectivity (typically ≥99% ee).

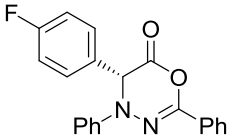


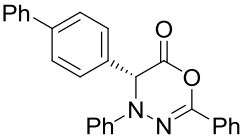

(5*R*)-**320**
89% Yield
>99% ee[a]

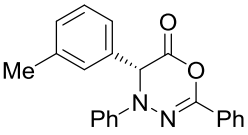

(5*R*)-**331**
78% Yield
>99% ee[a]

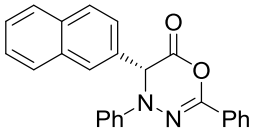

(5*R*)-**332**
80% Yield
99% ee[a]

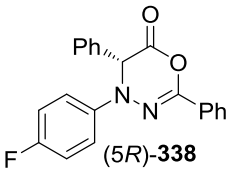

(5*R*)-**333**
66% Yield
>99% ee[a]

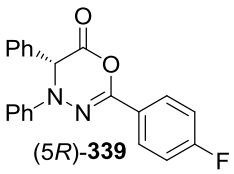

(5*R*)-**334**
77% Yield
>99% ee[a]

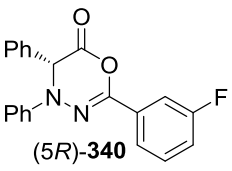

(5*R*)-**335**
88% Yield
98% ee[a]

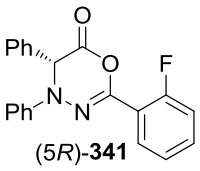

(5*R*)-**336**
79% Yield
>99% ee[a]

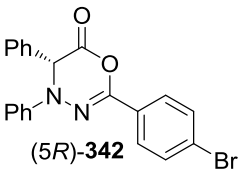

(5*R*)-**337**
76% Yield
99% ee[a]

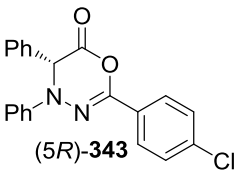

(5*R*)-**338**
82% Yield
>99% ee[a]

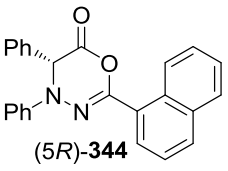

(5*R*)-**339**
88% Yield
99% ee[a]


(5*R*)-**340**
76% Yield
99% ee[a]


(5*R*)-**341**
70% Yield
99% ee[a]


(5*R*)-**342**
78% Yield
>99% ee[a]


(5*R*)-**343**
78% Yield
>99% ee[a]


(5*R*)-**344**
71% Yield
>99% ee[a]

[a] Determined by chiral HPLC analysis.

Table 15: Substrate scope - 1,3,4-oxadiazin-6(5*H*)-ones.

The absolute configuration of 1,3,4-oxadiazin-6(5*H*)-one (5*R*)-**332** was unambiguously confirmed by X-ray crystal structure analysis (Figure 45). All other 1,3,4-oxadiazin-6(5*H*)-one derivatives were assigned by analogy. For a detailed rationale regarding the observed enantioselectivity of these reactions, see Section 3.7.

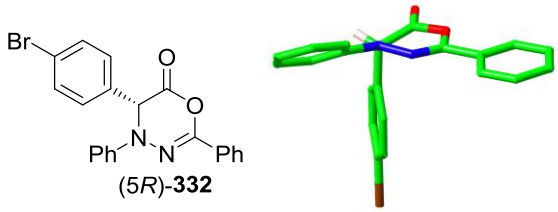
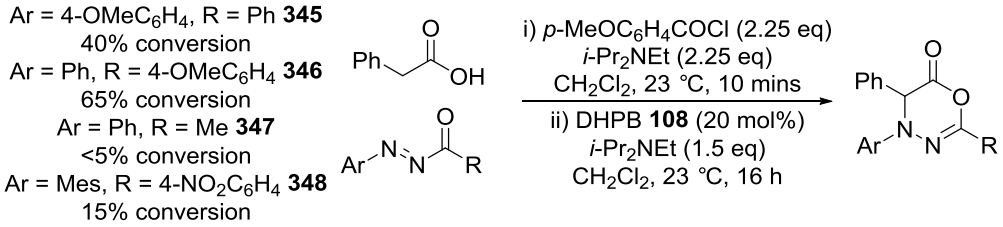


Figure 45: Crystal structure of (5*R*)-332 showing absolute configuration.

Michael acceptors **345-348** were not fully consumed after 16 h reaction time at 23 °C using the highly reactive DHPB **108** as catalyst (Scheme 92). Analysis of the crude reaction mixtures by ^{1}H NMR showed the presence unreacted diazene along with signals characteristic of product formation from which approximate conversions could be calculated. The poorer reactivity in these cases is attributed towards the Michael acceptors being too electron rich (**345-347**) or too sterically encumbered (**348**) for efficient reaction.

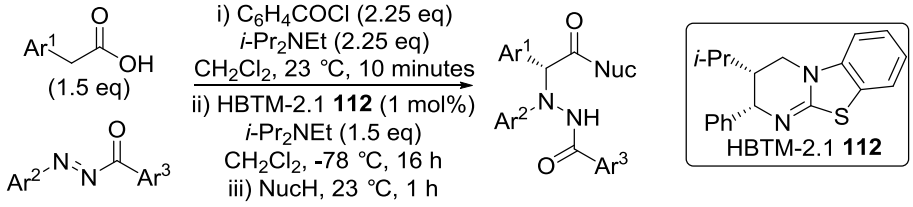


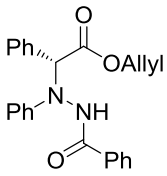
Scheme 92: Poorly reactive diazenes 345-348.

4.3.2 Substrate Scope – Hydrazides

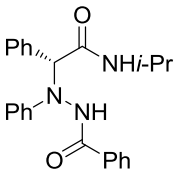
The generality of this procedure was further demonstrated through utilising the one-pot Michael-lactonisation/ring-opening sequence to access a range of hydrazides (Tables 16 and 17). In addition to *in situ* ring opening with methanol, alternative nucleophiles such as allyl alcohol, isopropylamine and pyrrolidine can also be used, leading to a variety of hydrazides in high yield and ee (products **321** and **349-351**). Heteroaryl and electron rich arylacetic acids are readily accommodated (products **352** and **353**). Within a series of diazene acceptors differing in *N*-aroyl substitution, the electron withdrawing *N*-4-nitrobenzoyl group results in increased reaction rate, with the electron rich *N*-4-

methylbenzoyl substituent giving reduced rate (products **354**-**356**). For example, in the case of forming hydrazide **354**, 3 eq of phenylacetic acid are required for complete diazene consumption, while *N*-heteroaroyl and *N*-4-nitrobenzoyl substitution are well tolerated (products **355** and **356**). The use of this highly electron-deficient *N*-4-nitrobenzoyl diazene allowed the incorporation of more challenging arylacetic acids bearing strongly electron-withdrawing substituents (less nucleophilic ammonium enolates) or 2-arylsubstitution (sterically encumbered ammonium enolates) which typically perform poorly in isothiourea-catalysed Michael addition lactonisation processes (products **357**-**359**).

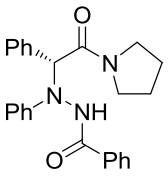




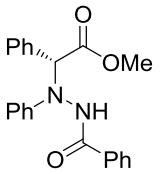
(2*R*)-**349**
83% Yield
98% ee[a]



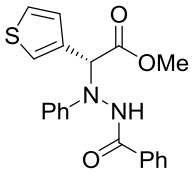
(2*R*)-**350**
92% Yield
99% ee[a]



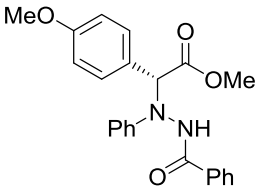
(2*R*)-**351**
87% Yield
99% ee[a]



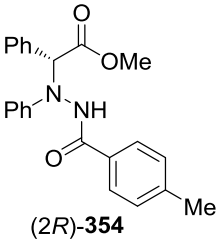
(2*R*)-**321**
94% Yield
99% ee[a]



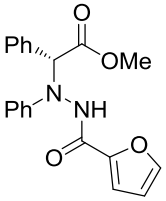
(2*R*)-**352**
86% Yield
>99% ee[a]



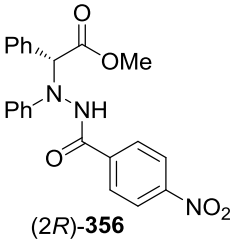
(2*R*)-**353**
76% Yield
98% ee[a]



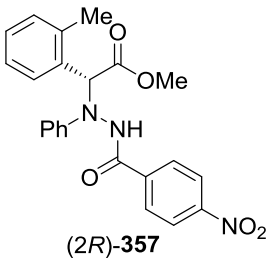
(2*R*)-**354**
66% Yield[b]
>99% ee[a]



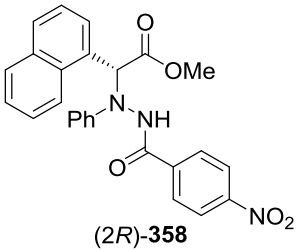
(2*R*)-**355**
85% Yield
99% ee[a]



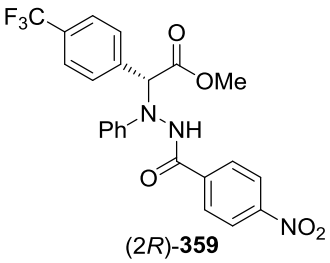
(2*R*)-**356**
84% Yield
99% ee[a]



(2*R*)-**357**
81% Yield
99% ee[a]



(2*R*)-**358**
79% Yield
99% ee[a]

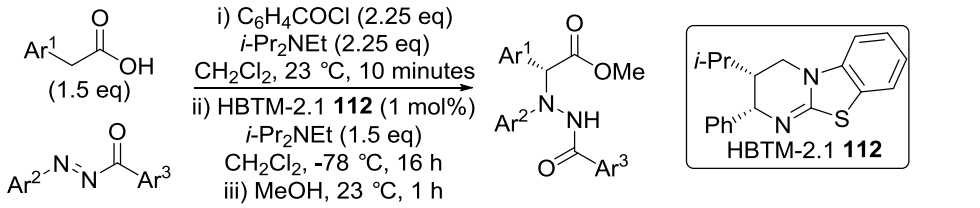


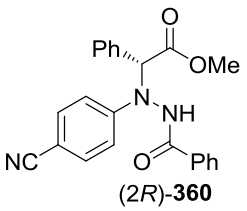
(2*R*)-**359**
83% Yield[c]
97% ee[a]

[a] Determined by chiral HPLC analysis. [b] 3 eq of phenylacetic acid used. [c] Methanolysis carried out at –78 °C.

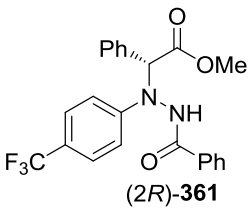
Table 16 - Substrate scope – hydrazides.

The generality of this protocol was also demonstrated through the incorporation of diazenes with electron deficient *N*-aryl groups (products **360** and **361**) and further variation of both the diazene and arylacetic acid component (products **362**-**364**) (Table 17). In all cases, the hydrazide is obtained in good yield (66-95%) and excellent enantioselectivity (up to >99% ee). Additionally, this reaction is readily suited to scale up, with hydrazide **362** prepared on a 6.5 mmol scale using HBTM-2.1 **112** (1 mol%) generating >2.5 g of product (95% yield, 99% ee).

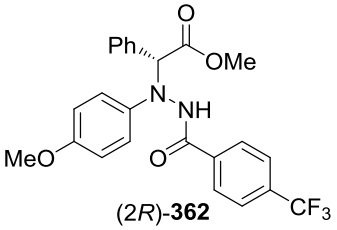




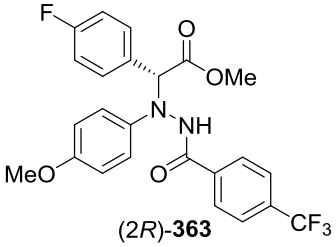
(2*R*)-**360**
93% Yield[b]
98% ee[a]



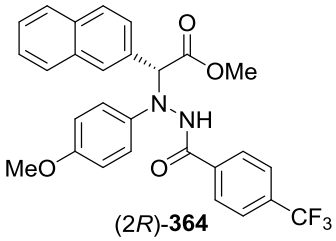
(2*R*)-**361**
86% Yield
99% ee[a]



(2*R*)-**362**
95% Yield (2.83 g)
99% ee[a]



(2*R*)-**363**
79% Yield
99% ee[a]

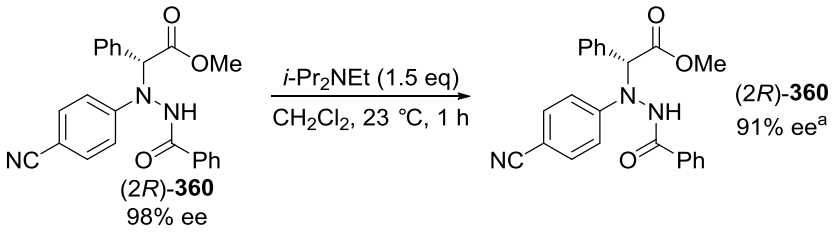


(2*R*)-**364**
80% Yield
98% ee[a]

[a] Determined by chiral HPLC analysis. [b] Methanolysis carried out at −78 °C.

Table 17 - Substrate scope – hydrazides (continued).

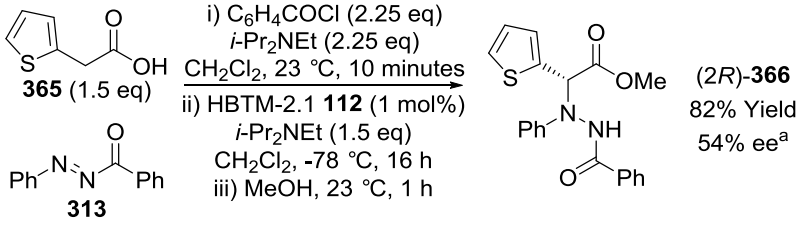
In practice, methanolysis to give hydrazides **360** and **361** at room temperature resulted in lower than expected ee (92% and 91% respectively). For these substrates, methanolysis at −78 °C led to optimal enantioselectivity, consistent with *in situ* racemisation of these particularly sensitive hydrazides at room temperature rather than decreased enantioselectivity in the key C-N bond forming step. This hypothesis was confirmed when an enantioenriched sample of (2*R*)-**360** (98% ee) was re-treated with *i*-Pr_2NEt in CH_2Cl_2 for 1 h at 23 °C, giving product in 91% ee, indicating that the product (2*R*)-**360** can racemise in the presence of base at 23 °C (Scheme 93).



[a] Determined by chiral HPLC analysis.

Scheme 93 – Control experiment testing base-mediated epimerisation of 360.

The reactivity of 2-thiopheneacetic acid **365** in isothiourea-catalysed Michael addition lactonisation reactions is particularly interesting. Using the optimised conditions outlined above, reaction with diazene **313** gives hydrazide (2*S*)-**366** in 82% yield but in only 54% ee which represents a significant deviation from the usual high enantiomeric excess observed (Scheme 94).



[a] Determined by chiral HPLC analysis.

Scheme 94: Unusual reactivity using 2-thiopheneacetic acid 365.

A similar reduction in enantioselectivity was observed when this acid was used in the formal [4+2] cycloaddition with α-keto-β,γ-unsaturated ester **146** (83% ee, see Section 2.4). In the stereochemical rationale for these processes, it is postulated that the observed

stereoselectivity can be explained *via* a transition state in which the enolate oxygen is orientated *syn* to the sulfur atom of the catalyst, allowing for a stablising n_o to $\sigma^*_{c\text{-}s}$ interaction (Figure 46).[101] This gives rise to a well defined ammonium enolate which can impart high levels of facial selectivity. A possible explanation for the unusually poor enantioselectivity when using 2-thiopheneacetic acid is that it may disrupt this important stabilising interaction as the enolate oxygen of the ammonium enolate can donate electron density into two different $\sigma^*_{c\text{-}s}$, one in the thiophene ring and the other in the isothiourea. This may allow some rotation around the C-N bond of the ammonium enolate, resulting in a less well defined transition state and lower facial selectivity.

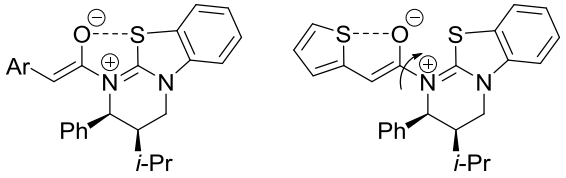
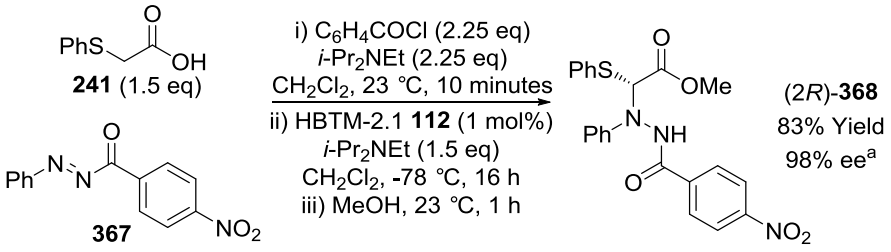


Figure 46: Possible explanation regarding poor enantioselectivity using 2-thiopheneacetic acid 365.

4.4 Expansion of Acid Scope

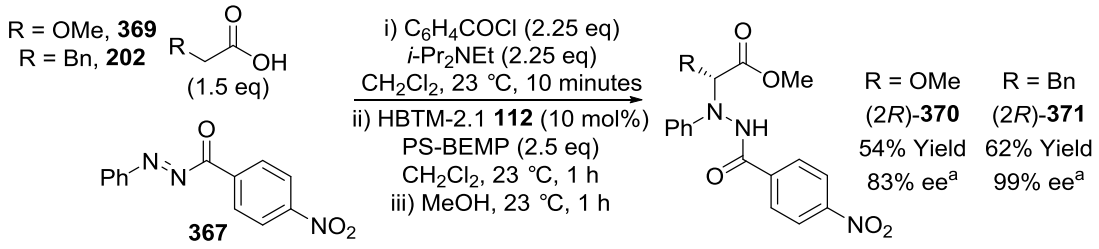
To this point, the scope of the intermolecular isothiourea-catalysed Michael addition lactonisation protocol has been limited to the use of monosubstituted arylacetic acids that represents a significant limitation of this methodology. Pleasingly, through the use of the highly reactive *N*-4-nitrobenzoyl diazene **367**, the scope of this carboxylic acid functionalisation methodology has been expanded. For example, (phenylthio)acetic acid **241** is readily tolerated using the standard optimised reaction conditions, giving hydrazide **368** in 83% yield and 98% ee (Scheme 95). Interestingly, under these reaction conditions acid **241** shows no reactivity with parent diazene **313** indicating that although the ammonium enolate clearly forms, the Michael acceptor must be highly electron deficient to lead to the observed products.



[a] Determined by chiral HPLC analysis.

Scheme 95: Functionalisation of (phenylthio)acetic acid 241.

Under these standard reaction conditions both methoxyacetic acid **369** and 3-phenylpropionic acid **202** show minimal reactivity. However, these acids can be functionalised using 10 mol% of HBTM-2.1 **112** and PS-BEMP as base at room temperature giving hydrazides **370** and **371** (Scheme 96). The lower enantioselectivity of **370** (83% ee) may be due to partial racemisation under the reaction conditions due to the two α-heteroatoms and the α-ester group increasing the acidity at the stereocentre.



Scheme 96: Functionalisation of methoxyacetic acid 369 and phenylpropionic acid 202.

The need for a phosphazene base in these processes presumably reflects the expected increased pK_a of the α-protons in the assumed intermediate acyl ammonium species derived from both methoxyacetic acid and 3-phenylpropionic acid. For comparison, the pK_as in DMSO of 1,2-diphenylethanone **372**, 1-phenyl-2-(phenylthio)ethanone **373**, 2-methoxy-1-phenylethanone **374** and propiophenone **375** are 17.7,[109] 17.1,[110] 22.9[111] and 24.4[109] respectively (Figure 47). However, an alternative reaction pathway involving ketene formation from an *in situ* formed mixed anhydride under these conditions cannot be ruled out (see Section 3.6 for mechanistic discussions).

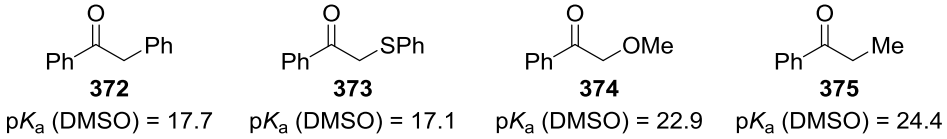


Figure 47: Comparison of relevant pKa's in DMSO.

Despite these advances in reaction scope, several carboxylic acids tested including cyanoacetic acid, propionic acid and 2-phenylpropionic acid remain incompatible with this methodology.

4.5 Derivatisations

The synthesis of *N*-aryl amino acid derivatives is of great importance due to their presence in various synthetically challenging and medicinally important molecules such

as protein kinase C activators indolactam-V **376**[112] and benzolactam-V8 **377**,[113] ACE inhibitors[114] and NMDA receptor antagonist L689560 **378**[115] (Figure 48).

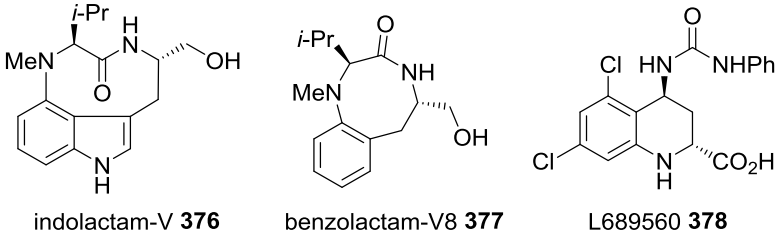
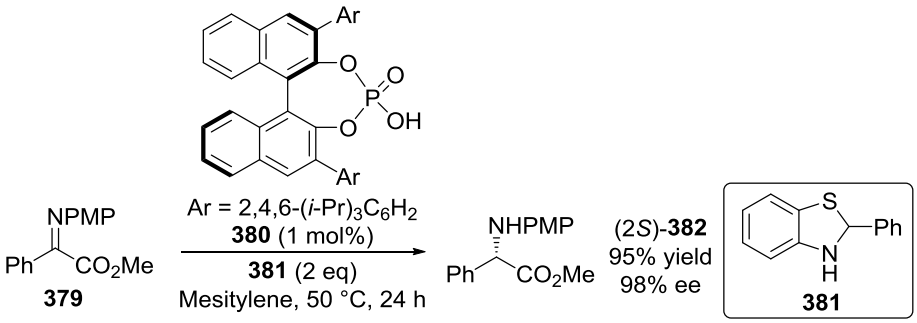


Figure 48: *N*-aryl amino acid containing biologically active molecules.

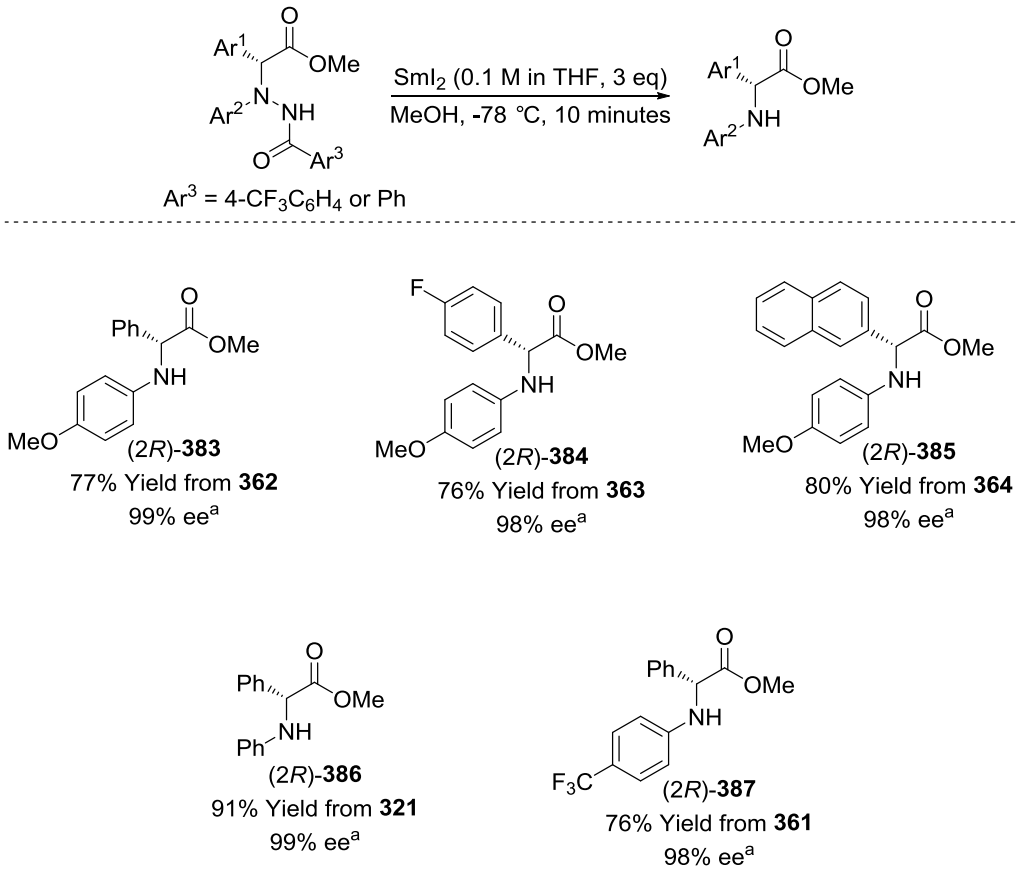
Direct *N*-arylation using Cu or Pd-mediated couplings is well established in organic chemistry.[116] However, direct *N*-arylation of α-arylglycines using these methods is limited, presumably due to facile racemisation,[117] although nucleophilic aromatic substitution of arylglycines can be used.[118] Catalytic asymmetric routes to *N*-aryl-α-arylglycines typically focus upon reduction of α-imino esters. For example, Akiyama has demonstrated that α-aryl imino ester **379** undergoes enantioselective transfer hydrogenation in the presense of chiral phosphoric acid **380** as catalyst and benzothiazoline **381** as reductant, giving α-aryl amino acid derivative **382** in 95% yield and 98% ee (Scheme 97).[119]



Scheme 97: Transfer hydrogenation of imino ester 379.

It was proposed that the catalytic asymmetric α-amination of carboxylic acids described could offer an alternative route to tailor-made *N*-aryl-α-arylglycines *via* selective deprotection of the hydrazide products. This was realised through treatment of hydrazide (2*R*)-**362** with SmI_2, giving *N*-phenyl-α-phenylglycine derivative (2*R*)-**383** in 77% yield and 99% ee. Notably, this transformation has to be carried out in THF:MeOH (3:1) at –78 °C to avoid partial racemisation of these sensitive compounds. For example, when SmI_2 mediated cleavage of (2*R*)-**361** to give *N*-aryl-α-aryglycine (2*R*)-**387** was carried

out at 23 °C the enantiomeric excess obtained was 91%. This simple SmI_2 mediated N-N cleavage procedure is general and tolerates various aryl substitution patterns in the hydrazide, delivering bespoke *N*-aryl-α-arylglycine derivatives **383-387** with minimal racemisation (≥98% ee) and in good yield >75% (Table 18). Representative examples of this approach indicate that *N*-aryl-α-arylglycine derivatives bearing Ph, 4-FC_6H_4 or 2-napththyl α-substitution can be readily accessed, in addition to electron rich (4-$OMeC_6H_4$) or electron deficient (4-$CF_3C_6H_4$) *N*-aryl substitution.

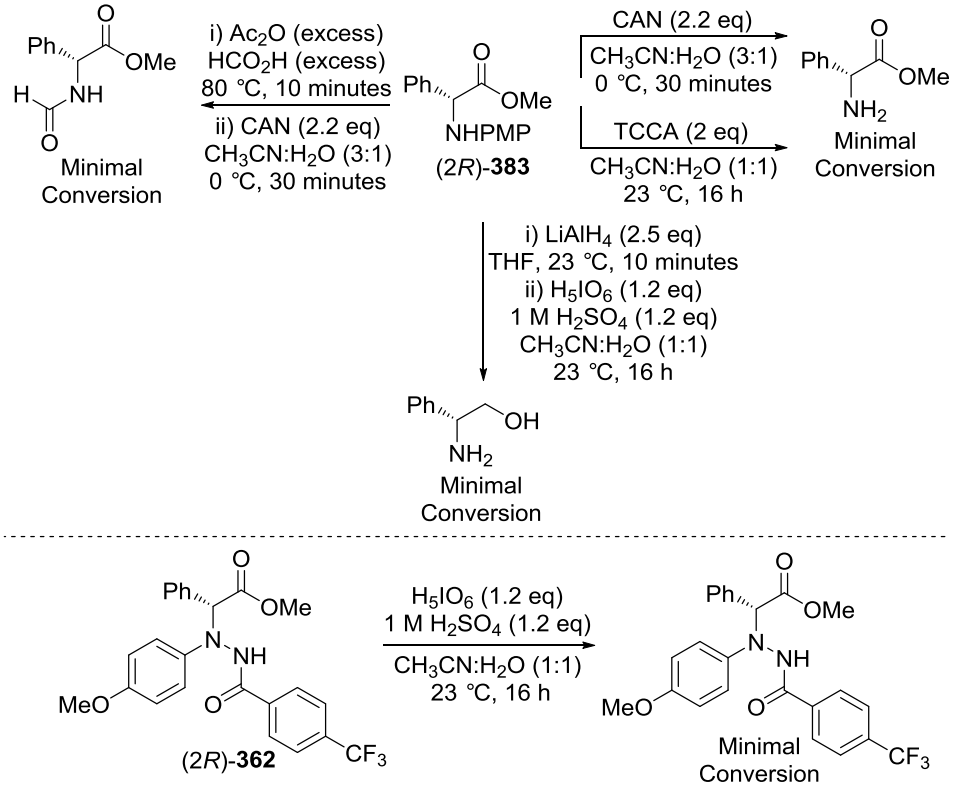


[a] Determined by chiral HPLC analysis.

Table 18 – Synthesis of bespoke *N*-aryl-α-aryl glycine derivatives.

The *p*-methoxyphenyl group was often incorporated into the hydrazide products and subsequently *N*-aryl-α-aryl glycine derivatives with the intention of removing this protecting group in order to access a range of bespoke α-aryl glycine derivatives. However, the PMP-deprotection of (2*R*)-**383** proved problematic, with minimal observed conversion to the desired free amine using CAN despite several related procedures being described in the literature.[120] An alternative deprotection reaction using trichloroisocyanuric acid also gave minimal conversion to the desired amine. Other

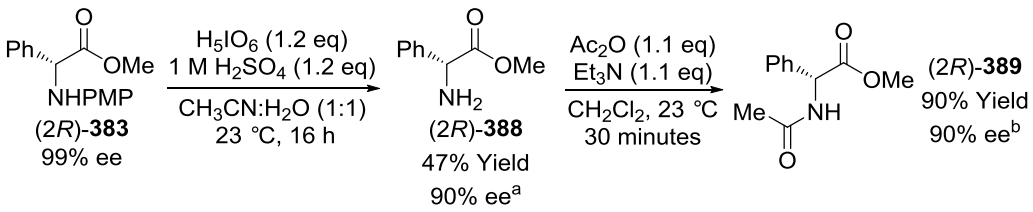
deprotection strategies including a) formylation of the amine with acetic anhydride and formic acid followed by PMP deprotection with CAN, b) reduction of the ester to the corresponding alcohol using $LiAlH_4$ followed by PMP deprotection with periodic acid and c) PMP deprotection with periodic acid directly on hydrazide (2*R*)-**362** all gave minimal conversions to the desired products (Scheme 98). In all cases the starting material was consumed, however the desired products could not be identified through analysis of the crude reaction mixtures by ^{1}H NMR or isolated after work-up/purification.



Scheme 98: Attempted PMP deprotections.

The best deprotection methodology found used periodic acid, giving phenylglycine methyl ester (2*R*)-**388** in 47% yield and 90% ee from (2*R*)-**383** (Scheme 99). The erosion of enantiopurity is likely due to the strongly acidic conditions causing partial racemisation of the sensitive stereocentre. The enantioselectivity of the product was determined *via* acylation with acetic anhydride in the presence of Et_3N, giving (2*R*)-**389** in 90% yield that could be analysed by chiral HPLC. The absolute configuration of (2*R*)-**388** was confirmed by comparison of the experimental optical rotation – $[\alpha]_D^{20}$-192 (*c*

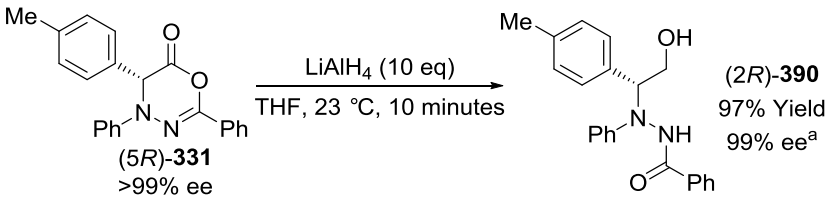
0.025, CH_2Cl_2) – to a literature value – $[\alpha]_D^{20}$+202.3 (c 0.49 in CH_2Cl_2) for a 91% ee sample (2*S*)-configuration.[121]



[a] Determined by derivatisation. [b] Determined by chiral HPLC analysis.

Scheme 99: Best deprotection conditions using periodic acid and subsequent derivatisation.

Finally, the synthetic utility of the 1,3,4-oxadiazin-6(5*H*)-one products was also demonstrated. The simple reductive ring-opening reaction of 1,3,4-oxadiazin-6(5*H*)-one (5*R*)-**331** with $LiAlH_4$ gave alcohol (2*R*)-**390** in 97% yield and 99% ee (Scheme 100).



[a] Determined by chiral HPLC analysis.

Scheme 100: Reductive ring-opening of 1,3,4-oxadiazin-6(5*H*)-one (5*R*)-331.

4.6 Conclusions

In conclusion, isothiourea HBTM-2.1 **112** catalyses the practical and scalable direct α-amination of carboxylic acids using low catalyst loadings (as low as 0.25 mol%), forming a range of 1,3,4-oxadiazin-6(5*H*)-ones or hydrazide products with excellent enantiocontrol (typically >99% ee).[103] Notably, the scope of this methodology has been expanded to allow the direct functionalisation of carboxylic acids bearing α-heteroatom and alkyl substitution for the first time in addition to aryl substitution. The synthetic utility of the hydrazide products was demonstrated through their derivatisation into a range of bespoke functionalised *N*-aryl-α-arylglycine derivatives in high enantiopurity.

4.7 References and Notes

[101] For n_o to $\sigma^*_{C\text{-}S}$ interactions discussed with respect to (acylimino)thiadiazoline derivatives see (a) Y. Nagao, T. Hirata, S. Goto, S. Sano, A. Kakehi, K. Iizuka and M. Shiro, *J. Am. Chem. Soc*., 1998, **120**, 3104-3110. For n_o to $\sigma^*_{C\text{-}S}$ interactions discussed

with respect to isothioureas see: (b) Ref 51; (c) Ref 55; (d) C. Leverett, V. C. Purohit and D. Romo, *Angew. Chem. Int. Ed*., 2010, **49**, 9479-9483; (e) E. Robinson, C. Fallan, C. Simal, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2013, **4**, 2193-2200; (f) G. Liu, M. E. Shirley, K. N. Van, R. L. McFarlin and D. Romo, *Nature Chem*., 2013, **5**, 1049-1057. For reviews that discusses the attractive n_o to σ^*_{C-S} interaction observed through the study of crystal structure data see: (g) K. A. Brameld, B. Kuhn, D. C. Reuter and M. Stahl, *J. Chem. Inf. Model*, 2008, **48**, 1-24; (h). V. I. Minkin and R. M. Minyaev, *Chem. Rev.* 2001, **101**, 1247-1265.

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[116] For a selected example of copper-mediated *N*-arylation see D. Ma and C. Xia, *Org. Lett.*, 2001, **3**, 2583-2586. For selected example of palladium-mediated *N*-arylation see T. Ooi, M. Kameda and K. J. Maruoka, *J. Am. Chem. Soc.,* 2003, **125**, 5139-5151.

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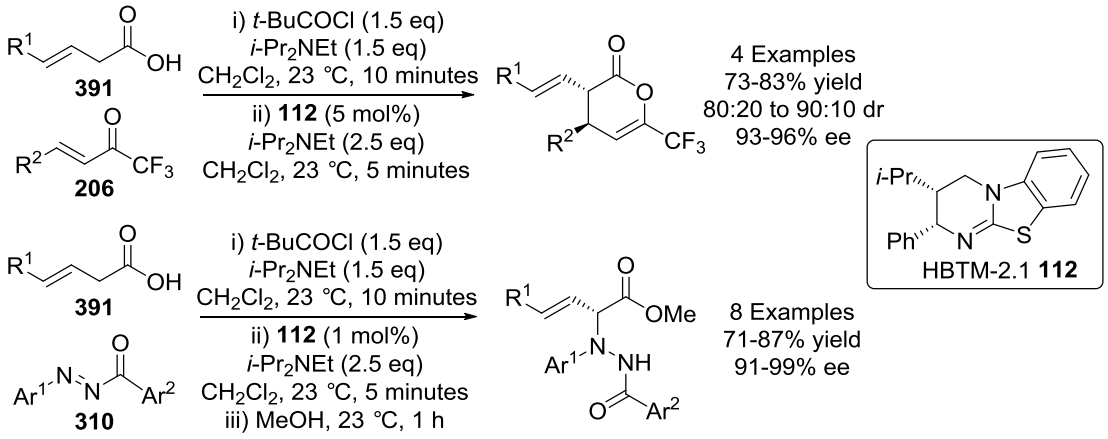
Chapter 5: Functionalisation of 3-Alkenoic Acids

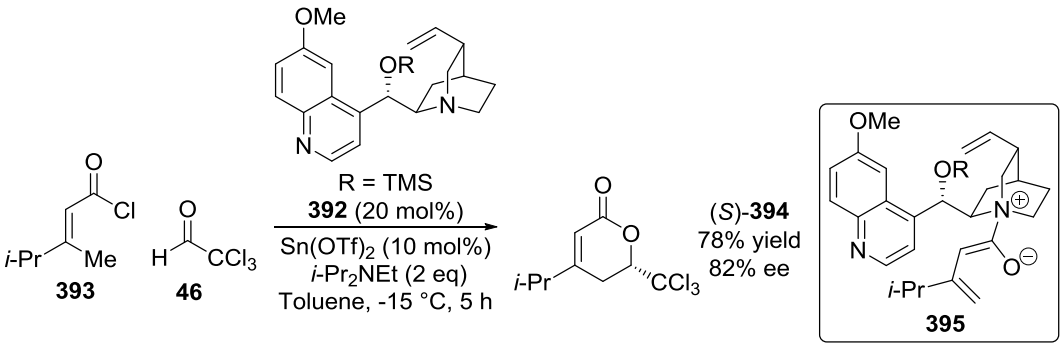
This chapter describes the use of 3-alkenoic acids **391** as suitable precursors to isothiourea-derived C1-ammonium dienolates that react to give exclusively α-functionalised products. The ability of HBTM-2.1 **112** to catalyse the α-functionalisation of 3-alkenoic acids **391** through formal [4+2] cycloadditions with both trifluoromethyl enones **206** and *N*-aryl-*N*-aroyl diazenes **310** in good yield and with excellent enantiocontrol is disclosed, providing access to useful synthetic building blocks amenable to further elaboration (Scheme 101).



Scheme 101: Functionalisation of 3-alkenoic acids *via* formal [4+2] cycloadditions.

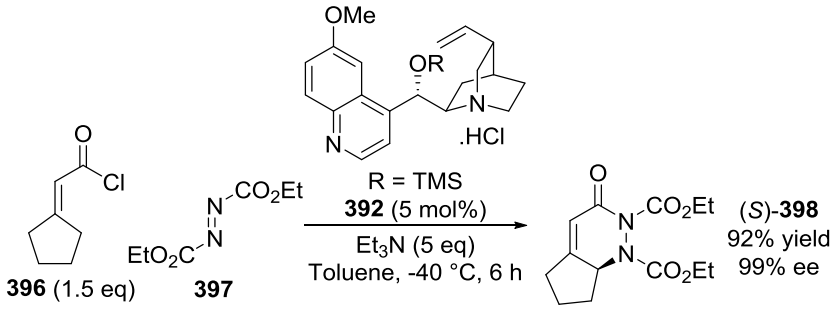
5.1 Introduction

The organocatalytic generation of dienolates or their dienamine equivalents is an increasingly popular area of research.[123] These intermediates have powerful synthetic potential due to their ability to react regio- and enantioselectively through either α- or γ-positions, allowing rapid access to diverse molecular scaffolds. In particular, recent research has demonstrated the ability of ammonium and azolium dienolates to participate in asymmetric transformations. Peters and co-workers have shown that cinchona alkaloid-derived C1-ammonium dienolates, prepared from α,β-unsaturated acid chloride starting materials, partake in formal [4+2] cycloadditions.[124] For example, TMS-quinidine **392** catalyses the reaction of α,β-unsaturated acid chloride **393** and chloral **46** in the presence of *i*-Pr_2NEt and $Sn(OTf)_2$ giving δ-lactone (*S*)-**394** in 78% yield and 82% ee *via* C1-ammonium dienolate **395** (Scheme 102).



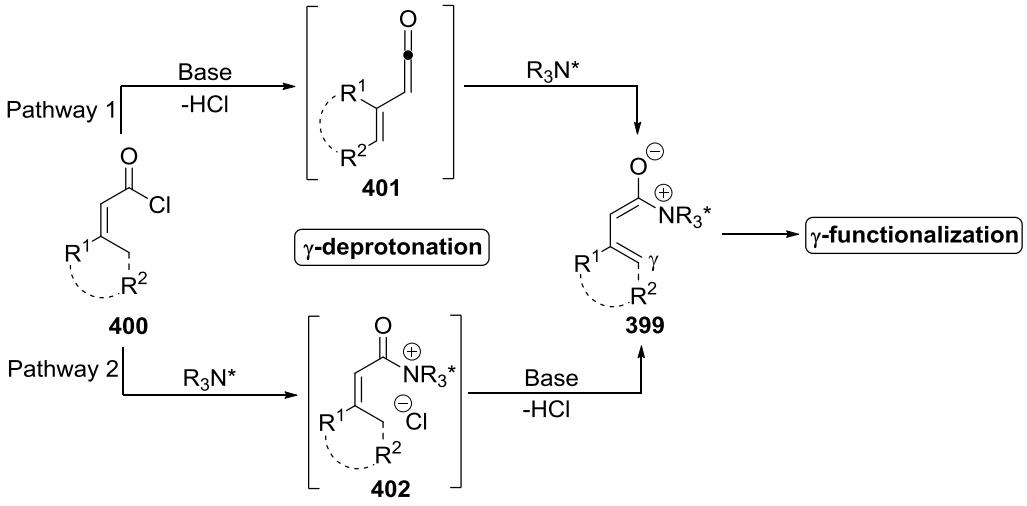
Scheme 102: Formal [4+2] cycloaddition of C1-ammonium dienolate with chloral 46.

Ye and co-workers have demonstrated the γ-amination of cinchona alkaloid-derived C1-ammonium dienolates.[125] For example, TMS-quinidine **392** catalyses the reaction of α,β-unsaturated acid chloride **396** and diazodicarboxylate **397** in the presence of Et_3N, giving (*S*)-**398** in 92% yield and 99% ee *via* a closely related C1-ammonium dienolate (Scheme 103).



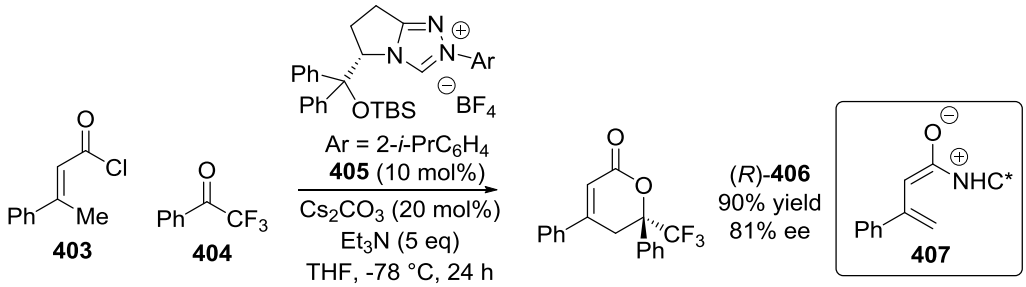
Scheme 103: γ-amination of C1-ammonium dienolate with diazodicarboxylate 397.

In both of the above examples, the C1-ammonium dienolate **399** may form either *via* initial dehydrohalogenation of α,β-unsaturated acid chloride **400** to form the vinyl ketene **401** that is intercepted by the Lewis base (pathway 1, Scheme 104), or from initial attack of the Lewis base to form α,β-acyl ammonium **402** followed by γ-deprotonation (pathway 2, Scheme 104). All catalytically generated β,β-disubstituted C1-ammonium dienolates documented in the literature react to give γ-functionalized products.



Scheme 104: Two possible routes towards C1-ammonium dienolate 399.

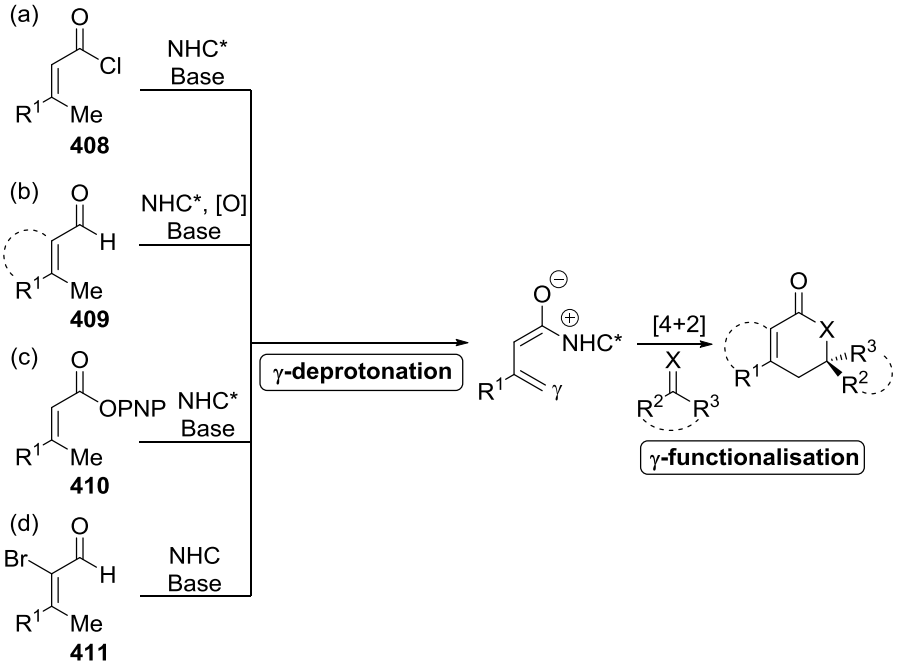
C1-azolium dienolates have also received considerable attention within the past two years. For example, Ye demonstrated that NHCs can activate α,β-unsaturated acid chlorides towards formal [4+2] cycloadditions *via* C1-azolium dienolates.[126] In a representative example, the reaction between α,β-unsaturated acid chloride **403** and trifluoromethyl ketone **404** catalysed by chiral NHC, generated from precatalyst **405** in the presence of Cs_2CO_3, gave (*R*)-**406** in 90% yield and 81% ee *via* C1-azolium dienolate **407** (Scheme 105).



Scheme 105: Formal [4+2] involving C1-azolium dienolate 407.

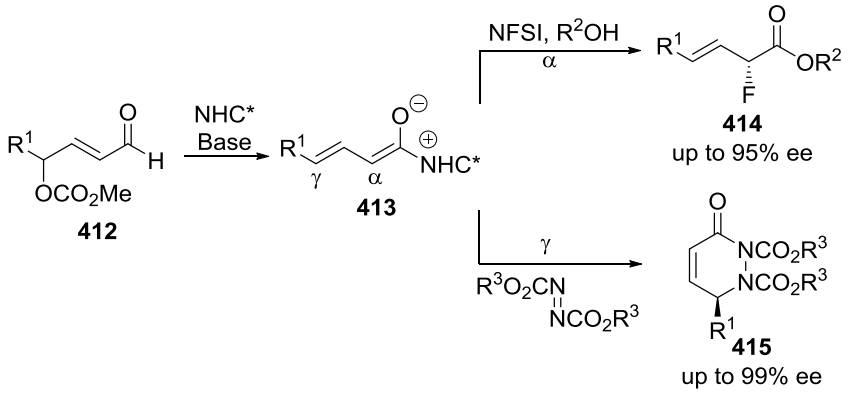
In addition to the α,β-unsaturated acid chlorides **408**, several different starting materials have been used to access the key C1-azolium dienolate that react *via* the γ-centre in asymmetric formal [4+2] cycloadditions with 2π electrophiles (Scheme 106). Chi disclosed the ability to access the same dienolate *via* both enals **409** (in the presence of a stoichiometric oxidant)[127,128] and α,β-unsaturated esters **410**.[129] Alternatively, enals bearing an α-bromo leaving group such as **411** have also been demonstrated as suitable azolium dienolate precursors.[130] In examples a-d, each process is postulated to involve γ-

deprotonation of the corresponding β,β-disubstituted-α,β-acyl azolium intermediate to generate the corresponding dienolate, often depicted in both (*E*)- and (*Z*)-configurations, followed by γ-functionalization of the resulting azolium dienolate.



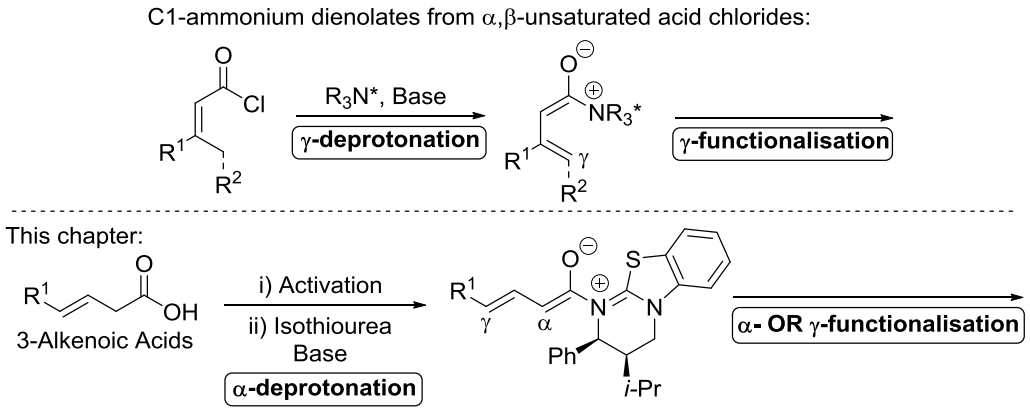
Scheme 106: Established methods to access C1-azolium dienolates.

Alternatively, aldehydes that contain a γ-leaving group such as **412** have been used to access C1-azolium dienolates **413** (Scheme 107). Interestingly, these dienolates give α-functionalization *via* fluorination with NFSI, and γ-functionalization in the formal [4+2] cycloaddition with diazodicarboxylates, affording esters **414**[131] and lactams **415**[132] respectively.



Scheme 107: α- and γ-functionalisation of C1-azolium dienolates 413.

Despite the advances made in the isothiourea-catalysed intermolecular Michael addition-lactonisation methodology outlined thus far, the difficulties in employing acids other than simple arylacetic acids constitutes a limitation of this organocatalytic strategy. To broaden the substrate scope of such processes, the use of 3-alkenoic acids would allow access to extended dienolates that could give rise to either α- or γ-functionalized products in a stereodefined manner (Scheme 108). In this chapter, the generation of isothiourea-derived C1-ammonium dienolates formed from 3-alkenoic acids and their subsequent reactivity is investigated.



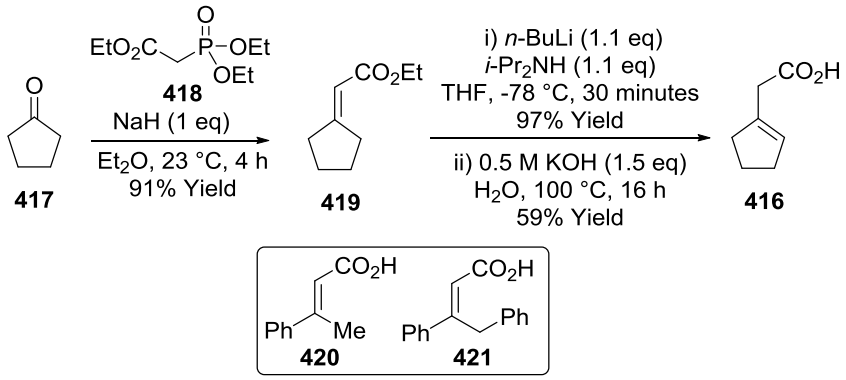
Scheme 108: Generation of C1-ammonium dienolates using isothioureas.

5.2 Reaction of C1-Ammonium Dienolates with 2π Electrophiles

Initial studies probed the ability of isothioureas to generate an ammonium dienolate from a 3-alkenoic acid, with subsequent reaction with a reactive 2π component used to test if α- or γ-selectivity is observed.

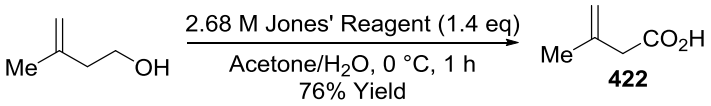
5.2.1 Synthesis of Carboxylic Acid Starting Materials

To test the ability of isothioureas to generate C1-ammonium dienolates, suitable carboxylic acid starting materials were identified and synthesised. Acid **416** was formed *via* a 3-step route beginning with a Horner-Wadsworth-Emmons (HWE) reaction between cyclopentanone **417** and phosphonate **418**, giving alkene **419** in 91% yield (Scheme 109). Subsequent isomerisation with LDA followed by ester hydrolysis gave carboxylic acid **416** in 57% yield over 2 steps. Closely related carboxylic acids **420** and **421** were made using the same HWE and ester hydrolysis steps from the corresponding ketone starting materials.



Scheme 109: Synthetic route towards carboxylic acids 416, 420 and 421.

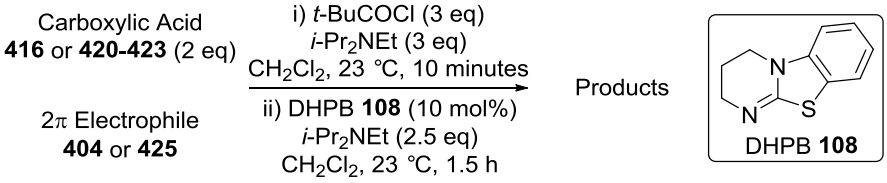
Carboxylic acid **422** was also obtained *via* Jones' oxidation of commercially available 3-methylbut-3-en-1-ol in 76% yield (Scheme 110).

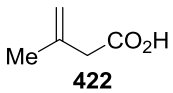
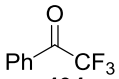
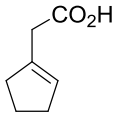
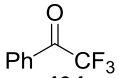
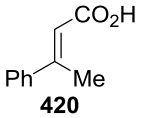
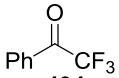
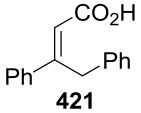
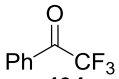
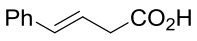
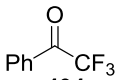
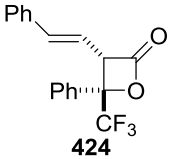
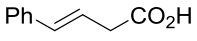
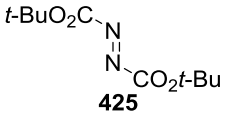


Scheme 110: Jones' oxidation towards carboxylic acid 422.

5.2.2 Functionalisation with 2π Electrophiles

With carboxylic acids **416** and **420**-**422** in hand, these were tested along with commercially available (*E*)-4-phenylbut-3-enoic acid **423** for their ability to act as C1-ammonium dienolate precursors. Encouraged by Ye's report demonstrating diazadicarboxylates as suitable reaction partners with C1-ammonium dienolates,[125] along with both Ye and Chi who showed that trifluoromethyl ketones are suitable partners in [4+2] cycloadditions with C1-azolium dienolates,[126,127] these 2π components were initially evaluated. Using carboxylic acids **416** and **420**-**422** with pivaloyl chloride as activating agent, achiral DHPB **108** as catalyst and trifluoromethyl ketone **404** as the 2π electrophile, no distinguishable cycloaddition products were observed (Table 19). However, under the same reaction conditions, **423** reacted with trifluoromethyl ketone **404**, giving solely the [2+2] cycloaddition product β-lactone **424** (60:40 dr *anti*:*syn*) derived from α-functionalisation in 71% combined yield. Unfortunately, diazodicarboxylate **425** proved incompatible with this system giving no distinguishable product despite full consumption of **425**.



Entry	Carboxylic Acid	2π Electrophile	Product (major)	Yield (% anti, syn)[a]	Dr (anti:syn)[b]
1	 **422**	 **404**	None	-	-
2	 **416**	 **404**	None	-	-
3	 **420**	 **404**	None	-	-
4	 **421**	 **404**	None	-	-
5	 **423**	 **404**	 **424**	43,29	60:40
6	 **423**	 **425**	None	-	-

[a] Isolated yield (≥98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Table 19: Evaluation of carboxylic acids 416 and 420-423 as C1-ammonium dienolate precursors.

The relative configurations of β-lactones (*anti* **424** and *syn* **426**) were unambiguously confirmed by X-ray crystal structure analysis (Figure 49).

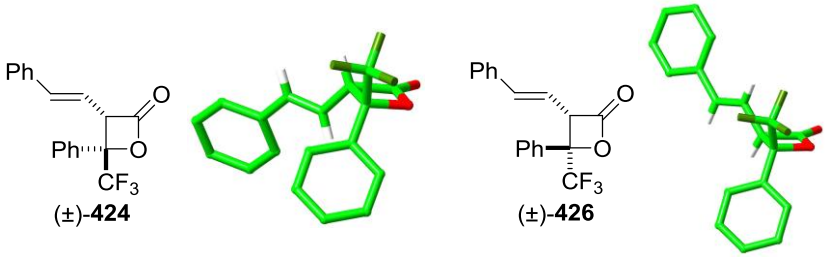
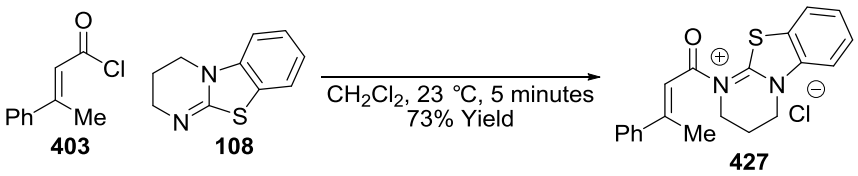


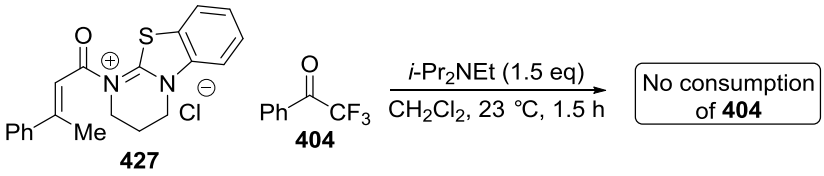
Figure 49: Crystal structures of 424 and 426 showing relative configuration.

When carboxylic acids **416** and **420**-**422** were used in this protocol, analysis of the crude reaction mixtures by ^{1}H NMR revealed that in all cases the corresponding mixed anhydride had formed and that trifluoromethyl ketone **404** remained. Possible reasons for the lack of reactivity include: 1) the acyl ammonium does not form from the mixed anhydride; 2) the γ-deprotonation of the acyl ammonium to form the C1-ammonium dienolate does not take place; 3) the C1-ammonium dienolate is poorly nucleophilic and does not react with the electrophile. In order to gain some insight into this problem, the corresponding acyl ammonium was synthesised by reaction of acid chloride **403** with DHPB **108** to give *N*-acyl isothiouronium chloride **427** in 73% yield (Scheme 111).



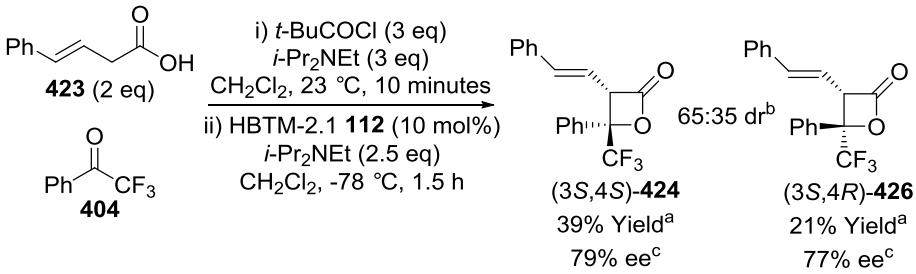
Scheme 111: Acyl ammonium formation.

The reaction with trifluoromethyl ketone **404** was carried out using 1 equivalent of **427** and no consumption of the electrophile was observed (Scheme 112). This result suggests that either γ-deprotonation does not take place or that the C1-ammonium dienolate is poorly nucleophilic. Employing a stronger base – PS-Bemp – also resulted in no consumption of the electrophile.



Scheme 112: Acyl ammonium 427 used directly in reaction.

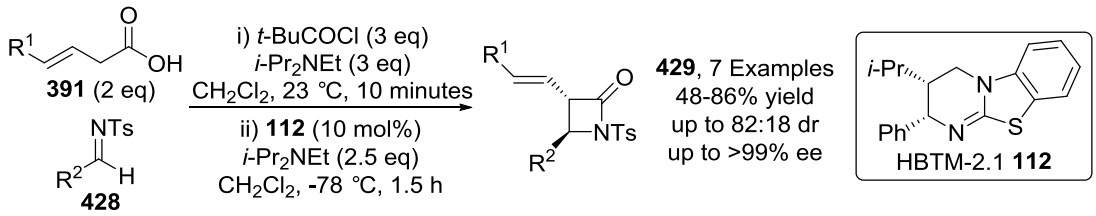
Due to the discovery that DHPB **108** catalyses the formal [2+2] cycloaddition between carboxylic acid **423** and trifluoromethyl ketone **404**, attention focused upon the development on suitable conditions to affect an asymmetric variant of this transformation. Preliminary studies showed that carrying out this reaction using HBTM-2.1 **112** at −78 °C allowed formation of β-lactone in 65:35 dr with the *anti*-diastereoisomer (3*S*,4*S*)-**424** formed in 79% ee and the *syn*-diastereoisomer (3*S*,4*R*)-**426** formed in 77% ee (Scheme 113). The absolute configurations are tentatively assigned by analogy to that typically observed using HBTM-2.1 **112** in these processes.



[a] Isolated yield (≥98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 113: Preliminary studies into asymmetric formal [2+2] cycloadditions.

The area of formal [2+2] cycloadditions of isothiourea-derived C1-ammonium dienolates was continued by an undergraduate project student.[133] It was found that HBTM-2.1 **112** efficiently catalysed the formal [2+2] cycloadditions between a range of 3-alkenoic acids **391** and *N*-tosyl aldimines **428**, affording a variety of *anti*-β-lactams **429** in high yield and with high levels of diastereo- and enantioselectivity (Scheme 114).

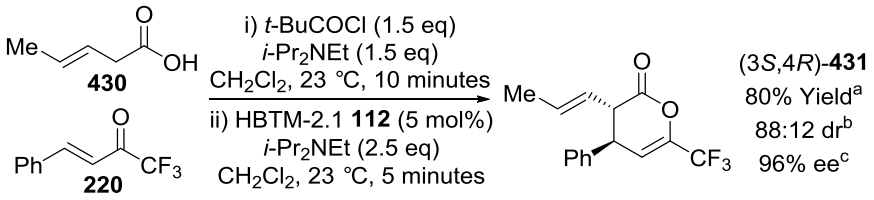


Scheme 114: Formal [2+2] cycloaddition of *N*-tosyl aldimines.

5.3 Functionalisation with 4π electrophiles

5.3.1 Formal [4+2] cycloadditions with trifluoromethyl enones

Having established the propensity of these ammonium dienolates to react at the α-position with 2π electrophiles, their ability to partake in formal [4+2] cycloadditions with electron deficient 4π Michael acceptors was investigated. It was found that HBTM-2.1 **112** efficiently catalyses the reaction between commercially available (*E*)-pent-3-enoic acid **430** and previously utilised trifluoromethyl enone **220** (see Chapter 3) in only 5 minutes at rt, giving *anti*-dihydropyranone (3*S*,4*R*)-**431** in 80% yield with good diastereoselectivity (88:12 dr) and excellent enantioselectivity (96% ee) (Scheme 115). The minor diastereoisomer was formed in only 15% ee. This reaction does not give full consumption of enone **220** at −78 °C even with extended reaction times.

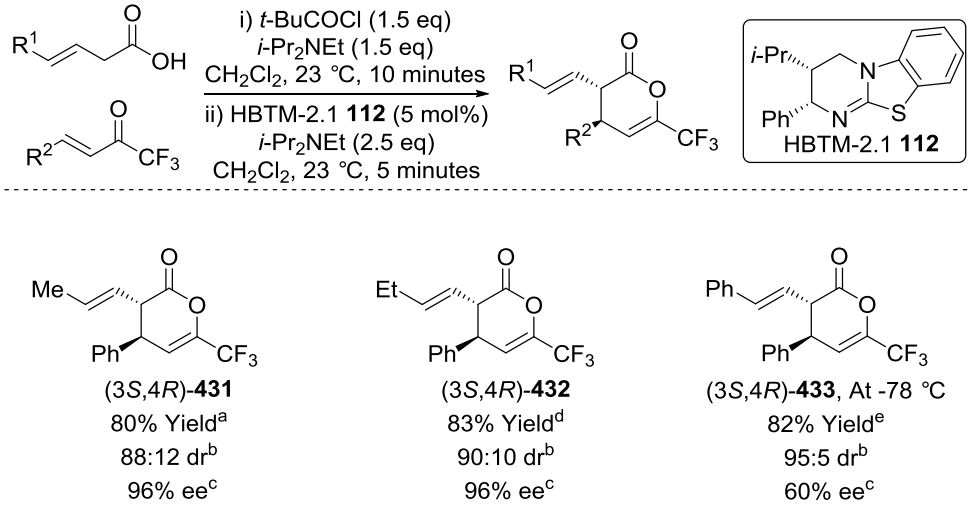


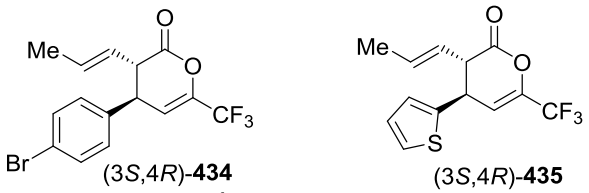
[a] Isolated yield (88:12 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 112: Formal [4+2] cycloaddition of carboxylic acid 430.

The relative and absolute configuration of (3*S*,4*R*)-**431** was assigned by comparison with the products formed in Chapter 3 and all other products in Table 20 were assigned by analogy. Racemic samples needed for chiral HPLC analysis for all dihydropyranones in this Section were made using HBTM-2.1 (±)-**112** as catalyst due to the higher diastereoselectivities obtained in comparison to DHPB **108**.

A brief examination of the scope revealed that the reaction proceeds efficiently using (*E*)-3-hexenoic acid, giving *anti*-dihydropyranone **432**, although when using the more reactive (*E*)-styrylacetic acid, the reaction has to be carried out at −78 °C to prevent product decomposition and gives the major diastereoisomer of **433** in reduced enantioselectivity (60% ee). Heteroaryl and 4-bromophenyl substituted trifluoromethyl enones are also tolerated giving **434** and **435** in good yields and high diastereo- and enantioselectivity (Table 20).





(3*S*,4*R*)-**434**
73% Yield[f]
80:20 dr[b]
92% ee[c]

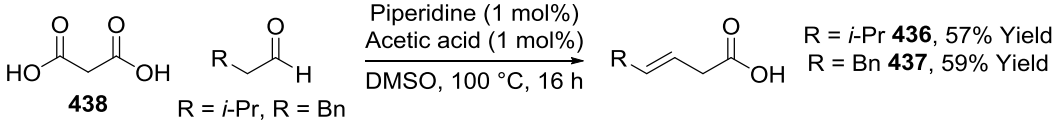
(3*S*,4*R*)-**435**
83% Yield[g]
84:16 dr[b]
93% ee[c]

[a] Isolated yield of major diastereoisomer (88:12 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yield of major diastereoisomer (93:7 dr). [e] Isolated yield of major diastereoisomer (≥98:2 dr). [f] Isolated yield of major diastereoisomer (95:5 dr). [g] Isolated yield of major diastereoisomer (84:16 dr).

Table 20: Substrate scope using trifluoromethyl enones.

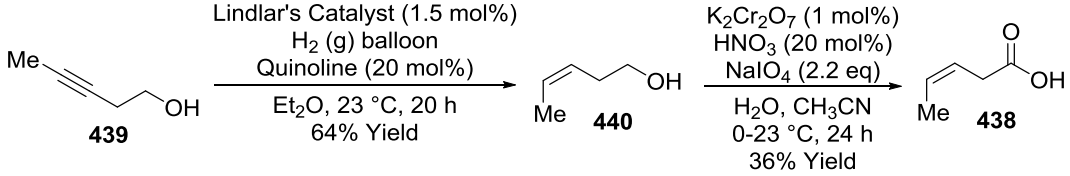
5.3.2 Synthesis of Carboxylic Acid Starting Materials

In order to further assess the scope of this methodology a range of additional 3-alkenoic acids were synthesised. 4-*i*-Pr substituted and 4-Bn substituted acids **436** and **437** were made according to the one-step method described by Tan.[134] Piperidine-acetic acid catalysed Doebner-modified Knoevenagel reaction between malonic acid **438** and the requisite aldehyde gave **436** and **437** in 57% and 59% yield respectively (Scheme 116).



Scheme 116: Synthetic route towards carboxylic acids 436 and 437.

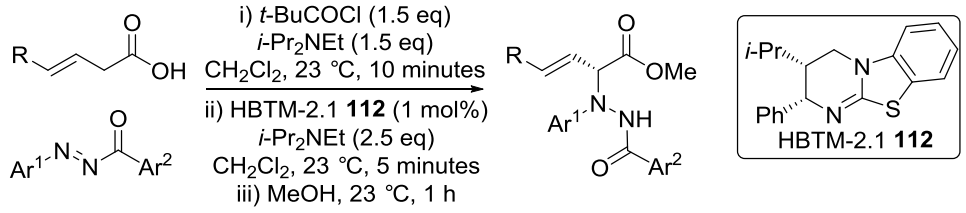
A carboxylic acid with a (*Z*)-double bond **438** was also synthesised *via* the two step procedure outlined by Breit.[135] Commercially available alkyne **439** was partially hydrogenated to (*Z*)-alcohol **440** using Lindlar's catalyst followed by oxidation to give (*Z*)-acid **438** in 23% yield over 2 steps (Scheme 117).

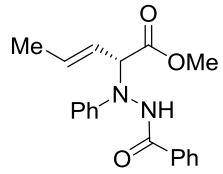


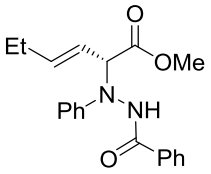
Scheme 117: Synthetic route towards (*Z*)-carboxylic acid 438.

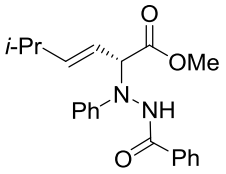
5.3.3 Formal [4+2] cycloadditions with *N*-aryl-*N*-aroyl diazenes

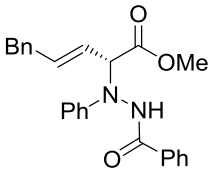
With these additional carboxylic acid starting materials in hand, the generality of this asymmetric Michael addition-lactonisation process was next investigated using the previously utilised *N*-aryl-*N*-aroyldiazenes as Michael acceptors (see Chapter 4), followed by *in situ* ring opening with MeOH. This catalytic methodology tolerates a range of 3-alkenoic acids bearing 4-alkyl (Me, Et, *i*-Pr), 4-benzyl and 4-phenyl substituents, in addition to (*E*)- and (*Z*)-alkene configurations, giving, after *in situ* ring-opening with methanol, a range of hydrazides **441**-**446** in high yields (71-85 %) and excellent enantioselectivity (91-99 % ee) (Table 21). Diazenes bearing electron deficient (4-FC_6H_4) and heteroaryl (2-furyl) *N*-aroyl substituents are also tolerated giving products **447** and **448** in excellent ee. The absolute configuration of hydrazide (2*R*)-**441** was assigned by comparison to the products formed in Chapter 4 and all other products in Table 21 were assigned by analogy. Racemic samples needed for chiral HPLC analysis for all hydrazides in this section were made using DHPB **108** as catalyst.

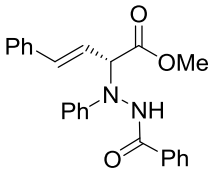


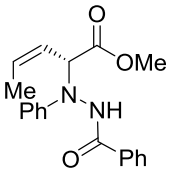

(2*R*)-**441**
80% Yield
96% ee[a]

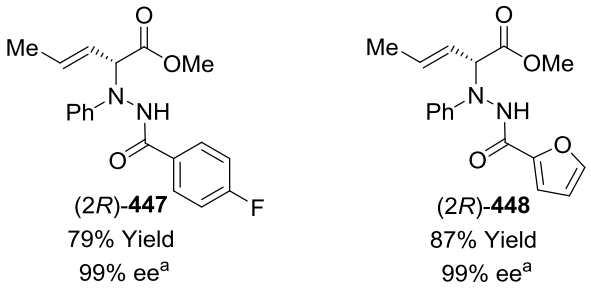

(2*R*)-**442**
85% Yield
99% ee[a]


(2*R*)-**443**
74% Yield
99% ee[a]


(2*R*)-**444**
77% Yield
99% ee[a]


(2*R*)-**445**
71% Yield
91% ee[a]

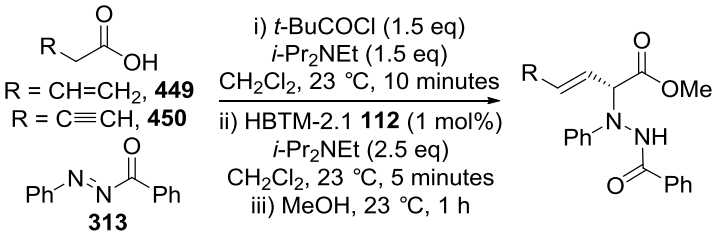

(2*R*)-**446**
72% Yield
91% ee[a]



[a] Determined by chiral HPLC analysis.

Table 21: Substrate scope using *N*-aryl-*N*-aroyl diazenes.

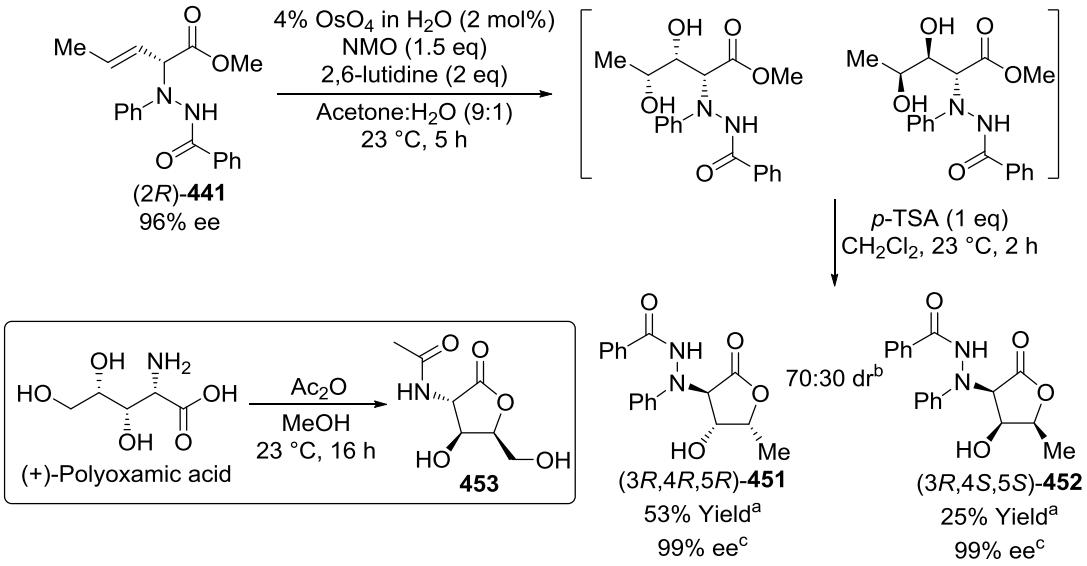
Unfortunately both but-3-enoic acid **449** and but-3-ynoic acid **450** gave no conversion to the desired hydrazide product when reacted with diazene Michael acceptor **313** using the optimised reaction conditions. ^{1}H NMR analysis of the crude reaction mixture revealed the presence of both the corresponding mixed anhydrides and remaining diazene **313** (Scheme 118).



Scheme 118: Unreactive carboxylic acid starting materials 449 and 450.

5.4 Derivatisations

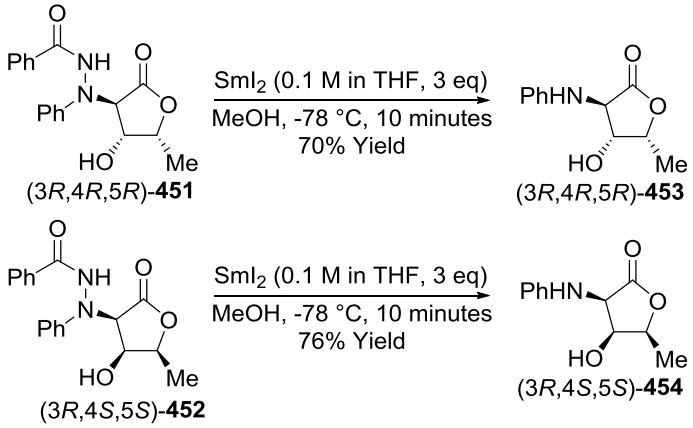
Having developed a highly enantioselective route to hydrazides **441**-**448**, their potential for further elaboration through functionalisation of the olefin was probed. Treatment of hydrazide **441** under Upjohn dihydroxylation conditions, followed by acid catalysed cyclisation using *p*-TSA, gave a 70:30 mixture of separable diastereomeric 5-membered lactones **451** and **452** in 85% combined yield, both in 99% ee (Scheme 119). These interesting aza-sugar derivatives structurally resemble the cyclized form of (+)-polyoxamic acid **453**, indicating their potential biological significance.



[a] Isolated yield of major diastereoisomer (≥98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 119: Derivatisation towards aza-sugar analogues.

It proved difficult to determine the relative configurations of lactones **451** and **452** at this stage by NOE or coupling constant analysis due to poorly resolved signals in the ^{1}H NMR. In order to simplify the ^{1}H NMR spectra the N-N bond in both lactones **451** and **452** was cleaved using SmI_2 giving **453** and **454** in 70% and 76% yield respectively (Scheme 120). The enantioselectivity of these products was not determined.



Scheme 120: Further derivatisation to allow for determination of relative configurations.

Diastereoisomers (3*R*,4*R*,5*R*)-**453** and (3*R*,4*S*,5*S*)-**454** were assigned based upon the ^3J coupling constant between C(3)*H* and C(4)*H* which is 7.3 Hz for (3*R*,4*R*,5*R*)-**453** due to the *anti* relationship and 2.9 Hz for (3*R*,4*S*,5*S*)-**454** due to the *syn* relationship (Figure 50). Additional evidence was found using NOE experiments. Upon irradiation of C(5)*H*

in (3*R*,4*R*,5*R*)-**453** there is a NOE with both C(4)*H* and CH_3. However, irradiation of C(5)*H* in (3*R*,4*S*,5*S*)-**454** gives NOE with C(4)*H*, CH_3 and importantly C(3)*H*, indicating that C(3)*H*, C(4)*H* and C(5)*H* are all on the same face of the 5-membered lactone. This analysis allowed the relative configuration of the lactone products to be assigned with the absolute configuration defined by the starting hydrazide (2*R*)-**441**.

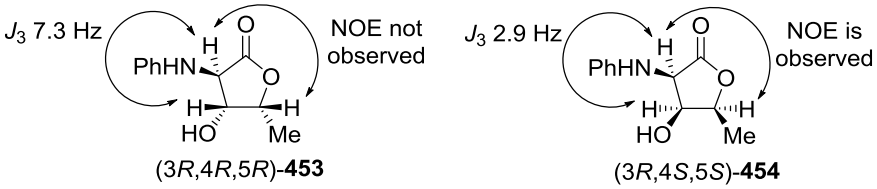


Figure 50: Determination of relative configurations of 453 and 454.

5.5 Reaction Mechanism

A plausible catalytic cycle for these transformations proceeds *via* initial *N*-acylation of HBTM-2.1 **112** with the pre-formed mixed anhydride to form the corresponding acyl ammonium ion. α-Deprotonation generates the (*Z,E*)-enolate (from the (*E*)-alkenoic acid), which undergoes stereoselective Michael addition *via* α-functionalization with electron deficient 4π Michael acceptors, followed by intramolecular cyclisation, to generate the corresponding heterocyclic species (Figure 51). The sense of stereoinduction in these transformations is consistent with the rationale outlined in Chapter 3. The origin of the observed α-functionalization in these processes can be tentatively assigned to preferential reaction *via* the assumed *s-trans* (*Z,E*)-dienolate conformation **455**, in preference to the *s-cis* (*Z,E*)-dienolate conformation **456** that is presumably necessary to participate in γ-functionalization.

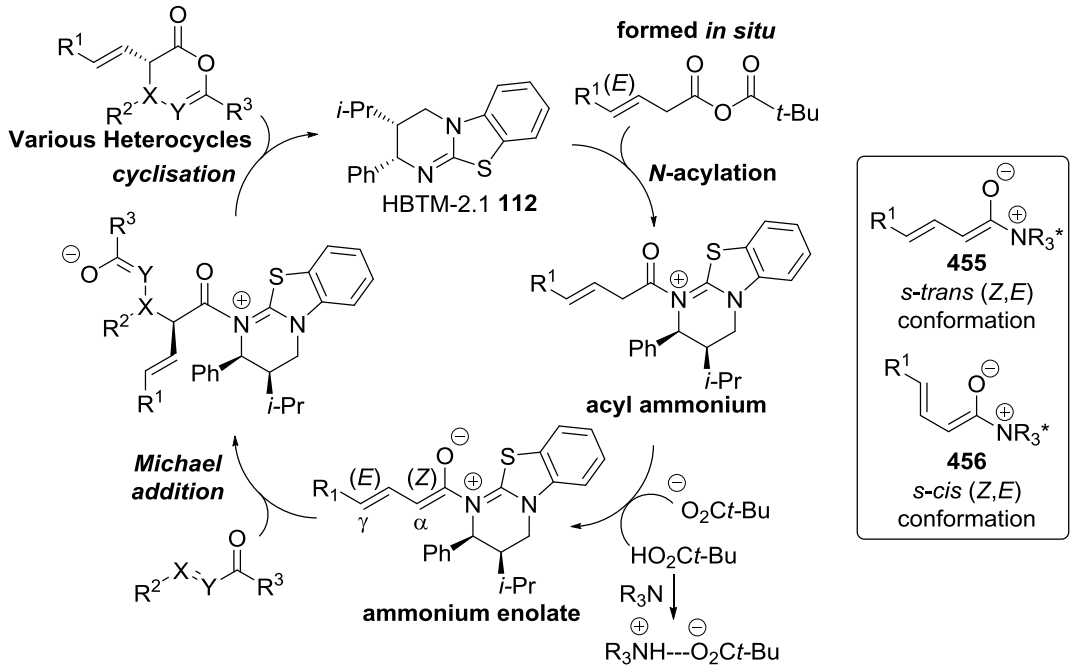


Figure 51: Proposed mechanism for heterocycle formation.

5.6 Conclusions

In conclusion, isothiourea-mediated functionalisation of 3-alkenoic acids occurs regioselectively, giving products derived from α-functionalisation of an intermediate C1-ammonium dienolate in a range of formal [2+2] and [4+2] cycloadditions. This contrasts with all other C1-ammonium dienolates reported in the literature that react at the γ-position. Formal [4+2] cycloadditions with either trifluoromethyl enones of *N*-aryl-*N*-aroyl diazenes are catalysed by HBTM-2.1, with products obtained in high diastereo- and enantiocontrol (up to 95:5 dr, up to 99% ee). The simple, two-step elaboration of stereodefined hydrazides into aza-sugar analogues without erosion of enantiopurity has also been demonstrated.

5.7 References and Notes

[123] For a selected review on dienamine catalysis, see: K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res.*, 2012, **45**, 248-264.

[124] (a) P. S. Tiseni and R. Peters, *Angew. Chem. Int. Ed.*, 2007, **46**, 5325-5328; (b) P. S. Tiseni and R. Peters, *Chem. Eur. J.*, 2010, **16**, 2503-2517.

[125] L-T. Shen, L-H. Sun and S. Ye, *J. Am. Chem. Soc.*, 2011, **133**, 15894-15897.

[126] L-T. Shen, P-L. Shao and S. Ye, *Adv. Synth. Catal.*, 2011, **353**, 1943-1948.

[127] J. Mo, X. Chen and Y. R. Chi, *J. Am. Chem. Soc.*, 2012, **134**, 8810-8813.

[128] X. Chen, S. Yang, B-A. Song and Y. R. Chi, *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201305861.

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[130] C. Yao, Z. Xiao, R. Liu, T. Li, W. Jiao and C. Yu, *Chem. Eur. J.*, 2013, **19**, 456-459.

[131] Y-M. Zhao, M. S. Cheung, Z. Lin and J. Sun, *Angew. Chem. Int. Ed.*, 2012, **51**, 10359-10363.

[132] X-Y. Chen, F. Xia, J-T. Chen and S. Ye, *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.201305571.

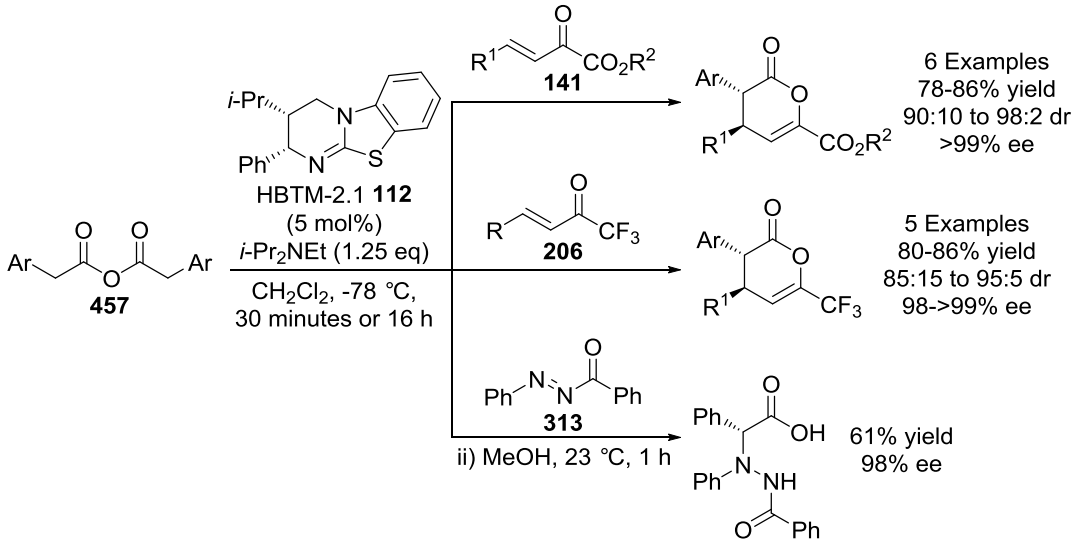
[133] Honours project student Sam Smith carried out this work which is documented in his MChem 4th year thesis "Asymmetric Organocatalytic Formal Cycloadditions using Isothioureas".

[134] J. Wang, J. Chen, C. W. Kee and C-H. Tan, *Angew. Chem. Int. Ed.*, 2012, **51**, 2382-2386.

[135] T. Smejkal and B. Breit, *Angew. Chem. Int. Ed.*, 2008, **47**, 311-315.

Chapter 6: 2-Arylacetic Anhydrides as Ammonium Enolate Precursors

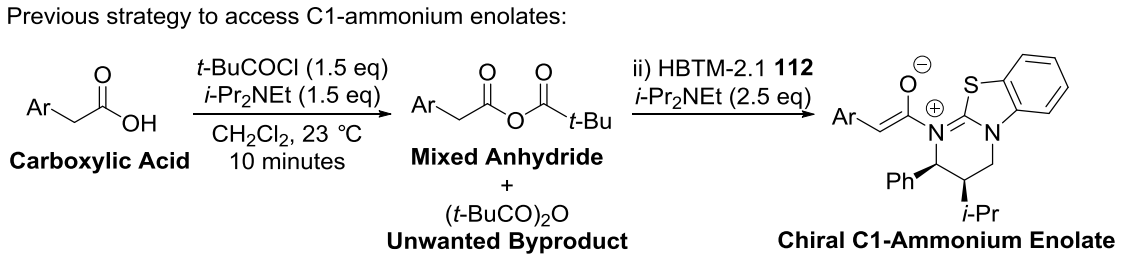
This chapter describes the use of 2-arylacetic anhydrides **457** as precursors to isothiourea-derived C1-ammonium enolates. HBTM-2.1 **112** efficiently catalyses the formal [4+2] cycloadditions between **457** and a range of electron deficient Michael acceptors, namely α-keto-β,γ-unsaturated esters **141**, trifluoromethyl enones **206** and *N*-aryl-*N*-aroyl diazene **313**, giving stereodefined products in good yield and with exquisite enantiocontrol (Scheme 121).[136]



Scheme 121: Functionalisation of 2-arylacetic anhydrides *via* formal [4+2] cycloadditions.

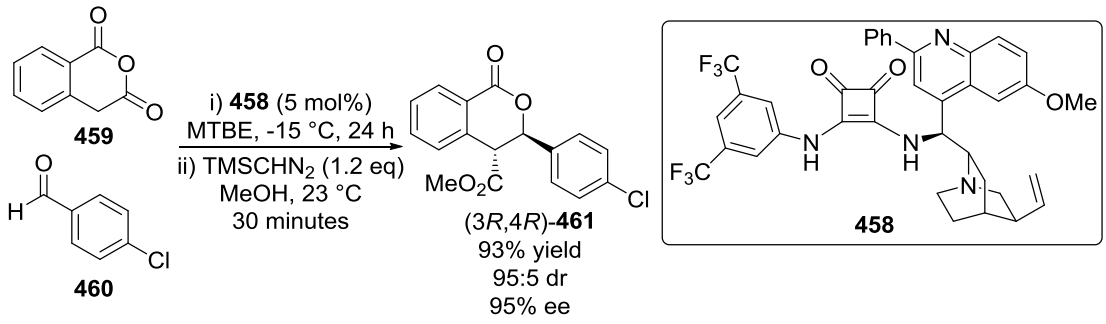
6.1 Introduction

The *in situ* activation and subsequent isothiourea-mediated functionalisation of carboxylic acids has been shown to be a highly powerful strategy, allowing access to a range of stereodefined product in high enantioselectivity. However, noteworthy drawbacks of this method include the use of excess sacrificial base (up to 4 eq of *i*-Pr_2NEt) and the generation of unwanted by-products derived from the acid activating agent (such as pivalic anhydride derived from pivaloyl chloride) that can be difficult to separate from the desired products as discussed in Section 4.2 (Scheme 122). These drawbacks led to the desire to identify alternative bench stable precursors to ammonium enolates at the carboxylic acid oxidation level.



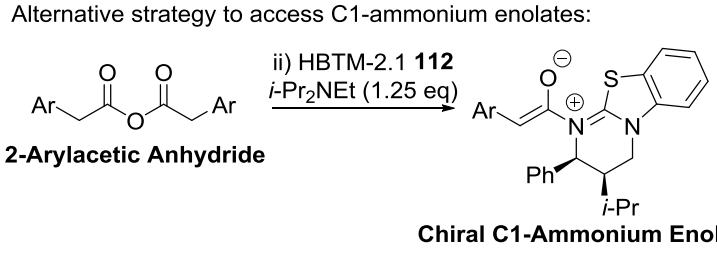
Scheme 122: Previous access to C1-ammonium enolates from carboxylic acids.

The group of Connon recently demonstrated the functionalisation of enolisable anhydrides using bifunctional squaramides.[137] For example, **458** catalyses the reaction of anhydride **459** and 4-chlorobenzaldehyde **460** giving, after *in situ* methyl ester formation, bicyclic ester (3*R*,4*R*)-**461** in 93% yield, 95:5 dr and 95% ee (Scheme 123).



Scheme 123: Functionalisation of enolisable anhydride 459.

Inspired by this report, in addition to the work of Chi using *p*-nitrophenyl esters as azolium enolate precursors (see Section 1.2.2),[42] it was proposed that readily available 2-arylacetic anhydrides could act as C1-ammonium enolate precursors (Scheme 124). Using this strategy, the only by-product from such a process would be an equivalent of the parent acid that would be easily removed *via* basic aqueous work-up. While one equivalent of the (generally cheap and commercially available) parent arylacetic acid would be discarded in this process, this may be offset by the use of less sacrificial base and easier product purifications.

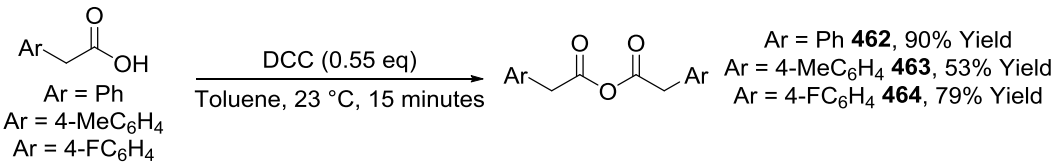


Scheme 124: Access to C1-ammonium enolates from 2-arylacetic anhydrides.

6.2 Formal [4+2] Cycloadditions of 2-Arylacetic Anhydrides

6.2.1 Synthesis of 2-Arylacetic Anhydrides

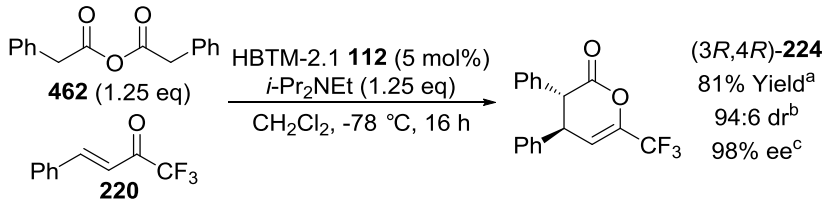
A variety of 2-arylacetic anhydrides **462**-**464** were synthesised in good yields *via* treatment of the parent arylacetic acid with DCC in toluene at rt for 15 minutes. These products are bench stable for approximately one week (Scheme 125). Several other anhydrides were synthesised and made available by colleagues.[138]



Scheme 125: Synthetic route towards 2-arylacetic anhydrides 462, 463 and 464.

6.2.2 Formal [4+2] Cycloadditions with Trifluoromethyl Enones

With 2-arylacetic anhydrides **462**-**464** in hand, these were tested in the isothiourea-catalysed formal [4+2] cycloaddition reaction with the previously utilised trifluoromethyl enones Michael acceptors (see Chapters 3 and 5). HBTM-2.1 **112** efficiently catalyses the reaction between 2-arylacetic anhydride **462** and trifluoromethyl enone **220** after 16 h at −78 °C, giving *anti*-dihydropyranone (3*R*,4*R*)-**224** in 81% yield with good diastereoselectivity (94:6 dr) and excellent enantioselectivity (98% ee) (Scheme 126). Notably, a slight excess of both anhydride **462** (1.25 eq) and *i*-Pr_2NEt (1.25 eq) was necessary for complete consumption of **220**, presumably due to competing Claisen-type self condensation of the anhydride. Approximately 80% conversion of enone **220** to (3*R*,4*R*)-**224** is achieved using 1 eq of anhydride **462**. As anticipated, highly pure material could be obtained after a simple acid/base work-up, with chromatographic purification used to obtain an analytical sample.

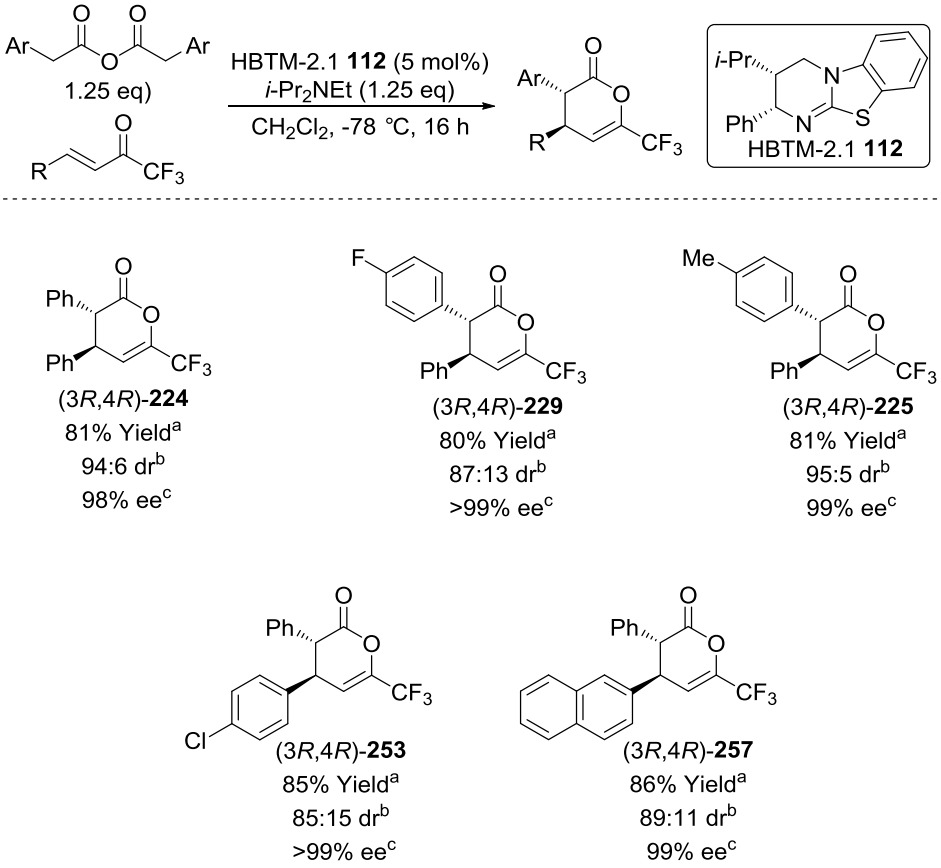


[a] Isolated yield of major diastereoisomer of **224** (≥98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Scheme 126: Formal [4+2] cycloaddition of 2-arylacetic anhydride 462.

The relative and absolute configuration of (3*R*,4*R*)-**224** was the same as that formed using the *in situ* carboxylic acid activation method used previously (see Chapter 3). All other products in Table 22 were assigned by analogy.[139]

A brief examination of the reaction scope revealed that the protocol tolerates 4-FC_6H_4 and 4-MeC_6H_4 substitution within the anhydride and 4-ClC_6H_4 and 2-naphthyl substitution within the enone, in each case giving the corresponding *anti*-dihydropyranones in good yields and high diastereo- and enantioselectivity (Table 22). Several other examples of this methodology was demonstrated by colleagues.[138]



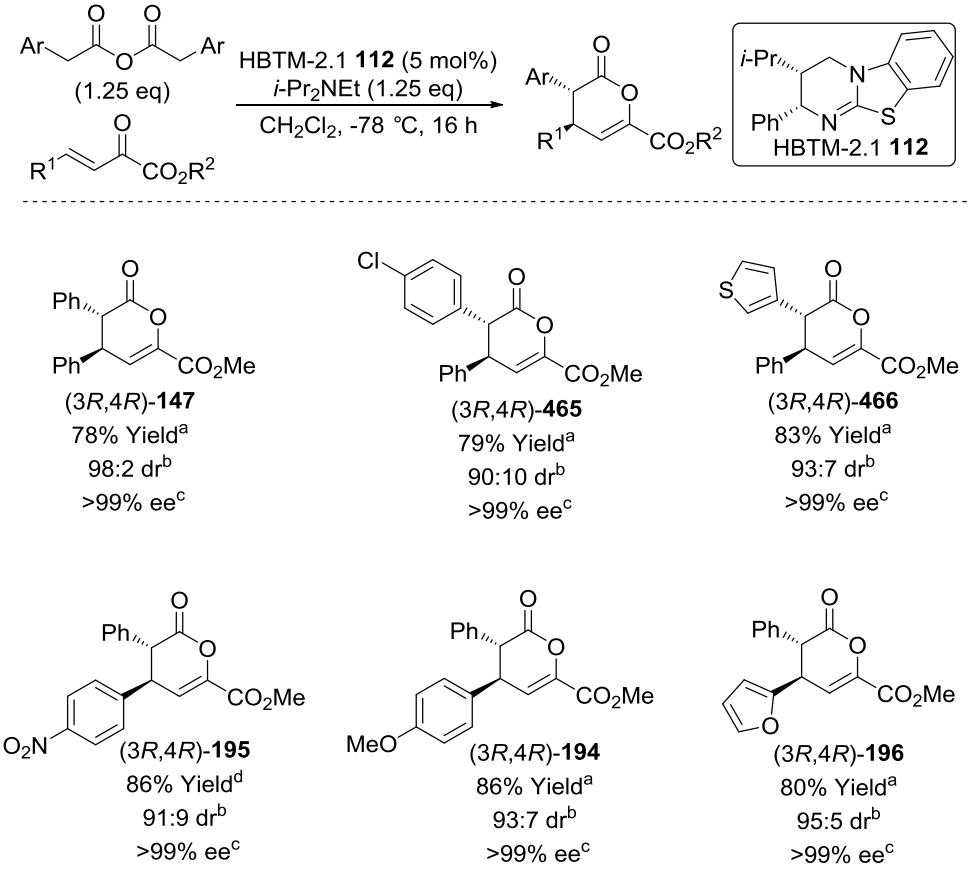
[a] Isolated yield of major diastereoisomer (≥98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis.

Table 22: Substrate scope using trifluoromethyl enones.

6.2.3 Formal [4+2] Cycloadditions with Other Michael Acceptors

Having developed an efficient protocol for the isothiourea catalysed Michael addition-lactonisation of anhydrides and trifluoromethylenones, this process was extended to other classes of suitably electron deficient Michael acceptors. α-Keto-β,γ-unsaturated

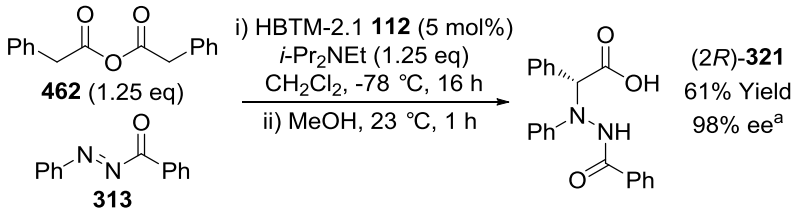
esters proved suitable partners within this process (Table 23). Once more, electron-donating and electron-withdrawing substituents, as well as heteroaryl substitution within both anhydride and α-keto-β,γ-unsaturated ester reaction components was tolerated, affording a range of *anti*-dihydropyranones in high yields (78-86%) and with high diastereo- and enantioselectivity (up to 98:2 dr, exclusively >99% ee).



[a] Isolated yield of major diastereoisomer (≥98:2 dr). [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Isolated yield of major diastereoisomer (93:7 dr).

Table 23: Substrate scope using α-keto-β,γ-unsaturated esters.

As a final demonstration of this methodology, HBTM-2.1 **112** catalysed functionalisation of 2-arylacetic anhydride **462** with diazene **313** using a tandem Michael addition-lactonisation ring-opening protocol with MeOH was achieved, afforded hydrazide **321** in 61% yield and 98% ee (Scheme 127). Several other examples of this methodology was demonstrated by a colleague.[140]



[a] Determined by chiral HPLC analysis.

Scheme 127: Formal [4+2] cycloaddition of using diazene 313.

6.3 Reaction Mechanism

A plausible catalytic cycle for these transformations proceeds *via* initial *N*-acylation of HBTM-2.1 **112** with the arylacetic anhydride to form the corresponding acyl ammonium ion. Deprotonation generates the (*Z*)-enolate, which undergoes stereoselective Michael addition, followed by intramolecular cyclisation, to generate the corresponding heterocyclic species (Figure 52). The sense of stereoinduction in these transformations is consistent with the rationale outlined in Section 3.7.

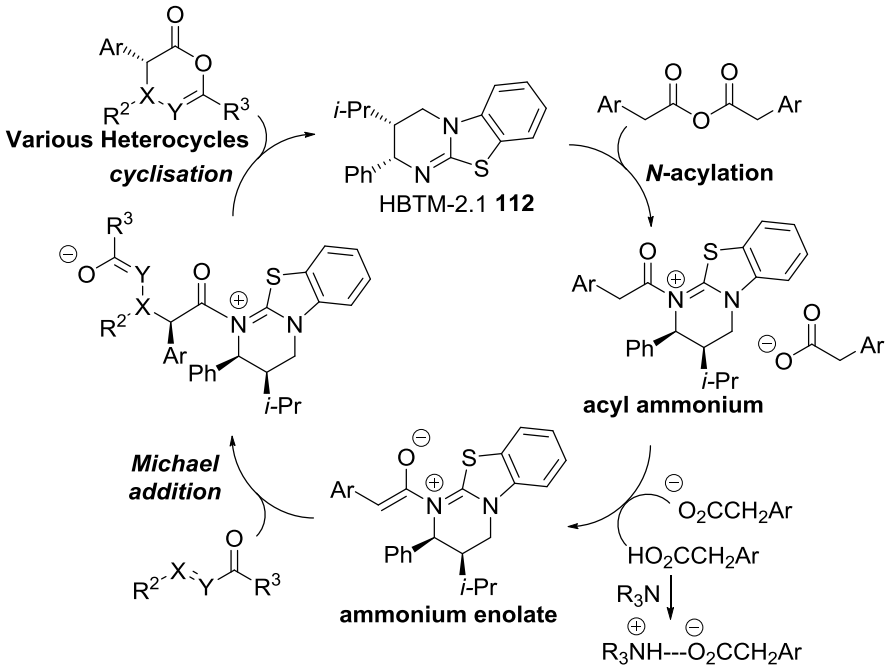


Figure 52: Proposed mechanism for functionalisation of 2-arylacetic acids.

6.4 Conclusions

In conclusion, it has been shown that 2-arylacetic anhydrides are convenient and readily prepared precursors for the formation of C1-ammonium enolates in isothiourea-mediated Michael addition-lactonisation processes. Trifluoromethylenones, α-keto-β,γ-unsaturated esters and *N*-aryl-*N*-aroyldiazenes are reactive Michael accceptors in this

process, with HBTM-2.1 (5 mol%) readily promoting heterocycle formation with high diastereo- and enantiocontrol (up to 95:5 dr, up to >99% ee).[136] This protocol offers a useful and practical alternative to the *in situ* carboxylic acid activation method, in which by-product formation and the amount of sacrificial base used is minimised.

6.5 References and Notes

[42] L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao and Y. R. Chi, *Org. Lett.*, 2012, **14**, 2154-2157.

[136] L. C. Morrill, L. A. Ledingham, J-P. Couturier, J. Bickel, A. D. Harper, C. Fallan and A. D. Smith, *Org. Biomol. Chem.*, 2014, DOI:10.1039/C3OB41869C.

[137] C. Cornaggia, F. Manoni, E. Torrente, S. Tallon and S. J. Connon, *Org. Lett.*, 2012, **14**, 1850-1853.

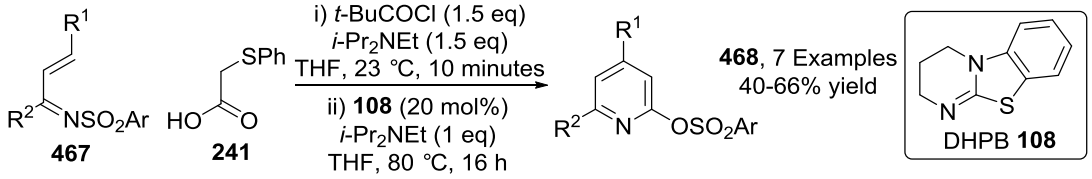
[138] Honours project student Lyndsay Anne Ledingham carried out this work which is documented in her MChem 5th year thesis "Use of Isothioureas in Michael-Addition Lactonisations" and in Ref 136. Undergraduate project student Jean-Philippe Couturier also contributed to this work.

[139] Racemic samples needed for chiral HPLC analysis for all dihydropyranones in this chapter were made using HBTM-2.1 (±)-**112** as catalyst due to the higher diastereoselectivities and cleaner reaction profiles obtained in comparison to DHPB **108**.

[140] Undergraduate project student Jasmine Bickel carried out this work which is documented in Ref 136.

Chapter 7: One-Pot Synthesis of Functionalised Pyridines

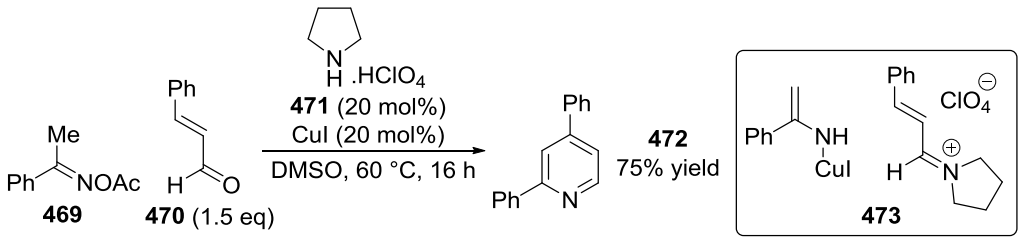
This chapter describes the discovery of reaction conditions to affect the DHPB **108** catalysed Michael addition-lactamisation reaction between (phenylthio)acetic acid **242** and α,β-unsaturated ketimines **467**, giving initially *anti*-dihydropyridone products which undergo subsequent elimination and *N*- to *O*-sulfonyl migration affording a variety of 2,4,6-substituted pyridines **468** in moderate to high yield (Scheme 128).[141] This represents a one-pot organocatalytic route towards highly functionalised pyridines bearing a 2-sulfonate group that is shown to be a highly versatile functional handle. An application of this methodology was demonstrated through the synthesis of a known COX-2 inhibitor.



Scheme 128: One-pot synthesis of functionalised pyridines.

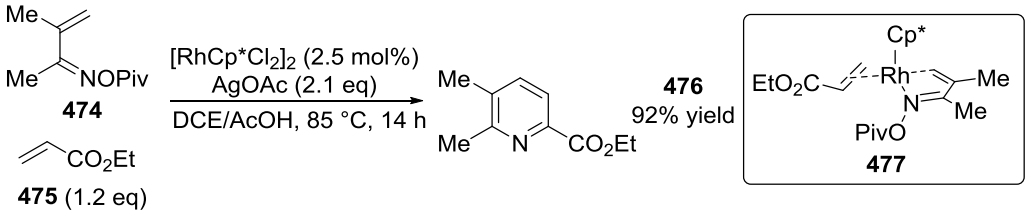
7.1 Introduction

Pyridines are an extremely privileged heterocyclic class commonly found in natural products and functional materials, as well as being important building blocks in both the agrochemical and pharmaceutical industries.[142] Consequently, a vast array of synthetic methods have been successfully developed to access these useful molecules.[143] A recent example from the group of Yoshikai demonstrated the modular synthesis of pyridines from oximes and enals using synergistic copper/iminium catalysis.[144] For example, condensation of oxime **469** with cinnamaldehyde **470**, catalysed by CuI and pyrrolidinium perchlorate **471** gave pyridine **472** in 75% yield *via* dually activated couple **473** (Scheme 129).



Scheme 129: Pyridine formation *via* synergistic copper/iminium catalysis.

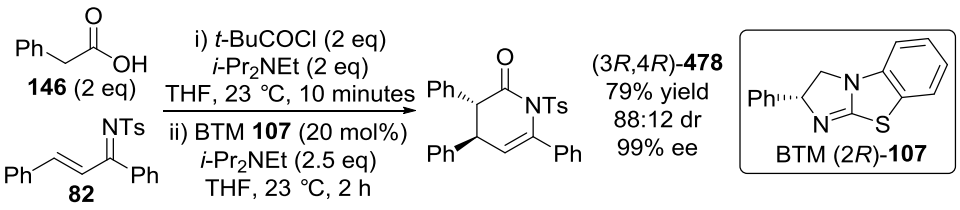
Another recent report from the Rovis group highlights the use of rhodium(III) catalysis to access pyridines from alkenes and α,β-unsaturated oximes.[145] In a representative example, formal [4+2] cycloaddition between *O*-pivaloyl ketoxime **474** and ethyl acrylate **475**, catalysed by $[RhCp^*Cl_2]_2$ (Cp* = pentamethylcyclopentadienyl) with AgOAc as oxidant, gave pyridine **476** in 92% yield with **477** a proposed reaction intermediate (Scheme 130).



Scheme 130: Rh(III)-catalysed pyridine synthesis.

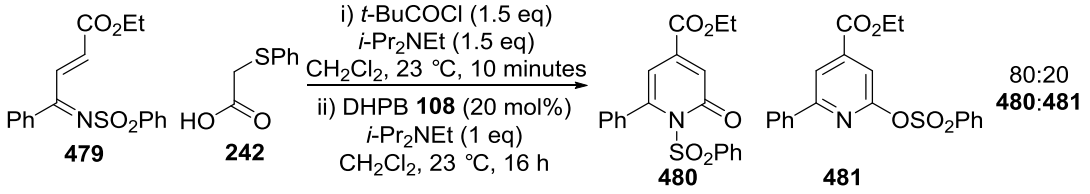
7.2 Previous Work in the Smith Group

In addition to the isothiourea-catalysed intermolecular Michael addition-lactonisation methodology outlined in this thesis, in 2012 the Smith group has also demonstrated an intermolecular Michael addition-lactamisation process using α,β-unsaturated ketimines as Michael acceptors.[146] For example, benzotetramisole (2*R*)-**107** is a highly efficient catalyst for the functionalisation of phenylacetic acid **146**, preactivated to the mixed anhydride with pivaloyl chloride and *i*-Pr_2NEt, with ketimine **82** giving *anti*-dihydropyridone (3*R*,4*R*)-**478** in 79% yield, 88:12 dr and 99% ee (Scheme 131).



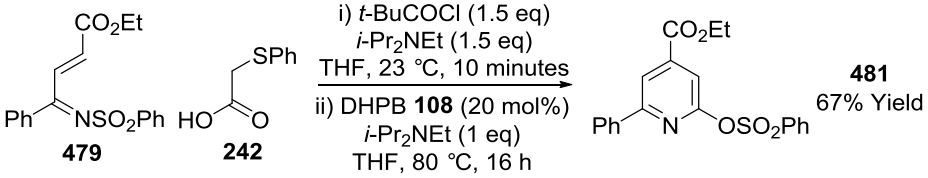
Scheme 131: Isothiourea-catalysed intramolecular Michael addition-lactamisation.

In Section 3.3 it was shown that (phenylthio)acetic acid **241** could be successfully functionalised using the isothiourea-catalysed Michael addition-lactonisation methodology developed to access pyrone **242** after elimination of thiophenol. Within the Smith group it was found that when α,β-unsaturated ketimine **479** was used as the Michael acceptor in this system it was fully consumed and that a mixture of the expected pyridone **480** and unexpected pyridine **481** (80:20 **480**:**481**) were present in the crude reaction mixture by ^{1}H NMR analysis (Scheme 132).[147]



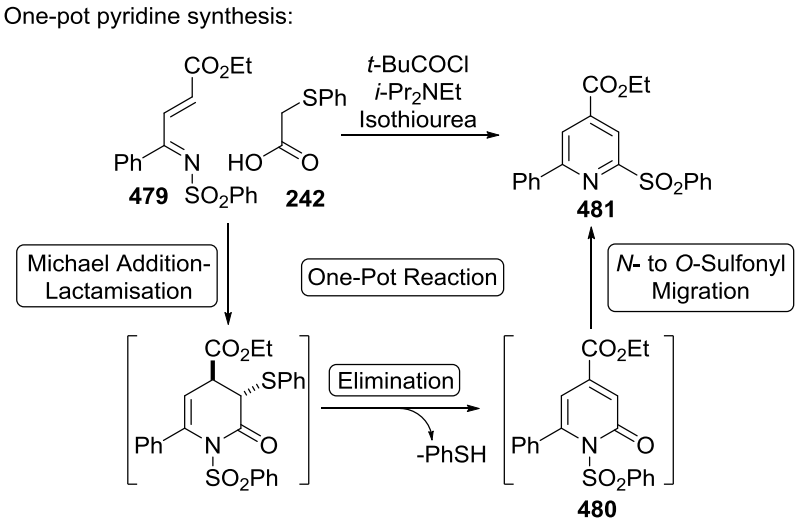
Scheme 132: Initial discovery.

After some optimisation, the Smith group discovered suitable conditions to selectively obtain pyridine products.[148] It was found that, after the initial activation step, heating the reaction mixture at 80 °C in THF for 16 h allowed access to pyridine **481** in 67% yield (Scheme 133). It was noted that increased temperatures were necessary to promote effective *N*- to *O*-sulfonyl migration in this process, with lower temperatures leading to mixtures of intermediate pyridone and desired pyridine. The use of alternative Lewis basic catalysts such as DBU, TBD and DMAP had a negative effect upon the isolated product yield in this process. Additionally, bromo- and chloroacetic acid were tested in this protocol although neither resulted in any conversion towards pyridine **481**.



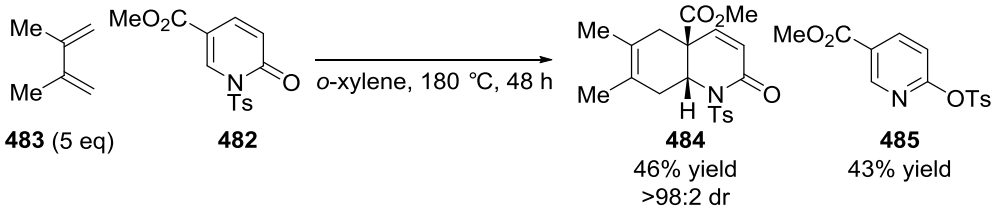
Scheme 133: Optimised reaction conditions for one-pot pyridine synthesis.

It is proposed that this reaction proceeds *via* initial Michael addition-lactamisation followed by elimination of thiophenol to form pyridone **480**. Subsequent *N*- to *O*-sulfonyl migration allows pyridine **481** to be accessed directly in one-pot (Scheme 134). Importantly, in this process the activating sulfonyl group on the ketimine is transformed into a synthetically useful functional handle (the 2-sulfonate group) in the resulting pyridine, allowing subsequent derivatisation into a variety of products.



Scheme 134: One-pot formation of pyridine from 479 and 242.

Several reports regarding the final *N*- to *O*-sulfonyl migration step to form pyridines from pyridones can be found in the literature,[149] with this rearrangement often considered to be an undesired, non productive pathway.[150] For example, the group of Fujita found that the Diels-Alder reaction between pyridone **482** and diene **483** to form bicycle **484** proceeded in 46% yield with significant amounts of the undesired pyridine **485** (arising from *N*- to *O*-sulfonyl migration) also formed (Scheme 135).[151]



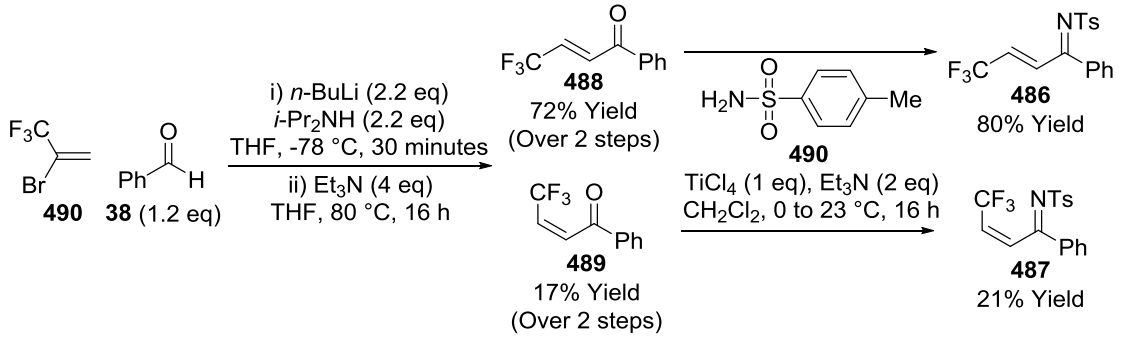
Scheme 135: Literature precedent for *N*- to *O*-sulfonyl migration.

In the context of the organocatalytic functionalisation of (phenylthio)acetic acid, *N*- to *O*-sulfonyl migration of intermediate pyridones would represent a highly desirable transformation, allowing direct access to valuable pyridine products in one-pot.

7.3 Synthesis and Reactivity of α,β-Unsaturated Ketimines 486 and 487

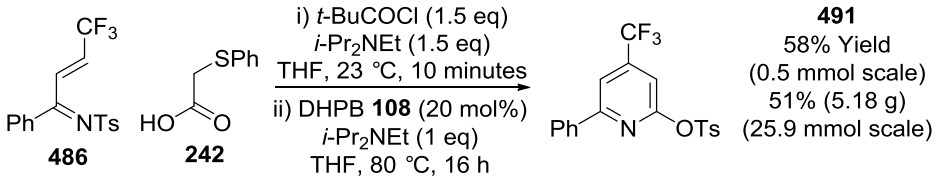
In order to expand the scope of the methodology described above a novel class of α,β-unsaturated ketimines was proposed and synthesised (Scheme 136). Following the procedures outlined by Yamazaki[152,153] trifluoromethyl enones **488** and **489** was obtained *via* a simple two-step procedure. Treatment of alkene **490** with LDA and subsequent reaction with benzaldehyde **38** affords an intermediate alkynyl alcohol that

isomerises to a mixture of (*E*)- and (*Z*)-enones **488** and **489** (80:20 **488**:**489** ratio) after treatment with Et_3N, which were isolated in 72% and 17% yield respectively over 2 steps. Treatment of (*E*)-**488** or (*Z*)-**489** with 4-toluenesulfonamide **490** in the presence of $TiCl_4$ and Et_3N gives α,β-unsaturated ketimines **486** and **487** in 80% and 21% yield respectively after recrystallisation.



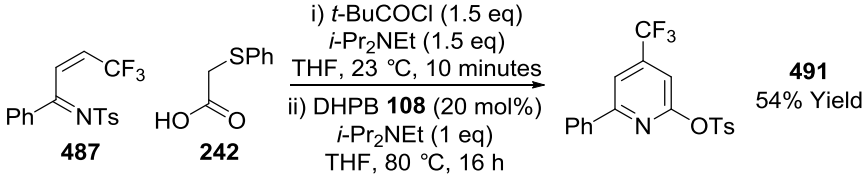
Scheme 136: Synthetic route towards α,β-unsaturated ketimines 486 and 487.

With α,β-unsaturated ketimine **486** in hand, its subsequent use in the isothiourea-catalysed one-pot formation of pyridines was investigated. Using the optimised reaction conditions already developed in the group, DHPB **108** efficiently catalysed the reaction between (phenylthio)acetic acid **242** and α,β-unsaturated ketimine **486** giving pyridine **491** in 58% yield (Scheme 137). It was found that this reaction is scalable, giving >5 g of pyridine **491** when carried out on 25.9 mmol scale.



Scheme 137: Reaction using novel α,β-unsaturated ketimine 486.

The reaction could also be performed using (*Z*)-**487**, forming pyridine **491** in 54% yield indicating the geometry of ketimine starting material is not important for product yield (Scheme 138).



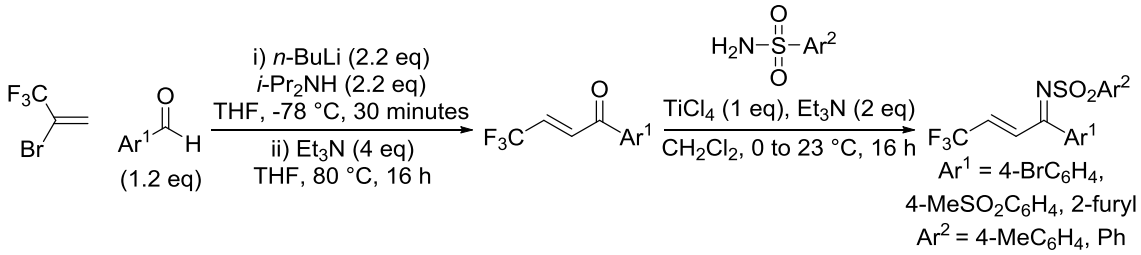
Scheme 138: Reaction using (*Z*)-487.

7.4 Substrate Scope – Variation of the Michael Acceptor

To further probe the generality of this protocol, the isothiourea-mediated one-pot pyridine synthesis procedure was studied using a range of synthesised α,β-unsaturated ketimines and aldimines. The objective being to synthesise and test a range of Michael acceptors which have different substitution patterns including α-substituted, α,β-disubstituted examples in order to access a vast array of pyridine architectures.

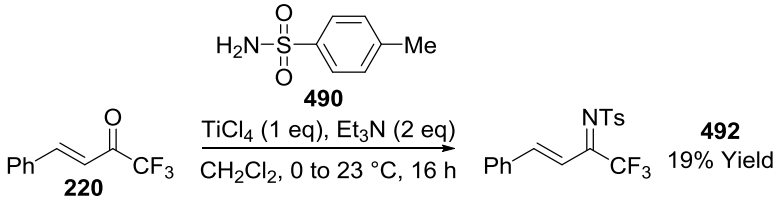
7.4.1 Synthesis and reactivity of CF_3-substituted α,β-unsaturated ketimines

Using the same synthetic route as described previously for α,β-unsaturated ketimine **486**, a variety of others were obtained through variation of the starting aldehyde including *p*-bromobenzaldehyde, *p*-methanesulfonylbenzaldehyde and furfural. Additionally, the *N*-sulfonyl group could also be easily varied by selecting a different sulfonamide (*p*-toluenesulfonamide and benzenesulfonamide) in the second condensation step (Scheme 139).



Scheme 139: Synthetic route towards α,β-unsaturated-β-CF_3-ketimines.

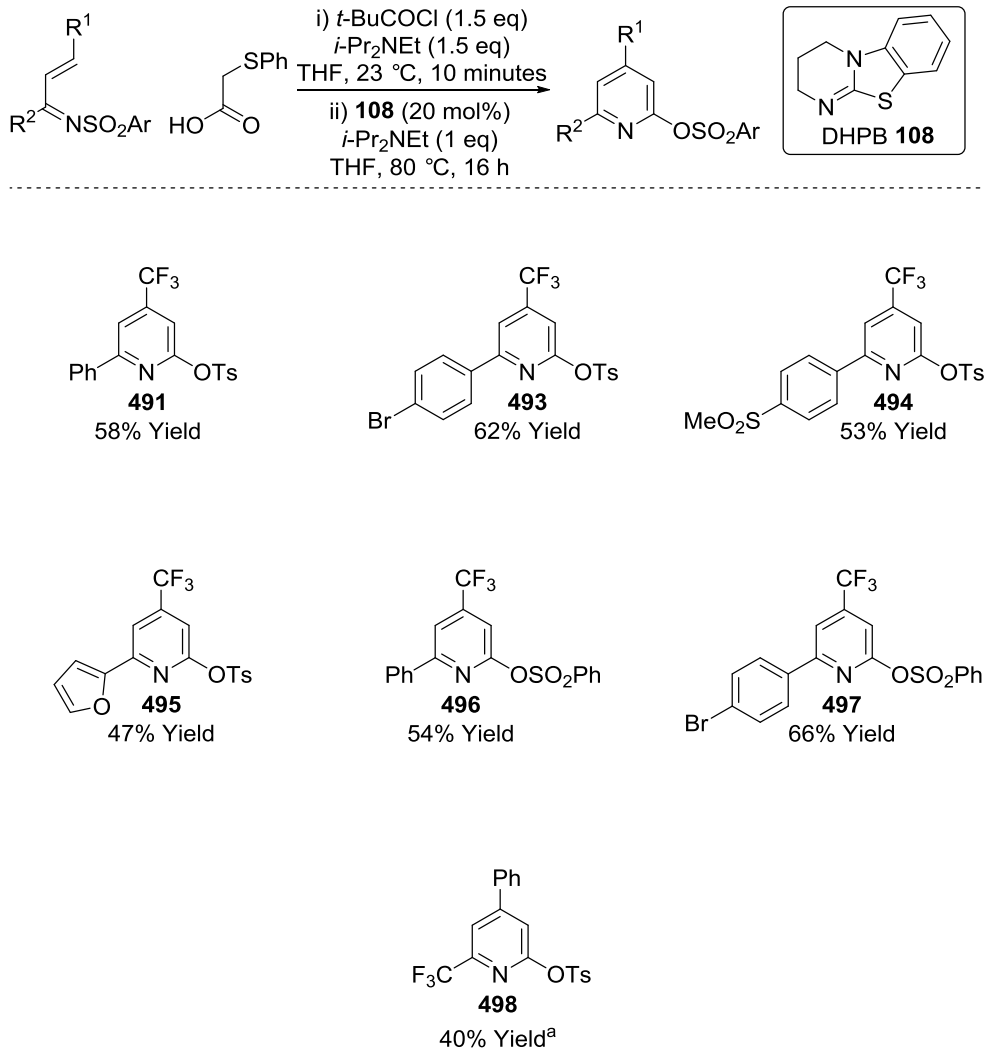
α,β-Unsaturated ketimine **492** was also made *via* the same condensation procedure as described previously for **486** (Scheme 140). Trifluoromethyl enone **220** was used as starting material, giving **492** in a poor 19% yield, largely due to product instability.



Scheme 140: Synthetic route towards α,β-unsaturated ketimine 492.

With a selection of CF_3-substituted-α,β-unsaturated ketimines in hand, their subsequent use in the isothiourea-mediated one-pot pyridine synthesis was evaluated (Table 24). Variation of the aryl group within the β-CF_3-α,β-unsaturated ketimines is tolerated in

this reaction to include phenyl, 4-BrC_6H_4, 4-$SO_2MeC_6H_4$ and 2-furyl substitution, all affording the corresponding pyridines **491** and **493-495** in moderate to good yields (47-66%). The nature of the *N*-sulfonyl group can also be altered (from tosyl to benzenesulfonyl) allowing access to pyridines **496** and **497** in good yields. Isomeric pyridine **498** could also be accessed in 40% yield when **492** is used as starting material although extended heating (48 h) is required to ensure full conversion to **498**. Several other examples of this methodology was demonstrated by a colleague.[148]



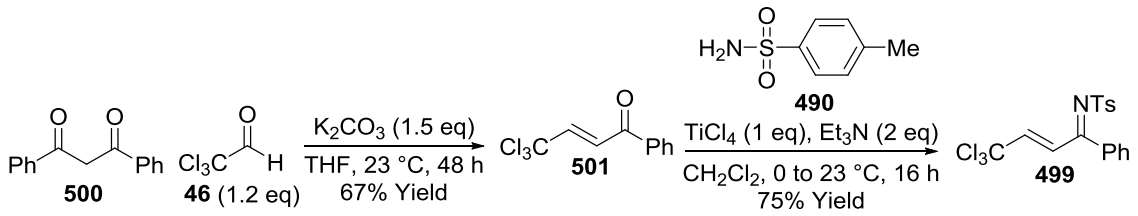
[a] Reaction time of 48 h.

Table 24 - Substrate scope - variation of α,β-unsaturated-β-CF_3-ketimine component.

7.4.2 Synthesis and reactivity of other ketimines and aldimines

α,β-Unsaturated ketimine **499** bearing a β-CCl_3 group was synthesised *via* a two step procedure (Scheme 141). Following the protocol described by Tsuboia,[154] diketone **500**

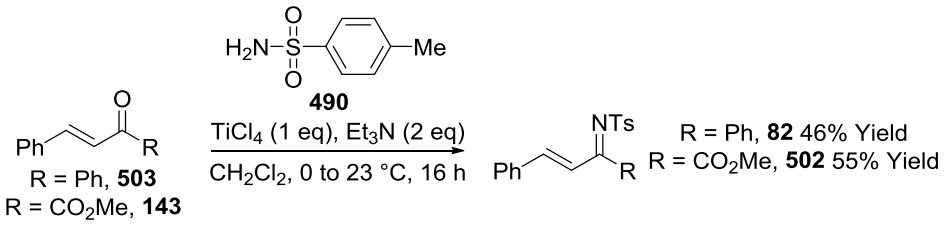
was reacted with chloral **46** in the presence of K_2CO_3 afforded enone **501** in 67% yield. Subsequent condensation with 4-toluenesulfonamide **490** in the presence of $TiCl_4$ and Et_3N gave α,β-unsaturated ketimine **499** in 75% yield.



Scheme 141: Synthetic route towards β-CCl_3-α,β-unsaturated ketimine.

Michael acceptor **499** did not undergo any observable reaction with (phenylthio)acetic aicd, preactivated to the mixed anhydride, after 16 h at 80 °C using DHPB as catalyst. The poorer reactivity may be attributed towards the Michael acceptor not being sufficiently electron-deficient for reaction. Analysis of the crude reaction mixture by ^1H NMR revealed the presence of mixed anhydride derived from (phenylthio)acetic acid and remaining Michael acceptor **499**.

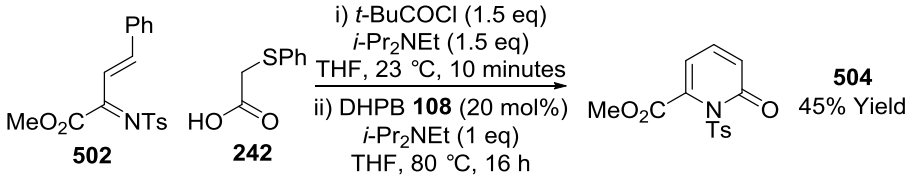
α,β-Unsaturated ketimines **82** and **502** were made *via* the same condensation procedure as described above for **499** (Scheme 142). Commercially available chalcone **503** and α-keto-β,γ-unsaturated ester **143** (synthesised previously) were used as starting materials.



Scheme 142: Synthetic route towards α,β-unsaturated ketimines 82 and 502.

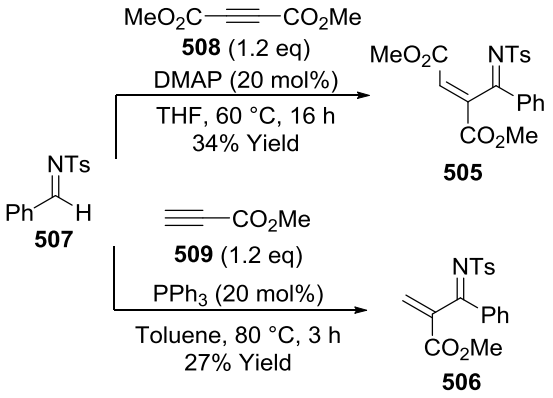
Chalcone-derived imine **82** was unreactive under the optimised one-pot pyridine synthesis conditions, presumably due to being insufficiently electron-deficient, similar to **499**. Interestingly, reaction using α,β-unsaturated ketimine **502** under the standard reaction conditions furnished pyridone **504** in 45% yield which had undergone thiophenol elimination but not the subsequent *N*- to *O*-sulfonyl migration step (Scheme 143). This result suggests that a strongly electron withdrawing substituent at C(6) significantly disfavours the ability of the pyridone to undergo *N*- to *O*-sulfonyl migration to the corresponding pyridine, presumably due to decreased nucleophilicity of the

nitrogen atom. The observation that the formation of pyridine **498** required heating for an extended time (48 h) is in accordance with this result.



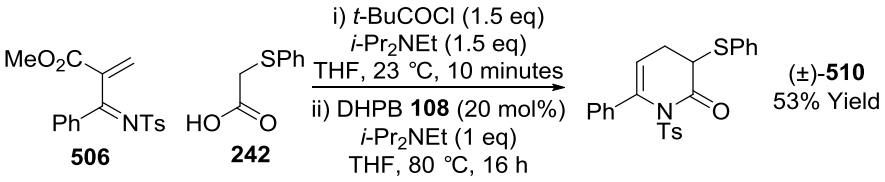
Scheme 143: Isolation of pyridone 504.

α,β-Unsaturated ketimines **505** and **506** substituted at the α-position were made *via* closely related routes (Scheme 144). Following the procedure outlined by Shi,[155] reaction of *N*-tosyl aldimine **507** with dimethyl acetylenedicarboxylate **508** in the presence of DMAP gave ketimine **505** in 34% yield. Alternatively, following the protocol described by Tong,[156] reaction of the same *N*-tosyl aldimine **507** with methyl propiolate **509** and PPh_3 affords ketimine **506** in 27% yield.



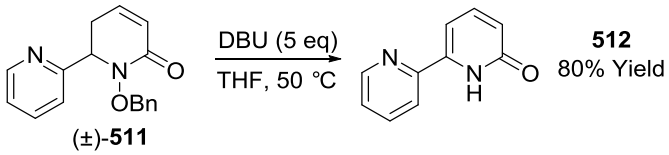
Scheme 144: Synthetic route towards α,β-unsaturated ketimines 505 and 506.

α,β-Disubstituted Michael acceptor **505** did not undergo any observable reaction with (phenylthio)acetic acid, preactivated to the mixed anhydride, after 16 h at 80 °C using DHPB as catalyst. The poor reactivity may be attributed towards the Michael acceptor being too sterically encumbered for efficient reaction. However, reaction using β-unsubstituted ketimine **506** under the standard reaction conditions furnished lactam (±)-**510** in 53% yield which had not undergone the thiophenol elimination and *N*- to *O*-sulfonyl migration steps (Scheme 145). This result suggests that a substituent at C(4) is necessary to acidify the C(4) proton allowing elimination of thiophenol to occur under the reaction conditions.



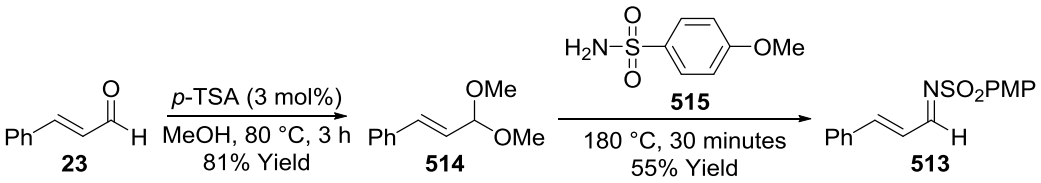
Scheme 145: Isolation of lactam (±)-510.

This observation can be related to an observation made by Donohoe and co-workers who identified the need for an acidifying group at C(6) to facilitate the elimination of benzyl alcohol from dihydropyridone **511** to form pyridone **512** (Scheme 146).[157] If the electron-withdrawing 2-pyridyl substituent is replaced by a phenyl substituent the elimination does not proceed.



Scheme 146: Elimination of benzyl alcohol in a related system.

Finally α,β-unsaturated aldimine **513** was synthesised according to the two step procedure outlined by Bode.[158] Reaction of cinnamaldehyde **23** with *p*-TSA in MeOH afforded acetal **514** which was heated with 4-methoxybenzenesulfonamide **515** to give aldimine **513** in 45% yield over 2 steps (Scheme 147).



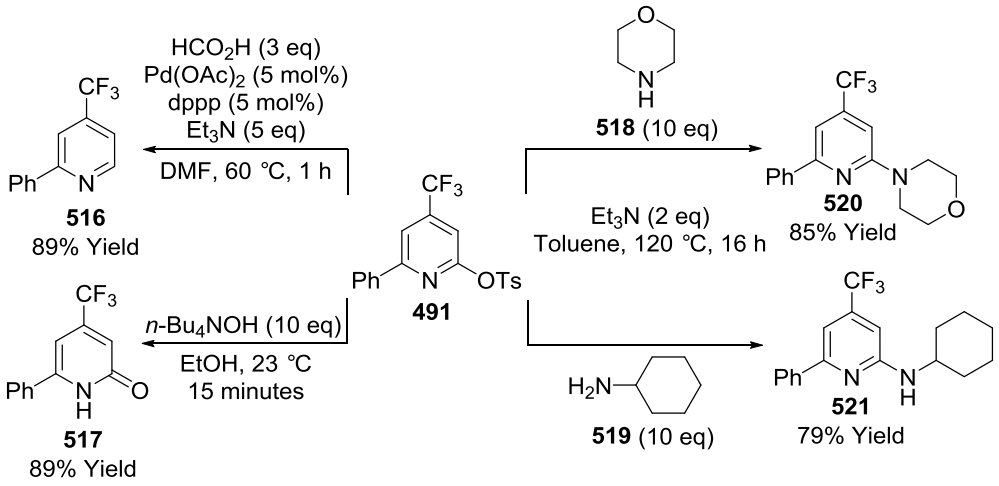
Scheme 147: Synthetic route towards α,β-unsaturated aldimine 513.

Unfortunately, α,β-unsaturated aldimine **513** was not a suitable Michael acceptor for this process, giving no observable conversion to the desired pyridine product after 16 h at 80 °C using DHPB as catalyst. Analysis of the crude reaction mixture by ^{1}H NMR revealed the presence of the mixed anhydride derived from (phenylthio)acetic acid and remaining **513**.

7.5 Derivatisations

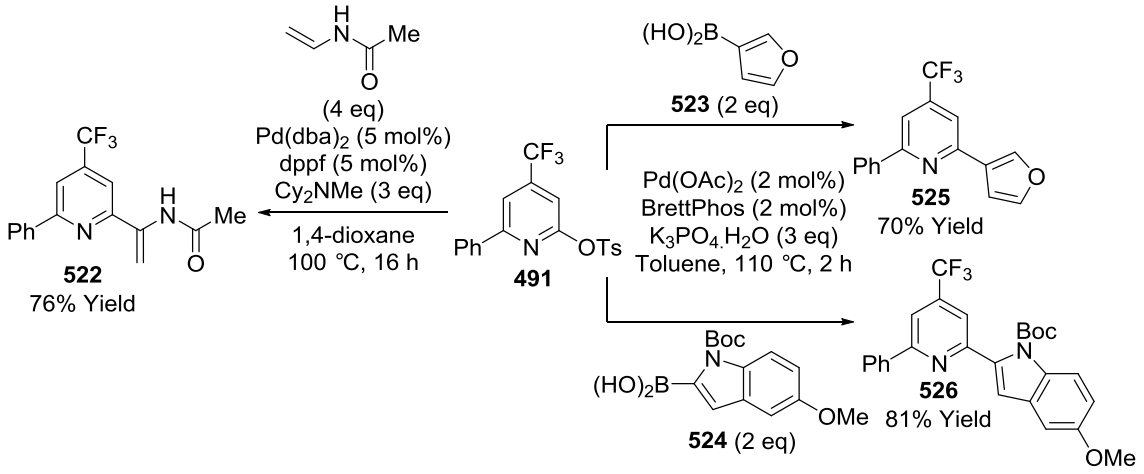
7.5.1 Elaboration of Pyridine 491

The synthetic utility of the newly installed 2-sulfonate functional handle within pyridine **491** was next demonstrated through a series of product derivatisations. Firstly, following the procedure described by Yamamoto,[159] pyridine **491** can be reduced using $Pd(OAc)_2$, dppp and HCO_2H as proton source to give 2,4-disubstituted pyridine **516** in 89% yield (Scheme 148). Pyridine **491** can also be hydrolysed using *n*-Bu_4NOH to give pyridone **517** in 89% yield as described by Grierson.[160] Alternatively, S_NAr with either morpholine **518** or cyclohexylamine **519** gives pyridines **520** and **521** in 85% and 79% yield respectively.



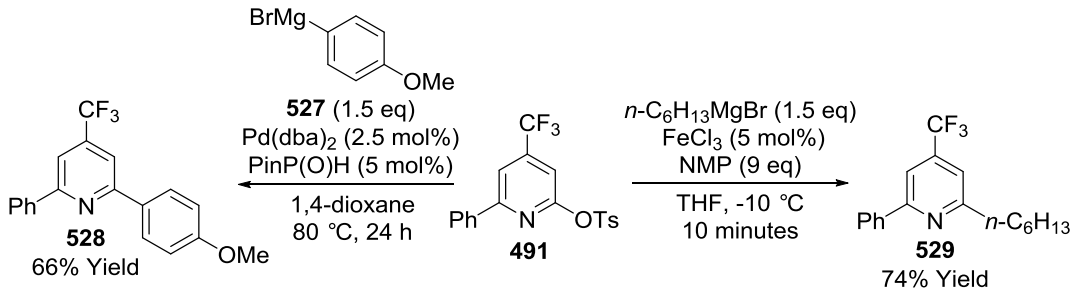
Scheme 148: Reduction, hydrolysis and S_NAr derivatisations.

Pyridine **491** was shown to be compatible with traditional cross-coupling methodologies, leading to diverse 2,4,6-substituted pyridines (Scheme 149). For example, following the procedure described by Skrydstrup,[161] **491** undergoes Mizoroki-Heck reaction with *N*-vinylacetamide using $Pd(dba)_2$ and dppf as ligand, affording pyridine **522** in 76% yield. In accordance with the procedure described by Buchwald,[162] pyridine **491** also undergoes Suzuki coupling with either 3-furanylboronic acid **523** or indole-derived boronic acid **524**, giving pyridines **525** and **526** in 70% and 81% respectively using $Pd(OAc)_2$ and BrettPhos as ligand.



Scheme 149: Mizoroki-Heck and Suzuki couplings.

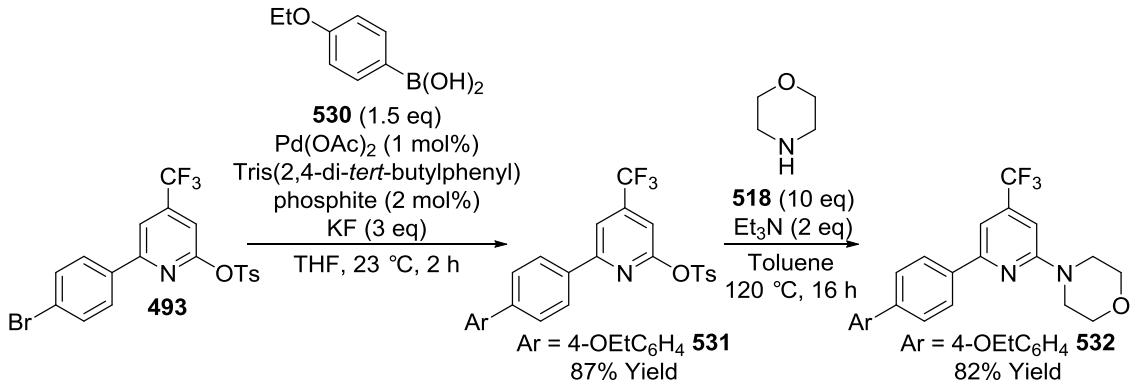
Following the procedure described by Ackermann,[163] Kumada cross-coupling of pyridine **491** with 4-methoxyphenylmagensium bromide **527** using $Pd(dba)_2$ and PinP(O)H as ligand, afforded pyridine **528** in 66% yield (Scheme 150). In addition to sp^2-sp^2 coupling reactions, Fe-catalysed sp^2-sp^3 coupling of pyridine **491** with *n*-hexylmagnesium bromide, as described by the group of Skrydstrup,[164] gave **529** in 74% yield.



Scheme 159: Kumada and Fe-catalysed cross-couplings.

7.5.2 Regiodivergence

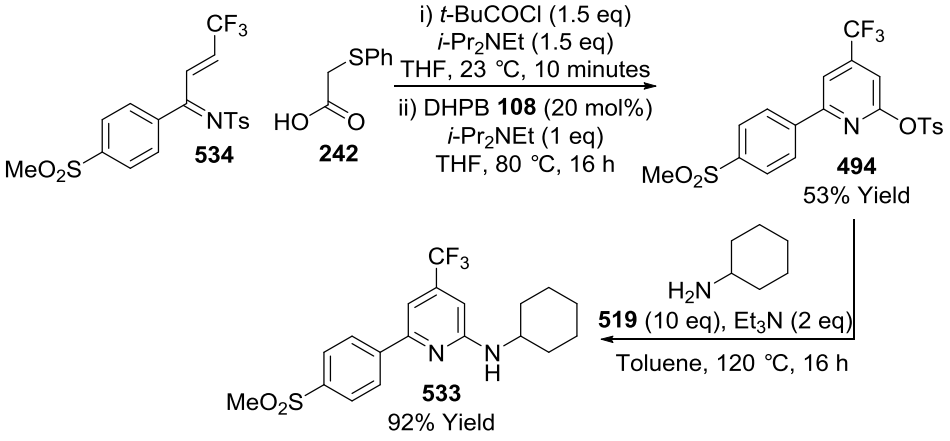
To further demonstrate the potential of these scaffolds the sequential functionalisation of pyridine **493** was explored. Selective arylation of the aryl-bromide through Suzuki coupling with 4-ethoxyphenylboronic acid **530** was readily achieved using the conditions outlined by Buchwald,[165] affording pyridine **531** in 87% yield, leaving the 2-sulfonate functional group untouched for further derivatisation through S_NAr with morpholine giving **532** in 82% yield (Scheme 151). This illustrates how this methodology can be used to build up bespoke pyridines in rapid fashion.



Scheme 151: Selective sequential pyridine derivatisations.

7.5.3 Synthesis of COX-2 Inhibitor

The utility of this approach for the synthesis of a medicinally relevant pyridine containing molecule was illustrated (Scheme 152). For example, pyridine **533**, which possesses activity as a COX-2 inhibitor (<0.5 mM activity, >100 fold selectivity for COX-2 vs. COX-1) for the treatment of depressive disorders,[166] can be made in 49% yield over two synthetic steps from α,β-unsaturated ketimine **534** (14% overall yield from commercially available starting materials).



Scheme 152: Synthesis of biologically activity pyridine 533.

7.6 Reaction Mechanism

The proposed reaction mechanism proceeds *via* initial formation of mixed anhydride **535** from (phenylthio)acetic acid **242** and pivaloyl chloride, followed by *N*-acylation of DHPB **108** to generate the corresponding acyl ammonium ion **536**. Deprotonation generates (*Z*)-enolate **537**, which undergoes Michael addition with the α,β-unsaturated ketimine **467**, followed by intramolecular lactamisation, to generate the corresponding dihydropyridone **538** and regenerate DHPB **108** (Figure 53). Subsequent elimination of

thiophenol gives pyridone **539**, which undergoes thermally promoted *N*- to *O*-sulfonyl migration to afford pyridine **540**.

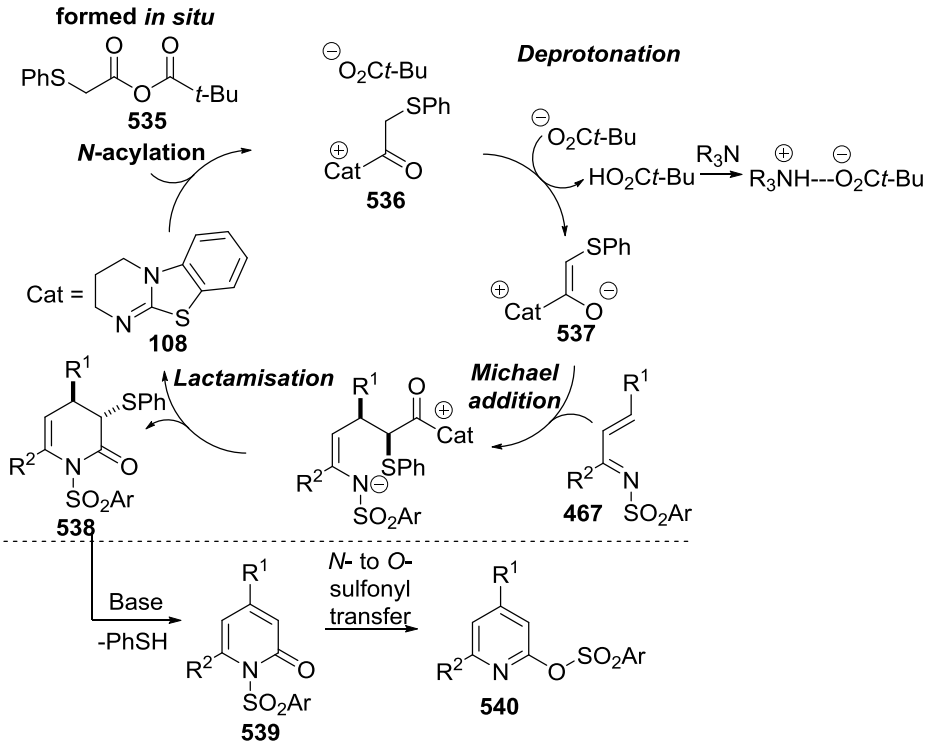
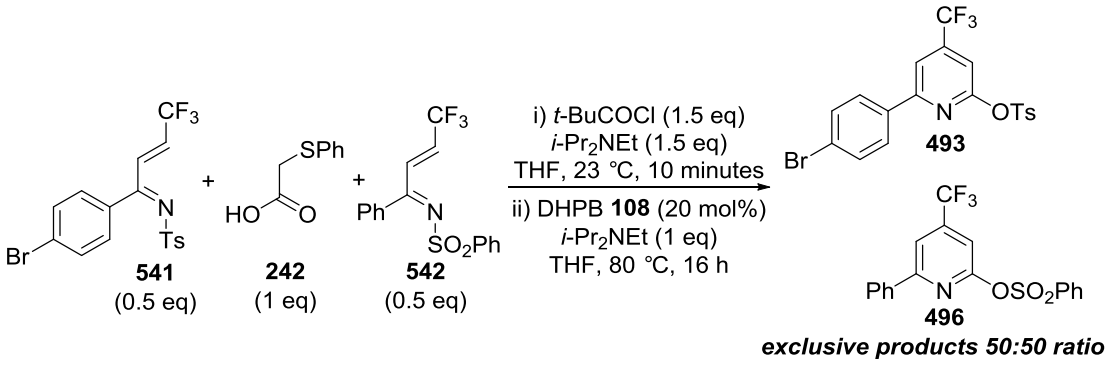


Figure 53: Proposed mechanism for one-pot pyridine formation.

Within the literature, sporadic examples of the key *N*- to *O*-sulfonyl rearrangement utilised in this process have been observed, usually as an undesired non-productive pathway in thermally promoted Diels-Alder reactions of sulfonyl pyridones.[150] To understand this process further, a crossover experiment was performed to determine if the *N*- to *O*-sulfonyl migration process involves an *intra*- or *intermolecular* transfer. Reaction of (phenylthio)acetic acid **242** (1 eq) with a 50:50 mixture of ketimines **541** and **542** under optimised conditions led exclusively to a 50:50 mixture of pyridines **493** and **496**, consistent with *intramolecular N*- to *O*-sulfonyl transfer from an intermediate pyridone being involved within this process (Scheme 153).



Scheme 153: Crossover experiment indicating *intramolecular N*- to *O*-sulfonyl migration.

7.7 Conclusions

In conclusion, it has been shown that DHPB **108** promotes the one-pot synthesis of 2,4,6-subsituted pyridines bearing a readily derivatised 2-sulfonate functionality from (phenylthio)acetic acid and a range of α,β-unsaturated ketimines.[141] This process proceeds *via* intermolecular Michael addition-lactamisation, thiophenyl elimination and *N*- to *O*-intramolecular sulfonyl migration, with the *N*-sulfonyl activating group within the α,β-unsaturated ketimine transformed into a valuable 2-sulfonate functional handle in the resulting pyridine. Functionalisation of this group *via* various methodologies allows the rapid assembly of both novel and biologically relevant pyridines.

7.8 References and Notes

[141] D. G. Stark, L. C. Morrill. P-P. Yeh, A. M. Z. Slawin, T. J. C. O'Riordan and A. D. Smith, *Angew. Chem. Int. Ed.*, 2013, **125**, 11856-11860.

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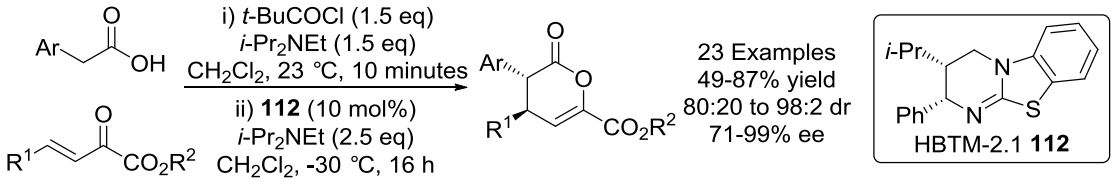
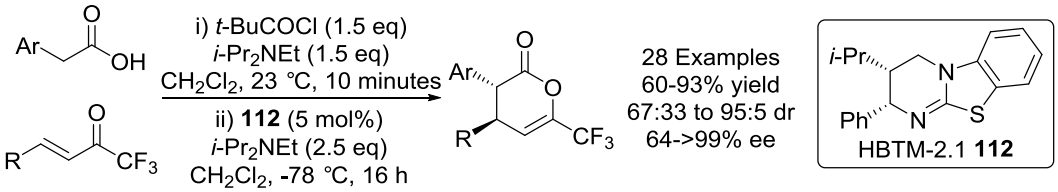
Chapter 8: Conclusions and Outlook

This thesis has documented investigations into the ability of isothioureas to act as organocatalysts in the functionalisation of carboxylic acid and anhydride starting materials *via* C1-ammonium enolates. A variety of methodologies have been developed which add to the current literature on formal [4+2] cycloadditions catalysed by tertiary amines.

Firstly the isothiourea-catalysed formal [4+2] cycloaddition between arylacetic acids and α-keto-β,γ-unsaturated esters has been reported. This methodology represents the first time that carboxylic acid derived ammonium enolates have been successfully applied towards an intermolecular reaction process. The protocol is scalable and can be carried out using open flasks and bench-grade solvents. A variety of *anti*-dihydropyranones were accessed in high yield (49-87%) and with good diastereo- and enantioselectivity (up to 98:2 dr, up to 99% ee).

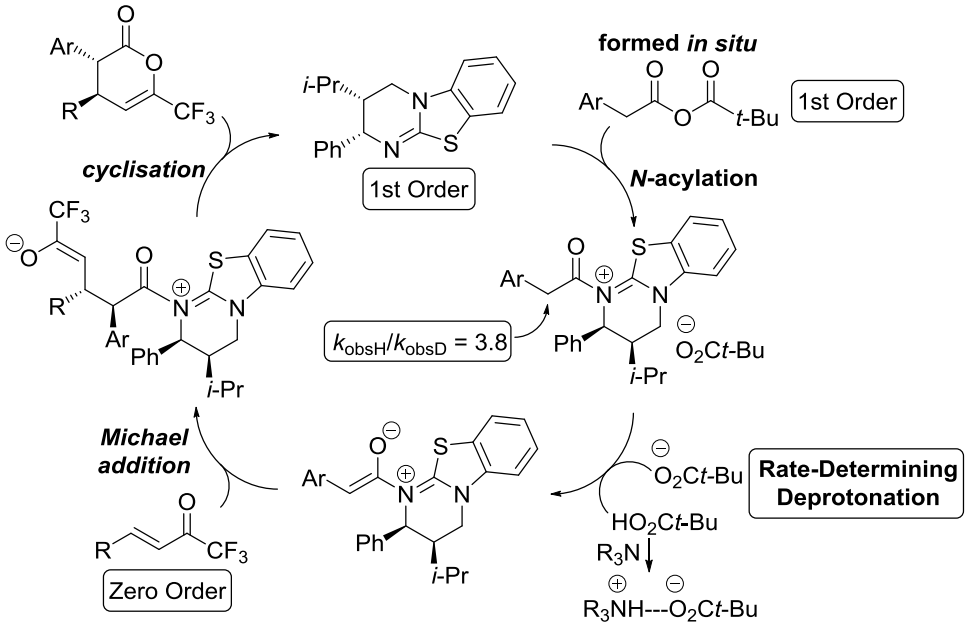


Subsequent studies focused on the use of trifluoromethyl enones as Michael acceptors in the isothiourea-catalysed formal [4+2] cycloaddition protocol with arylacetic acids. A range of C(6)-trifluoromethyl *anti*-dihydropyranones were accessed in high yield (60-93%) with good diastereo- and enantioselectivity (up to 95:5 dr, up to >99% ee).

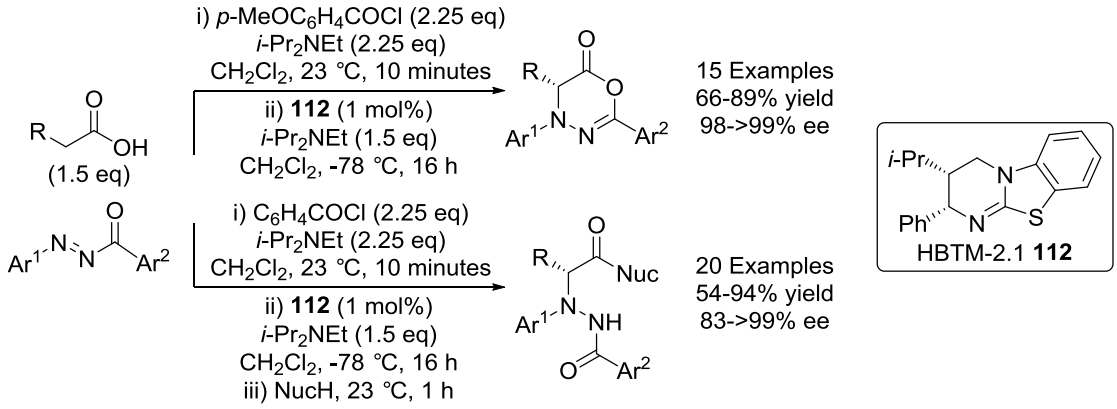


Detailed mechanistic studies were carried out, revealing that the process was stereospecific, with the diastereoisomer of product formed dependent upon the configuration of trifluoromethyl enone used. A variety of product derivatisations were demonstrated including those which introduce additional trifluoromethyl-bearing stereogenic centres with high diastereoselectivity. Kinetic studies indicated that this Michael addition-lactonisation process is first order with respect to both *in situ* formed

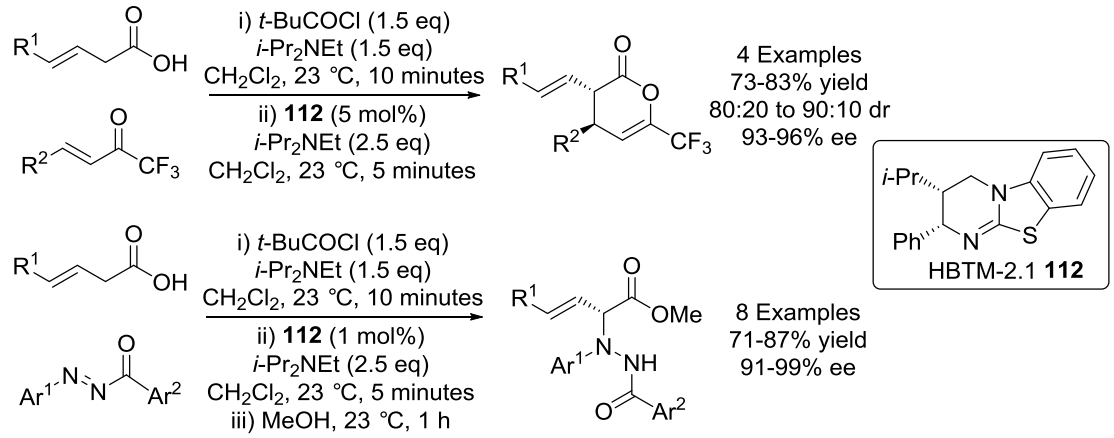
anhydride and catalyst concentration, with a primary kinetic isotope effect observed using α,α-di-deuterio 4-fluorophenylacetic acid. DFT computational studies support a rate-determining formation of a reactive ammonium enolate prior to a stereochemistry-determining enone conjugate-addition step.



In addition to C-C bond-forming processes, it was shown that isothioureas efficiently catalyse the α-amination of carboxylic acids *via* a formal [4+2] cycloaddition process with *N*-aryl-*N*-aroyldiazene Michael acceptors using low catalyst loadings (as low as 0.25%). Either 1,3,4-oxadiazin-6-ones or *N*-protected α-substituted amino acid derivatives (upon ring opening) were accessed in high yields and excellent enantioselectivity (up to >99% ee). Importantly, the scope of this methodology was expanded to allow the direct functionalisation of carboxylic acids bearing α-heteroatom and alkyl substitution for the first time in addition to aryl substitution. The synthetic utility of the hydrazide products was demonstrated through their derivatisation into a range of bespoke functionalised *N*-aryl-α-arylglycine derivatives in high enantiopurity (up to 99% ee).

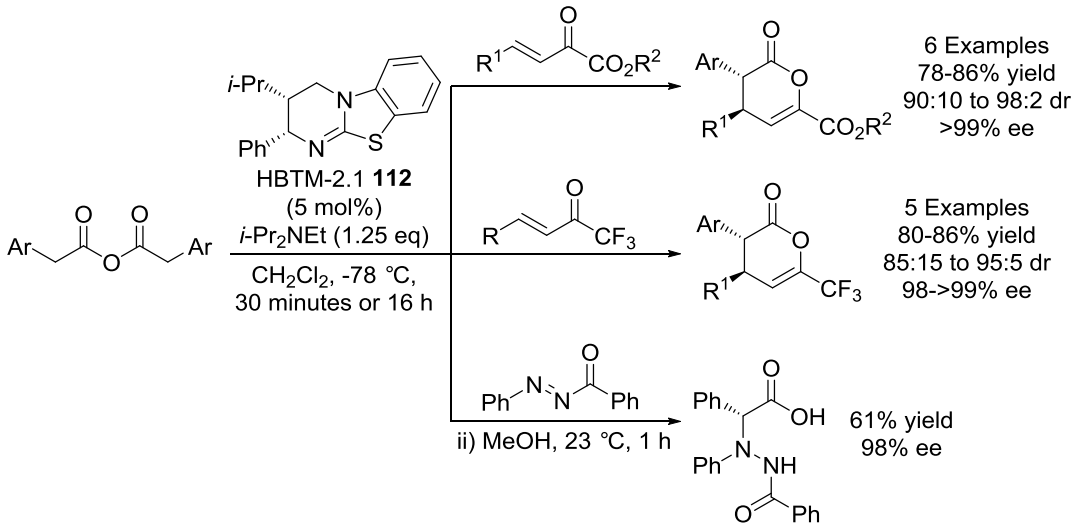


Efforts to further expand the acid scope of this methodology led to the discovery that 3-alkenoic acids are suitable precursors to isothiourea-derived C1-ammonium dienolates that react to give exclusively α-functionalised products in a range of formal [2+2] and [4+2] cycloadditions. This contrasts with all other C1-ammonium dienolates reported in the literature that react at the γ-position. It was shown that HBTM-2.1 efficiently catalysed the α-functionalisation of 3-alkenoic acids through formal [4+2] cycloadditions with both trifluoromethyl enones and *N*-aryl-*N*-aroyl diazenes in good yield and with high diastereo- and enantiocontrol (up to 90:10 dr, up to 99% ee). The simple, two-step elaboration of stereodefined hydrazides into aza-sugar analogues without erosion of enantiopurity was also demonstrated.

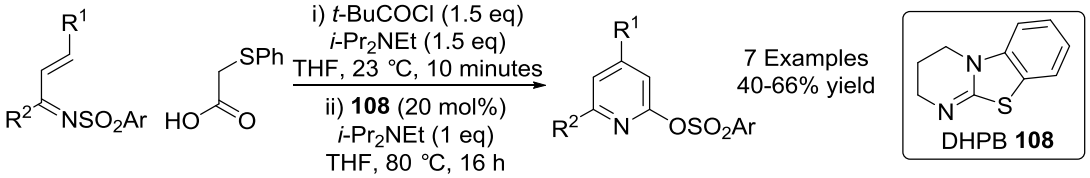


2-Arylacetic anhydrides were found to be convenient and readily prepared precursors to isothiourea-derived C1-ammonium enolates. HBTM-2.1 efficiently catalysed the formal [4+2] cycloadditions between 2-arylacetic anhydrides and a range of electron deficient Michael acceptors, giving stereodefined products in good yield and with high diastereo- and enantiocontrol (up to 95:5 dr, up to >99% ee). This protocol offers a useful and

practical alternative to the *in situ* carboxylic acid activation method, in which by-product formation and the amount of sacrificial base used is minimised.



Finally it was found that the isothiourea-catalysed formal [4+2] cycloaddition methodology developed could also be utilised to access important aromatic heterocycles. DHPB was shown to promote the one-pot synthesis of 2,4,6-subsituted pyridines bearing a readily derivatised 2-sulfonate functionality from (phenylthio)acetic acid and a range of α,β-unsaturated ketimines in moderate yields (40-66%). This proceeds *via* intermolecular Michael addition-lactamisation, thiophenyl elimination and *N*- to *O*-intramolecular sulfonyl migration, with the *N*-sulfonyl activating group within the α,β-unsaturated ketimine transformed into a valuable 2-sulfonate functional handle in the resulting pyridine. This represents a novel one-pot organocatalytic route towards highly functionalised pyridines. Functionalisation of 2-sulfonate group *via* various methodologies allows the rapid assembly of both novel and biologically relevant pyridines. An application of this methodology was demonstrated through the synthesis of a known COX-2 inhibitor.



At the outset of this thesis in late 2010, carboxylic acid starting materials had been sparsely utilised as ammonium enolate precursors with Romo and co-workers the only contributor, demonstrating a variety of elegant *intramolecular* nucleophile-catalysed

aldol-lactonisation (NCAL) procedures. Additionally, at the outset of these studies, isothioureas had not been demonstrated in any catalytic generation of ammonium enolates. This thesis details investigations that significantly add to the existing research within the ammonium enolate literature. For the first time, carboxylic acid-derived ammonium enolates have been applied towards *intermolecular* reactions. Additionally, isothioureas have been shown to be highly useful nucleophilic Lewis base organocatalysts for the generation of highly defined C1-ammonium enolates that are capable of imparting exceptionally high levels of stereocontrol upon reactions.

It appears likely that building upon this established precedent further, undocumented reactions employing isothiourea-derived C1-ammonium enolates will be investigated. One can envisage many other suitable electrophilic species which may act as suitable partners in other formal [4+2], [2+2] and perhaps the less common formal [3+2] cycloadditions. Research is currently underway to investigate the potential for these enolates to participate in formal [3+2] cycloaddition processes. Additionally, it would be of widespread interest to the scientific community if isothioureas could be demonstrated in a wider range of organocatalytic methodologies. For instance, are isothioureas suitable Lewis bases to access the C2- or C3-ammonium enolate reaction modes that have previously been accessed mainly through the use of cinchona alkaloids? These are the types of questions that are likely to be addressed by researchers in the field over the coming years.

Chapter 9: Experimental

9.1 General Information

Reactions involving moisture sensitive reagents were carried out under an argon atmosphere using standard vacuum line techniques in addition to dry solvents. All glassware used was flame dried and cooled under vacuum.

For moisture sensitive reactions, solvents (THF, CH_2Cl_2, toluene, hexane and Et_2O) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and −78 °C were obtained using ice/water and CO_2(s)/acetone baths respectively. Temperatures of 0 °C to −50 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reflux conditions were obtained using an oil bath equipped with a contact thermometer. *In vacuo* refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC_2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F_{254} silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz, ^{1}H, 75 MHz $^{13}C\{1H\}$, 282 MHz $^{19}F\{1H\}$), Bruker Avance II 400 (400 MHz, ^{1}H, 100 MHz $^{13}C\{1H\}$, 376 MHz $^{19}F\{1H\}$) or a Bruker Avance II 400 (500 MHz, ^{1}H, 125 MHz $^{13}C\{1H\}$, 470 MHz $^{19}F\{1H\}$) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent as the internal standard. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), ABq (AB quartet), oct (octet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets, dt (doublet of triplets), dq (doublet of quartets) and td (triplet of doublets). The abbreviation Ar is used to denote aromatic, Ph to denote phenyl, Bn to denote benzyl, br to denote broad and *app* to denote apparent. NMR peak assignments were confirmed using 2D 1H correlated spectroscopy (COSY), 2D 1H nuclear Overhauser effect spectroscopy (NOESY), 2D

1H−13C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D 1H−13C heteronuclear single quantum coherence (HSQC) where necessary.

Infrared spectra (ν_{max}/cm^{-1}) were recorded on either a Perkin-Elmer Spectrum GX FT-IR spectrometer using either thin films on NaCl plates or KBr discs or a Shimadzu IRAffinity-1 using a Pike attenuated total reflectance (ATR) accessory. Only the characteristic peaks are quoted.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected. *Dec* refers to decomposition.

HPLC analyses were obtained on two separate machines; a Gilson HPLC consisting of a Gilson 305 pump, Gilson 306 pump, Gilson 811C dynamic mixer, Gilson 805 manometric module, Gilson 401C dilutor, Gilson 213XL sample injector and sample detection was performed with a Gilson 118 UV/vis detector while the temperature was assumed to be 23 °C; a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25-40 °C. Separation was achieved using DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns. All chiral HPLC traces were compared to the authentic racemic trace prepared in analogous fashion.

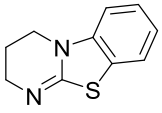
Mass spectrometry (*m/z*) data were acquired by electrospray ionisation (ESI), chemical ionisation (CI), electron impact (EI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionization (APCI) or nanospray ionisation (NSI) either at the University of St Andrews or the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS were carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, low resolution NSI MS was carried out on a Micromass Quattro II spectrometer and high resolution NSI MS on a Thermofisher LTQ Orbitrap XL spectrometer.

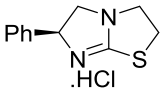
Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at rt.

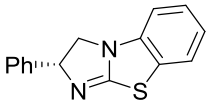
9.2 Experimental for Chapter 2

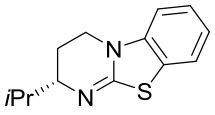
9.2.1 Experimental Procedures and Characterisation Data

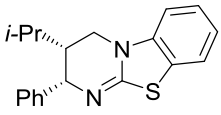
Isothiourea Catalysts


DHPB **108**


Tetramisole.HCl (2*S*)-**106**

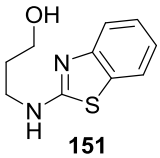

Benzotetramisole (2*R*)-**107**


(2*S*)-**148**


HBTM-2.1 (2*S*,3*R*)-**112**

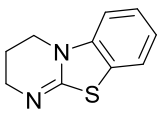
Tetramisole hydrochloride (2*S*)-**106** was used as supplied. Benzotetramisole (2*R*)-**107** and (2*S*)-**148** were readily available in the group. DHPB **108** and HBTM-2.1 (2*S*,3*R*)-**112** were synthesised as outlined below.

3-(benzo[d]thiazol-2-ylamino)propan-1-ol


151

To a sealed pressure tube was charged 2-chlorobenzothiazole (1.02 mL, 8.00 mmol), *i*-Pr_2NEt (2.11 mL, 12.0 mmol) and 3-amino-1-propanol (0.61 mL, 8.00 mmol). The tubes were purged with argon and then sealed and heated at 110 °C for 24 h. The reaction mixture was allowed to cool to rt. Chromatographic purification (eluent *i*-PrOH:CH_2Cl_2 10:90) gave alcohol **151** as a white solid (1.24 g, 80%); mp 120-122 °C; {lit.[52] mp 123-123.5 °C}; δ_H (400 MHz, $CDCl_3$) 1.82-1.88 (2H, m, $CH_2CH_2CH_2$), 3.69 (2H, t, *J* 6.0, CH_2), 3.74 (2H, t, *J* 5.6, CH_2), 7.09 (1H, ddd, *J* 7.9, 7.4, 1.2, Ar(6)*H*), 7.29 (1H, ddd, *J* 8.1, 7.4, 1.3, Ar(5)*H*), 7.50-7.56 (2H, m, Ar(4)*H* and Ar(7)*H*). Spectroscopic data are in accordance with the literature.[52]

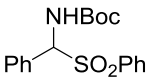
3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine


108

To a solution of alcohol **151** (4.97 g, 25.6 mmol) in dry CH_2Cl_2 (250 mL) at 0 °C under argon was added Et_3N (10.7 mL, 76.8 mmol) and methanesulfonyl chloride (2.99 mL, 38.4 mmol). The reaction mixture was allowed to stir at 0 °C for 1 h. The solution was then warmed to rt and MeOH (6 mL) was added to quench any remaining

methanesulfonyl chloride. A further portion of Et_3N (42.0 mL, 0.30 mol) was added to the solution and it was stirred at reflux for 16 h. The cooled reaction mixture was washed with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_3N:*i*-PrOH:CH_2Cl_2 1:9:89) gave DHPB **108** as a white solid (4.41 g, 91%); mp 120-121 °C; {lit.[52] mp 122-123 °C}; δ_H (400 MHz, $CDCl_3$) 1.95 (2H, quintet, *J* 5.7, $CH_2CH_2CH_2$), 3.50 (2H, t, *J* 5.6, =NCH_2), 3.70 (2H, t, *J* 6.1 NCH_2), 6.66 (1H, dd, *J* 8.0, 0.7, Ar(9)*H*), 6.91 (1H, td, *J* 7.6, 1.1, Ar(7)*H*), 7.11 (1H, td, *J* 7.6, 1.1, Ar(8)*H*), 7.19-7.22 (1H, m, Ar(6)*H*). Spectroscopic data are in accordance with the literature.[52]

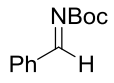
tert-butyl (phenyl(phenylsulfonyl)methyl)carbamate



153

To a stirred solution of *t*-butyl carbamate (2.68 g, 22.9 mmol) in THF (10 mL) under argon was added H_2O (20 mL), sodium benzenesulfinate (3.76 g, 22.9 mmol) and benzaldehyde (2.37 mL, 23.3 mmol) sequentially followed by formic acid (5.00 mL, 133 mmol). The reaction mixture was stirred under nitrogen for 16 h at rt. The resulting precipitate was filtered and washed with H_2O. Trituration with hexane/CH_2Cl_2 (91/9) gave sulfone **153** as a white solid (6.49 g, 82%); mp 158-160 °C (hexane/CH_2Cl_2); {lit.[67] mp 153-154 °C (hexane/CH_2Cl_2)}; δ_H (400 MHz, $(CD_3)_2CO$) 1.26 (9H, s, $C(CH_3)_3$), 5.75-5.94 (2H, m, C*H* and N*H*), 7.39-7.46 (5H, m, Ar*H*), 7.52-7.56 (2H, m, SO_2Ar(3,5)*H*), 7.62-7.66 (1H m, SO_2Ar(4)*H*), 7.90-7.92 (2H, m, SO_2Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[67]

tert-butyl benzylidenecarbamate

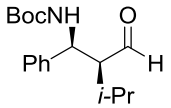


154

To a stirred solution of K_2CO_3 (23.9 g, 0.17 mol) and Na_2SO_4 (30.0 g, 0.21 mol) in THF (250 mL) under argon was added sulfone **153** (10.0 g, 28.8 mmol). The reaction mixture was heated at reflux under argon for 16 h. Once cooled to rt the solids were removed by filtration. The filtrate was concentrated *in vacuo* to give imine **154** as a colourless oil (5.04 g, 85%); δ_H (300 MHz, $(CD_3)_2CO$) 1.54 (9H, s, $C(CH_3)_3$), 7.52-7.66 (3H, m,

Ar(3,5)*H* and Ar(4)*H*), 7.92-7.97 (2H, m, Ar(2,6)*H*), 8.80 (1H, s, =C*H*). Spectroscopic data are in accordance with the literature.[67]

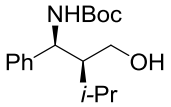
tert-butyl ((1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutyl)carbamate



(1*S*,2*S*)-**152**

To a stirred solution of imine **154** (5.00 g, 24.4 mmol) in anhydrous CH_3CN (240 mL) under argon was added isovaleraldehyde (5.23 mL, 48.8 mmol). The resulting solution was cooled to 0 °C. (*S*)-proline (561 mg, 4.87 mmol) was added and the reaction mixture was stirred for 18 h at 0 °C. Distilled H_2O (80 mL) was added and the reaction mixture was allowed to warm to rt whilst maintaining vigorous stirring. Et_2O (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (x 3). The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Trituration of the resulting solid with hexane gave aldehyde (1*S*,2*S*)-**152** as a white solid (4.97 g, 70%); mp 135-136 °C (hexane); {lit.[56] mp 146-148 °C (hexane)}; $[\alpha]_D^{20}$–70.0 (c 1.0 in $CHCl_3$); {lit.[56] $[\alpha]_D^{20}$–71.2 (c 0.5 in $CHCl_3$)}; δ_H (300 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.9, C*H*$_3$), 1.07 (3H, d, *J* 6.9, C*H*$_3$), 1.34 (9H, s, C(C*H*$_3$)$_3$), 2.02-2.11 (1H, m, C(3)*H*), 2.40-2.43 (1H, m, C(2)*H*), 5.02-5.03 (2H, m, C(1)*H* and N*H*), 7.15-7.29 (5H, m, Ar*H*), 9.43 (1H, d, *J* 4.2, C(O)*H*). Spectroscopic data are in accordance with the literature.[167]

tert-butyl ((1*S*,2*S*)-2-(hydroxymethyl)-3-methyl-1-phenylbutyl)carbamate

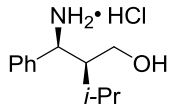


(1*S*,2*S*)-**156**

To a stirred solution of aldehyde (1*S*,2*S*)-**152** (4.45 g, 15.3 mmol) in MeOH (125 mL) under argon was added $NaBH_4$ (0.87 g, 23.0 mmol) and the reaction mixture was left to stir for 2 h at rt. Saturated aqueous $NaHCO_3$ was added and the MeOH was removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (x 3). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give alcohol (1*S*,2*S*)-**156** as a white solid (4.45 g, 99%); mp 78-79 °C; {lit.[56] mp 106-108 °C}; $[\alpha]_D^{20}$–25.4 (c 0.5 in $CHCl_3$); {lit.[56] $[\alpha]_D^{20}$–26.7 (c 0.7 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.78 (3H, d, *J*

6.9, C*H*$_3$), 0.93 (3H, d, *J* 6.9, C*H*$_3$), 1.35 (9H, s, C(C*H*$_3$)$_3$), 1.63-1.80 (2H, m, C(2)*H* and C(3)*H*), 2.00-2.10 (1H, br s, O*H*), 3.40-3.46 (1H, m, C*H*H), 3.60-3.63 (1H, m, CH*H*), 4.96 (1H, br s, C(1)*H*), 5.43-5.45 (1H, m, N*H*), 7.17-7.30 (5H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[56]

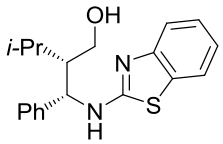
(*S*)-2-((*S*)-amino(phenyl)methyl)-3-methylbutan-1-ol hydrochloride



(1*S*,2*S*)-**157**

To a flask containing alcohol (1*S*,2*S*)-**156** (4.45 g, 15.2 mmol) under argon was added HCl (4 M in dioxane, 47.8 mL, 0.19 mol) and the reaction mixture was left to stir for 4 h at rt. The reaction mixture was concentrated *in vacuo* to give amino alcohol (1*S*,2*S*)-**157** as a white solid (3.48 g, 99%); mp 163-165 °C; {lit.[56] mp 168-170 °C}; $[\alpha]_D^{20}$–23.0 (c 1.0 in CH_3OH); {lit.[56] $[\alpha]_D^{20}$–22.9 (c 0.98 in CH_3OH)}; δ_H (400 MHz, CD_3OD) 0.84 (3H, d, *J* 6.8, C*H*$_3$), 1.15 (3H, d, *J* 6.8, C*H*$_3$), 1.53 (1H, *app* dq, *J* 13.7, 6.8, C(3)*H*), 1.99-2.05 (1H, m, C(2)*H*), 3.49 (1H, *app* t, *J* 10.2, C(1)*H*H), 3.76 (1H, dd, *J* 10.5, 4.3, C(1)H*H*), 4.58 (1H, d, *J* 4.3, C*H*N), 7.42-7.54 (5H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[56]

(*S*)-2-((*S*)-(benzo[d]thiazol-2-ylamino)(phenyl)methyl)-3-methylbutan-1-ol

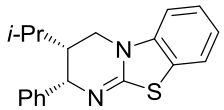


(1*S*,2*S*)-**158**

To a sealed pressure tube containing amino alcohol (1*S*,2*S*)-**157** (3.31 g, 14.4 mmol) and *i*-Pr$_2$NEt (9.76 mL, 56.0 mmol) under argon at 135 °C was added 2-chlorobenzothiazole (1.92 mL, 15.2 mmol) and the reaction mixture was left to stir for 2 days at 135 °C. The reaction mixture was allowed to cool to rt. Chromatographic purification (eluent EtOH:CH_2Cl_2 2:98) gave alcohol (1*S*,2*S*)-**158** as a white solid (4.55 g, 97%); mp 131-133 °C; {lit.[56] mp 137-139 °C}; $[\alpha]_D^{20}$–54.8 (c 1.0 in $CHCl_3$); {lit.[56] $[\alpha]_D^{20}$–54.8 (c 0.5 in $CHCl_3$)}; δ_H (300 MHz, $CDCl_3$) 0.75 (3H, d, *J* 6.8, C*H*$_3$), 1.04 (3H, d, *J* 6.8, C*H*$_3$), 1.56-1.68 (1H, m, C(3)*H*), 2.01-2.09 (1H, m, C(2)*H*), 3.57 (1H, *app* t, *J* 10.4, C(1)*H*H), 3.80 (1H, dd, *J* 11.2, 3.6, C(1)H*H*), 4.17 (1H, br s, N*H*), 4.91 (1H, dd, *J* 7.0, 4.2 C*H*N), 6.91-

6.98 (1H, m, Benzothiazole Ar(6)*H*), 7.12-7.29 (3H, m, Ar*H*), 7.31-7.48 (5H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[56]

(2*S*,3*R*)-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine



(2*S*,3*R*)-**112**

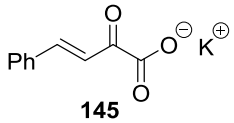
To a stirred solution of alcohol (1*S*,2*S*)-**158** (4.40 g, 13.5 mmol) in toluene (70 mL) under argon was added thionyl chloride (2.16 mL, 29.7 mmol) and the reaction mixture was heated at reflux for 3 h with no condenser fitted. The reaction mixture was allowed to cool to rt. The reaction mixture was quenched by addition of a few drops of MeOH and was concentrated *in vacuo*. 10% aqueous NaOH solution (110 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (x 3). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent MeOH:petrol 5:95) gave HBTM-2.1 (2*S*,3*R*)-**112** as a light brown solid (1.42 g, 34%); mp 140-142 °C; {lit.[56] mp 136-138 °C}; $[\alpha]_D^{20}$+280.0 (c 0.5 in $CHCl_3$); {lit.[56] $[\alpha]_D^{20}$+288.4 (c 0.5 in $CHCl_3$)}; Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 254 nm, 20 °C) t_R(2*S*,3*R*): 17.6 min, t_R(2*R*,3*S*): 30.7 min, >99% *ee*; δ_H (300 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.6, CH_3), 1.17 (3H, d, *J* 6.6, CH_3), 1.26-1.40 (1H, m, C*H*(CH_3)$_2$), 1.94-2.04 (1H, m, C(2)*H*), 3.38 (1H, app. t, *J* 11.6, C(4)*H*H), 3.91 (1H, ddd, *J* 11.6, 5.2, 1.7, C(4)*H*H), 4.96 (1H, dd, *J* 4.4, 1.6, C(3)*H*), 6.84 (1H, d, *J* 7.5, Ar(9)*H*), 7.07 (1H, td, *J* 7.6, 1.1, Ar(7)*H*), 7.22-7.38 (7H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[56] Note: Racemic sample for HPLC analysis already available in group.

General procedure A: *Preparation of potassium salts.*

To a solution of pyruvic acid (1 eq) and arylaldehyde (1 eq) in MeOH at 0 °C was added a solution of KOH (1.5 eq) in MeOH. The first 1 eq of the KOH solution was added dropwise over 30 minutes. The last third was added as one portion and the reaction mixture was stirred at 40 °C for 1 h followed by 0 °C for 16 h. The precipitate was collected by filtration, washed twice with cold MeOH, once with ether and dried under vacuum to furnish the potassium salt which was used as an intermediate, without further purification. Note: These compounds, if novel, were characterised only *via* ^{1}H NMR and

mp due to poor solubility in deuterated solvents (for ^{13}C NMR) and difficulties in observing molecular ions during mass spec analysis.

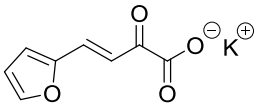
potassium (*E*)-2-oxo-4-phenylbut-3-enoate



145

Following general procedure A, benzaldehyde (5.09 mL, 50.0 mmol) in MeOH (4 mL), pyruvic acid (3.52 mL, 50.0 mmol) and KOH (4.21 g, 75.0 mmol) in MeOH (15 mL) gave potassium salt **145** as a yellow solid (8.85 g, 83%); mp 246-248 °C; {lit.[168] mp 248 °C}; δ_H (400 MHz, D_2O) 6.80 (1H, d, *J* 16.5, C(3)*H*), 7.37-7.46 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.59-7.65 (3H, m, C(4)*H* and Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[168]

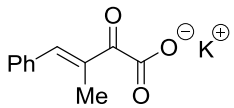
potassium (*E*)-4-(furan-2-yl)-2-oxobut-3-enoate



175

Following general procedure A, furfuraldehyde (4.14 mL, 50.0 mmol) in MeOH (15 mL), pyruvic acid (3.52 mL, 50.0 mmol) and KOH (4.21 g, 75.0 mmol) in MeOH (15 mL) gave potassium salt **175** as a yellow solid (7.25 g, 71%); mp 178-180 °C (*Decomp*); δ_H (400 MHz, D_2O) 6.53 (1H, dd, *J* 3.5, 1.6, Ar(4)*H*), 6.58 (1H, d, *J* 16.1, C(3)*H*), 6.88 (1H, d, *J* 3.5, Ar(3)*H*), 7.39 (1H, d, *J* 16.1, C(4)*H*), 7.61 (1H, d, *J* 1.6, Ar(5)*H*). Spectroscopic data are in accordance with the literature.[168]

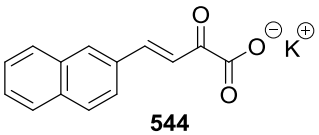
potassium (*E*)-3-methyl-2-oxo-4-phenylbut-3-enoate



543

Following a general procedure A, benzaldehyde (2.55 mL, 25.0 mmol) in MeOH (4 mL), 2-ketobutyric acid (2.55 g, 25.0 mmol) and KOH (2.10 g, 37.5 mmol) in MeOH (15 mL) gave potassium salt **543** as a yellow solid (4.53 g, 79%); mp 310 °C (*Decomp*); {lit.[169] mp 319 °C (*Decomp*)}; δ_H (300 MHz, D_2O) 1.93 (3H, d, *J* 1.3, CH_3), 7.32-7.48 (6H, m, C(4)*H* and Ar*H*). Spectroscopic data are in accordance with the literature.[169]

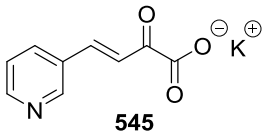
potassium (*E*)-4-(2-naphthyl)-2-oxobut-3-enoate



544

Following general procedure A, 2-naphthaldehyde (5.33 g, 34.2 mmol) in MeOH (15 mL), pyruvic acid (2.37 mL, 34.2 mmol) and KOH (2.87 g, 51.2 mmol) in MeOH (15 mL) gave potassium salt **544** as a yellow solid (6.90 g, 77%); mp 270-272 °C (*Decomp*); δ_H (400 MHz, D_2O) 6.86 (1H, d, *J* 16.4, C(3)*H*), 7.44-7.54 (2H, m, Ar*H*), 7.67-7.74 (2H, m, C(4)*H* and Ar*H*), 7.81-7.88 (3H, m, Ar*H*), 8.01 (1H, s, Ar(1)*H*).

potassium (*E*)-2-oxo-4-(pyridin-3-yl)but-3-enoate



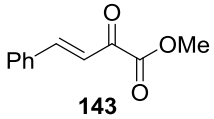
545

Following general procedure A, nicotinaldehyde (4.69 mL, 0.05 mol) in MeOH (15 mL), pyruvic acid (3.52 mL, 0.05 mol) and KOH (4.21 g, 0.075 mol) in MeOH (15 mL) gave potassium salt **545** as a yellow solid (6.53 g, 61%); mp 218-220 °C (*Decomp*); δ_H (300 MHz, D_2O) 6.88 (1H, d, *J* 16.6, C(3)*H*), 7.36-7.42 (1H, m, Ar(5)*H*), 7.58 (1H, d, *J* 16.6, C(4)*H*), 8.00-8.06 (1H, m, Ar(4)*H*), 8.43 (1H, dd, *J* 5.0, 1.6, Ar(6)*H*), 8.62 (1H, d, *J* 1.6, Ar(2)*H*). All spectroscopic data are in accordance with the literature.[168]

General Procedure B*:* *Preparation of γ-aryl-β,γ-unsaturated α-ketoesters*.

Acetyl chloride (11.5 eq) was added to the desired alcohol at 0 °C to generate HCl. Potassium salt (1 eq) was added and the mixture stirred at 0 °C for thirty minutes then warmed to rt for 2 h before heating at reflux for 16 h. Concentration *in vacuo* gave a solid which was dissolved in H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were washed with sat. aq. $NaHCO_3$, H_2O and brine before being dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture.

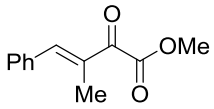
(*E*)-methyl 2-oxo-4-phenylbut-3-enoate



143

Following general procedure B, acetyl chloride (28.6 mL, 0.40 mol) in MeOH (200 mL) and potassium salt **145** (7.48 g, 35.0 mmol) gave, after chromatographic purification (eluent EtOAc:petrol 10:90), ketoester **143** as a yellow solid (2.85 g, 43%); mp 67-69 °C (CH_3OH); {lit.[170] mp 69-70 °C (CH_3OH)}; ν_{max} (KBr)/cm^{-1} 3075, 2957 (C-H), 1736 (C=O ketone), 1691 (C=O ester), 1607, 1572; δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s, CH_3), 7.32 (1H, d, *J* 16.1, C(3)*H*), 7.34-7.43 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.56-7.60 (2H, m, Ar(2,6)*H*), 7.82 (1H, d, *J* 16.1, C(4)*H*); δ_C (75 MHz, $CDCl_3$) 53.1 (*C*H_3), 120.5 (*C*(3)), 129.1 (*ArC*), 129.1 (*ArC*), 131.8 (*ArC*(4)), 134.0 (*ArC*(1)), 148.7 (*C*(4)), 162.6 (*C*(1)), 182.4 (*C*(2)); *m*/*z* (NSI^+) 191 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{11}H_{11}O_3^+$ ($[M+H]^+$) requires 191.0703; found 191.0701 (-0.9 ppm).

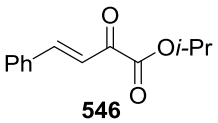
(*E*)-methyl 3-methyl-2-oxo-4-phenylbut-3-enoate



173

Following general procedure B, acetyl chloride (16.1 mL, 0.23 mol) in MeOH (125 mL) and potassium salt **543** (4.50 g, 19.7 mmol) gave, after chromatographic purification (eluent EtOAc:petrol 7.5:92.5), ketoester **173** as a light yellow oil (1.27 g, 32%); ν_{max} (ATR)/cm^{-1} 2955 (C-H), 1732 (C=O ketone), 1665 (C=O ester), 1614; δ_H (500 MHz, $CDCl_3$) 2.16 (3H, s, =CH_3), 3.97 (3H, s, OCH_3), 7.40-7.50 (6H, m, C(4)*H* and Ar*H*); δ_C (100 MHz, $CDCl_3$) 12.2 (C(3)*C*H_3), 52.7 (O*C*H_3), 128.7 (*ArC*), 129.9 (*ArC*(4)), 130.3 (*ArC*), 133.4 (*C*(3)), 134.8 (*ArC*(1)), 147.1 (*C*(4)), 165.5 (*C*(1)), 189.8 (*C*(2)); *m*/*z* (NSI^+) 205 ($[M+H]^+$, 53%); HRMS (NSI^+) $C_{12}H_{13}O_3^+$ ($[M+H]^+$) requires 205.0859; found 205.0859 (-0.1 ppm).

(*E*)-isopropyl 2-oxo-4-phenylbut-3-enoate

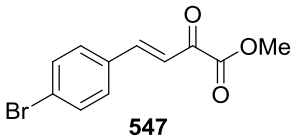


546

Following general procedure B, acetyl chloride (28.6 mL, 0.40 mol) in *i*-PrOH (200 mL) and potassium salt **145** (7.48 g, 35.0 mmol) gave, after chromatographic purification (eluent EtOAc:petrol 5:95), ketoester **546** as a yellow oil (1.88 g, 25%); ν_{max} (thin film)/cm^{-1} 3063, 3029, 2984 (C-H), 2938, 1723 (C=O ketone), 1695 (C=O ester), 1604, 1576; δ_H (400 MHz, $CDCl_3$) 1.41 (6H, d, *J* 6.3, CH(CH_3)$_2$), 5.24 (1H, sept, *J* 6.3,

C*H*(CH_3)$_2$), 7.35 (1H, d, *J* 16.1, C(3)*H*), 7.40-7.49 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.61-7.66 (2H, m, Ar(2,6)*H*), 7.85 (1H, d, *J* 16.1, C(4)*H*); δ_C (75 MHz, $CDCl_3$) 22.1 (CH(*C*H_3)$_2$), 71.1 (*C*H(CH_3)$_2$), 121.1 (*C*(3)), 129.4 (*ArC*), 129.5 (*ArC*), 132.0 (*ArC*(4)), 134.5 (*ArC*(1)), 148.7 (*C*(4)), 162.3 (*C*(1)), 183.7 (*C*(2)); *m*/*z* (NSI^+) 219 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{13}H_{15}O_3^+$ ($[M+H]^+$) requires 219.1016; found 219.1018 (+1.0 ppm).

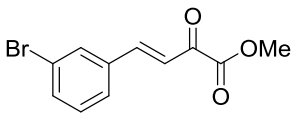
(*E*)-methyl 4-(4-bromophenyl)-2-oxobut-3-enoate



547

Following general procedure B, acetyl chloride (8.37 mL, 0.12 mol) in MeOH (70 mL) and potassium (*E*)-4-(4-bromophenyl)-2-oxobut-3-enoate[5] (3.00 g, 10.2 mmol) gave, after chromatographic purification (eluent EtOAc:petrol 10:90), ketoester **547** as a yellow solid (0.65 g, 24%); mp 116-118 °C (CH_3OH); {lit.[170] mp 120 °C (CH_3OH)}; ν_{max} (KBr)/cm^{-1} 3073, 3030, 2961 (C-H), 1728 (C=O ketone), 1691 (C=O ester), 1607, 1586, 1561; δ_H (400 MHz, $CDCl_3$) 3.96 (3H, s, C*H*$_3$), 7.40 (1H, d, *J* 16.1, C(3)*H*), 7.50-7.55 (2H, m, Ar*H*), 7.57-7.62 (2H, m, Ar*H*), 7.83 (1H, d, *J* 16.1, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 53.2 (*C*H$_3$), 120.9 (*C*(3)), 126.3 (*ArC*(4)), 130.4 (*ArC*), 132.5 (*ArC*), 132.9 (*ArC*(1)), 147.1 (*C*(4)), 162.4 (*C*(1)), 182.1 (*C*(2)); *m*/*z* (ES^+) 293 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{11}H_9{}^{81}BrNaO_3^+$ ($[M+Na]^+$) requires 292.9612; found 292.9611 (-0.4 ppm).

(*E*)-methyl 4-(3-bromophenyl)-2-oxobut-3-enoate

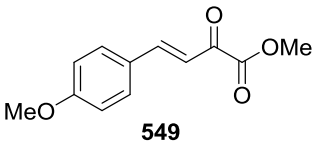


548

Following general procedure B, acetyl chloride (8.37 mL, 0.12 mol) in MeOH (70 mL) and potassium (*E*)-4-(3-bromophenyl)-2-oxobut-3-enoate[171] (3.00 g, 10.2 mmol) gave, after chromatographic purification (eluent EtOAc:petrol 10:90), ketoester **548** as a yellow solid (850 mg, 31%); mp 96-98 °C (CH_3OH); {lit.[172] mp 127-128 °C (CH_3OH)}; ν_{max} (KBr)/cm^{-1} 3025, 2968 (C-H), 1733 (C=O ketone), 1698 (C=O ester), 1611, 1560; δ_H (400 MHz, $CDCl_3$) 3.87 (3H, s, C*H*$_3$), 7.24 (1H, t, *J* 7.9, Ar(5)*H*), 7.30 (1H, d, *J* 16.1,

C(3)*H*), 7.46-7.53 (2H, m, Ar*H*), 7.69-7.74 (2H, m, C(4)*H* and Ar*H*); δ_C (100 MHz, $CDCl_3$) 53.2 (*C*H_3), 121.6 (*C*(3)), 123.3 (*ArC*(3)), 127.7 (*ArC*), 130.6 (*ArC*), 131.5 (*ArC*), 134.4 (*ArC*), 136.0 (*ArC*(1)), 146.6 (*C*(4)), 162.2 (*C*(1)), 182.0 (*C*(2)); *m*/*z* (ES^+) 291 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{11}H_9{}^{79}BrNaO_3{}^+$ ($[M+Na]^+$) requires 290.9633; found 290.9637 (+1.5 ppm).

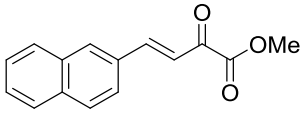
(*E*)-methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate



549

Following general procedure B, acetyl chloride (6.70 mL, 94.3 mmol) in MeOH (70 mL) and potassium (*E*)-4-(4-methoxyphenyl)-2-oxobut-3-enoate[171] (2.00 g, 8.20 mmol) gave, after chromatographic purification (eluent EtOAc:petrol 10:90), ketoester **549** as a yellow solid (652 mg, 24%); mp 86-88 °C (CH_3OH); {lit.[173] mp 99-100 °C (CH_3OH)}; ν_{max} (KBr)/cm^{-1} 3071, 3028, 2961 (C-H), 1729 (C=O ketone), 1696 (C=O ester), 1608, 1583, 1561; δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 3.95 (3H, s, CO_2CH_3), 6.93-6.98 (2H, m, Ar(3,5)*H*), 7.28 (1H, d, *J* 16.0, C(3)*H*), 7.60-7.65 (2H, m, Ar(2,6)*H*), 7.87 (1H, d, *J* 16.0, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 53.0 (CO_2CH_3), 55.5 (O*C*H_3), 114.6 (*ArC*(3,5)), 118.1 (*C*(3)), 126.8 (*ArC*(1)), 131.2 (*ArC*(2,6)), 148.6 (*C*(4)), 162.7 (*C*(1) or *ArC*(4), 162.9 (*C*(1) or *ArC*(4)), 182.2 (*C*(2)); *m*/*z* (ES^+) 243 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{12}H_{12}NaO_4{}^+$ ($[M+Na]^+$) requires 243.0633; found 243.0625 (-3.2 ppm).

(*E*)-methyl 4-(naphthalen-2-yl)-2-oxobut-3-enoate

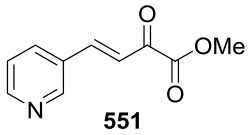


550

Following general procedure B, acetyl chloride (12.4 mL, 0.17 mol) in MeOH (100 mL) and potassium salt **544** (4.00 g, 15.2 mmol) gave, after chromatographic purification (eluent EtOAc:petrol 10:90), ketoester **550** as a yellow solid (1.32 g, 36%); mp 70-72 °C (CH_3OH); ν_{max} (KBr)/cm^{-1} 3051, 2965 (C-H), 1736 (C=O ketone), 1691 (C=O ester), 1608; δ_H (400 MHz, $CDCl_3$) 3.99 (3H, s, CH_3), 7.52 (1H, d, *J* 16.1, C(3)*H*), 7.54-7.62 (2H, m, Ar*H*), 7.77-7.82 (1H, m, Ar*H*), 7.86-7.94 (3H, m, Ar*H*), 8.05-8.11 (2H, m, C(4)*H* and Ar(1)*H*); δ_C (100 MHz, $CDCl_3$) 53.1 (*C*H_3), 120.5 (*C*(3)), 123.6 (*ArC*), 127.0

(*ArC*), 127.9 (*ArC*), 128.1 (*ArC*), 128.9 (*ArC*), 129.0 (*ArC*), 131.6 (*ArC*), 132.1 (*ArC*), 133.2 (*ArC*), 134.9 (*ArC*), 148.8 (*C*(4)), 162.7 (*C*(1)), 182.3 (*C*(2)); *m*/*z* (ES^+) 263 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{15}H_{12}NaO_3^+$ ($[M+Na]^+$) requires 263.0684; found 263.0688 (+1.4 ppm).

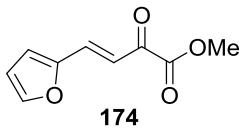
(*E*)-methyl 2-oxo-4-(pyridin-3-yl)but-3-enoate



551

Following general procedure B, acetyl chloride (11.4 mL, 0.16 mol) in MeOH (100 mL) and potassium salt **545** (3.00 g, 14.0 mmol) gave, after chromatographic purification (eluent EtOAc:petrol 80:20), ketoester **551** as a yellow solid (0.20 g, 8%); mp 56-58 °C (CH_3OH); ν_{max} (KBr)/cm^{-1} 3075, 3023, 2960 (C-H), 1731 (C=O ketone), 1687 (C=O ester), 1607, 1585; δ_H (400 MHz, $CDCl_3$) 3.89 (3H, s, C*H*$_3$), 7.32 (1H, dd, *J* 8.0, 4.8, Ar(5)*H*), 7.39 (1H, d, *J* 16.2, C(3)*H*), 7.81 (1H, d, *J* 16.2, C(4)*H*), 7.87-7.92 (1H, m, Ar(6)*H*), 8.61 (1H, dd, *J* 4.8, 1.6, Ar(4)*H*), 8.77 (1H, d, *J* 1.6, Ar(2)*H*); δ_C (100 MHz, $CDCl_3$) 53.3 (*C*H$_3$), 122.2 (*C*(3)), 123.9 (*ArC*(5)), 129.8 (*ArC*(3)), 134.8 (*ArC*(6)), 144.7 (*C*(4)), 150.7 (*ArC*(2)), 152.2 (*ArC*(4)), 162.1 (*C*(1)), 181.8 (*C*(2)); *m*/*z* (ES^+) 192 ($[M+H]^+$, 100%); HRMS (ES^+) $C_{10}H_{10}NO_3^+$ ($[M+H]^+$) requires 192.0661; found 192.0655 (-2.8 ppm).

(*E*)-methyl 4-(furan-2-yl)-2-oxobut-3-enoate

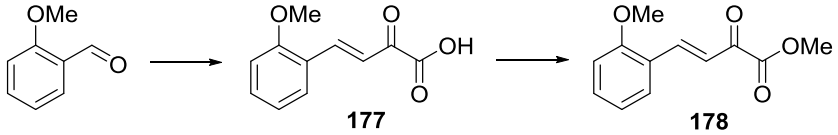


174

To a solution of potassium salt **175** (3.00 g, 14.7 mmol) in DMF (40 mL) was added methyl iodide (1.01 mL, 16.2 mmol) and the reaction mixture was heated at 75 °C for 4 h. Once cool the reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (x 3). The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent EtOAc:petrol 15:85) gave ketoester **174** as a yellow solid (0.73 g, 27%); mp 56-58 °C (CH_3OH); {lit.[174] mp 58-60 °C (petroleum ether)}; ν_{max} (KBr)/cm^{-1} 3138, 3091, 3035, 2959 (C-H), 1736 (C=O ketone), 1680 (C=O ester), 1595, 1545; δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, C*H*$_3$), 6.48 (1H, dd, *J* 3.5, 1.8, Ar(4)*H*), 6.77 (1H, d, *J* 3.5, Ar(3)*H*), 7.16 (1H, d, *J* 15.7,

C(3)*H*), 7.50-7.52 (1H, m, Ar(5)*H*), 7.56 (1H, d, *J* 15.7, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 53.0 (*C*H_3), 113.2 (*ArC*(4)), 118.0 (*C*(3)), 118.7 (*ArC*(3)), 133.7 (*C*(4)), 146.4 (*ArC*(5)), 151.0 (*ArC*(2)), 162.4 (*C*(1)), 182.0 (*C*(2)); *m*/*z* (ES^+) 203 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_9H_8NaO_4^+$ ($[M+Na]^+$) requires 203.0320; found 203.0318 (-1.4 ppm).

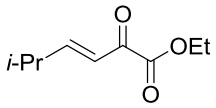
(*E*)-methyl 4-(2-methoxyphenyl)-2-oxobut-3-enoate



To a solution of 2-methoxybenzaldehyde (3.02 mL, 25.0 mmol) in MeOH (4 mL) was added pyruvic acid (1.76 mL, 25.0 mmol). To this was added a solution of KOH (2.10 g, 37.5 mmol) in MeOH (15 mL) at 0 °C. The solution was stirred for 1 h at 40 °C followed by addition of concentrated HCl at 0 °C. The reaction mixture was extracted with Et_2O (x 3), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the intermediate acid **177** as an orange solid which was used without purification.

Acetyl chloride (20.4 mL, 0.29 mol) was added to MeOH (150 mL) at 0 °C to generate HCl. The previously synthesised acid (5.15 g, 25.0 mmol assuming 100% conversion) was added and the mixture was stirred at 0 °C for thirty minutes then warmed to rt for two hours before heating at reflux overnight. Concentration *in vacuo* gave a solid which was dissolved in H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were washed with sat. aq. $NaHCO_3$, H_2O and brine before being dried ($MgSO_4$), filtered and concentrated *in vacuo* to give keto ester **178** as a yellow solid (2.55 g, 46% over 2 steps); mp 49-51 °C; {lit.[70] mp 48 °C}; ν_{max} (ATR)/cm^{-1} 3011, 2949 (C-H), 2839, 1726 (C=O ketone), 1686 (C=O ester), 1591; δ_H (400 MHz, $CDCl_3$) 3.94 (3H, s, OC*H*$_3$), 3.96 (3H, s, CO_2C*H*$_3$), 6.68 (1H, d, *J* 8.4, Ar(3)*H*), 7.02 (1H, t, *J* 7.5, Ar(5)*H*), 7.43-7.48 (2H, m, C(3)*H* and Ar(4)*H*), 7.66 (1H, dd, *J* 7.7, 1.6, Ar(6)*H*), 8.24 (1H, d, *J* 16.3, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 52.9 (CO_2*C*H_3), 55.6 (O*C*H_3), 111.3 (*ArC*(3)), 120.8 (*C*(3)), 120.8 (*ArC*(4)), 122.9 (*ArC*(1)), 129.5 (*ArC*(6)), 133.2 (*ArC*(4)), 144.1 (*C*(4)), 159.2 (*ArC*(2)), 162.9 (*C*(1)), 183.0 (*C*(2)); *m*/*z* (NSI^+) 221 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{12}H_{13}O_4^+$ ($[M+H]^+$) requires 221.0808; found 221.0806 (-1.1 ppm).

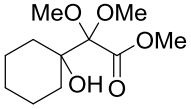
(*E*)-ethyl 5-methyl-2-oxohex-3-enoate



179

To a solution of ethyl pyruvate (11.1 mL, 0.10 mol) in toluene (70 mL) at rt was added DMAP (24.4 mg, 0.20 mmol), trimethylsilyl chloride (19.0 mL, 0.15 mol) and Et_3N (20.9 mL, 0.15 mol) and the reaction mixture was heated at reflux for 2 h. Once cool the reaction mixture was filtered under a flow of argon gas and the toluene was removed under reduced pressure to give crude silylated enol ester. This was subsequently added *via* cannula to a solution of 1,1-dimethoxy-2-methylpropane (9.83 g, 83.3 mmol) in CH_2Cl_2 (350 mL). Trifluoroboron etherate (11.5 mL, 91.6 mmol) was added dropwise at −78 °C and the reaction mixture was allowed to stir at 0 °C for 3 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude reaction mixture. Kugelrohr distillation and chromatographic purification (eluent EtOAc:petrol 4:96) gave ketoester **179** as a yellow oil (268 mg, 2%); ν_{max} (thin film)/cm^{-1} 2966 (C-H), 2936, 2872, 1734 (C=O ketone), 1702 (C=O ester), 1678, 1624; δ_H (400 MHz, $CDCl_3$) 1.14 (6H, d, *J* 6.8, $CH(CH_3)_2$), 1.41 (3H, t, *J* 6.8, CH_2CH_3), 2.54-2.64 (1H, m, $CH(CH_3)_2$), 4.38 (2H, q, *J* 7.1, CH_2CH_3), 6.64 (1H, dd, *J* 16.0, 1.4, C(3)*H*), 7.18 (1H, dd, *J* 16.0, 6.6, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_2CH_3), 21.0 ($CH(CH_3)_2$), 31.8 ($CH(CH_3)_2$), 62.3 (CH_2CH_3), 122.4 (*C*(3)), 160.8 (*C*(4)), 162.5 (*C*(1)), 183.8 (*C*(2)); *m*/*z* (ES^+) 193 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_9H_{14}NaO_3^+$ ($[M+Na]^+$) requires 193.0841; found 193.00841 (+0.1 ppm).

methyl 2-(1-hydroxycyclohexyl)-2,2-dimethoxyacetate

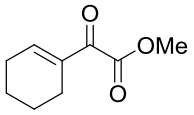


185

To a solution of *i*-Pr_2NH (3.95 mL, 28.0 mmol) in THF (30 mL) at −78 °C under argon was added n-BuLi (2.5M in hexanes, 12.0 mL, 30.0 mmol) and the solution was stirred at −78 °C for 30 minutes. A solution of methyl dimethoxyacetate (3.66 mL, 30.0 mmol) in THF (25 mL) was then added dropwise over 15 minutes at −78 °C and the reaction mixture was stirred for a further 15 minutes. A solution of cyclohexanone (2.07 mL, 20.0 mmol) in THF (25 mL) was then added over 15 minutes at −78 °C and the solution

was stirred at −78 °C for a further 30 minutes. The reaction mixture was poured into H_2O and extracted with Et_2O (x 3). The organic fraction was washed with H_2O, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent EtOAc:petrol 10:90) gave acetal **185** as a colourless oil (4.29 g, 92%); δ_H (500 MHz, $CDCl_3$) 1.07-1.75 (10H, m, 5 CH_2), 2.27 (1H, s, O*H*), 3.48 (6H, s, 2 OCH_3), 3.82 (3H, s, CO_2CH_3). Spectroscopic data are in accordance with the literature.[73]

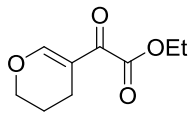
methyl 2-(cyclohex-1-en-1-yl)-2-oxoacetate



182

To a solution of acetal **185** (2.00 g, 8.62 mmol) in CH_2Cl_2 (80 mL) was added pyridine (6.95 mL, 86.2 mmol) and thionyl chloride (2.51 mL, 34.5 mmol) slowly at 0 °C. The reaction mixture was allowed to stir for 1 h before being concentrated *in vacuo*. The residue was dissolved in dioxane (50 mL) and treated with HCl (4 M in dioxane, 30.0 mL, 0.12 mol) for 15 minutes at rt. The reaction mixture was placed in a separating funnel and the organic fraction was washed with H_2O, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent EtOAc:petrol 7.5:92.5) gave cyclic keto ester **182** as a colourless oil (125 mg, 9%); δ_H (400 MHz, $CDCl_3$) 1.58-1.64 (4H, m, 2 CH_2), 2.19-2.29 (4H, m, 2 CH_2), 3.81 (3H, s, CH_3), 6.92-6.94 (1H, m, C*H*=C). Spectroscopic data are in accordance with the literature.[175]

ethyl 2-(3,4-dihydro-2*H*-pyran-5-yl)-2-oxoacetate



186

To a solution of 3,4-dihydro-2*H*-pyran (1.37 mL, 15.0 mmol) in Et_2O (10 mL) at 0 °C was added a solution of ethyl chlorooxoacetate (1.12 mL, 10.0 mmol) in Et_2O (10 mL) over 1 h. The reaction mixture was stirred at rt for 16 h. Et_3N (1.54 mL, 11.0 mmol) was added and the reaction mixture was stirred for a further 4 h. Et_2O was added a precipitate formed which was removed by filtration. Concentration of the filtrate *in vacuo* gave cyclic keto ester **186** as a colourless oil (0.40 g, 22 %); ν_{max} (KBr)/cm^{-1} 2984 (C-H), 2943, 1732 (C=O ketone), 1690 (C=O ester) 1652, 1607; δ_H (400 MHz, $CDCl_3$) 1.39 (3H,

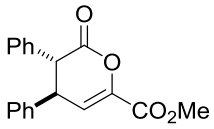
t, *J* 7.2, CH_2CH_3), 1.92-1.98 (2H, m, $CH_2CH_2CH_2$), 2.34 (2H, t, *J* 6.3, $=CH_2$), 4.19 (2H, t, *J* 5.3, OCH_2), 4.35 (2H, q, *J* 7.2, CH_2CH_3), 7.85 (1H, s, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_2CH_3), 17.5 (CH_2), 20.6 (CH_2), 62.0 (CH_2CH_3), 67.9 (OCH_2), 114.2 (*C*(3)), 163.3 (*C*(4)), 163.9 (*C*(1)), 185.0 (*C*(2)); *m*/*z* (NSI^+) 185 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_9H_{13}O_4^+$ ($[M+H]^+$) requires 185.0808; found 185.0807 (-0.7 ppm).

General procedure C: *Intermolecular Michael addition-lactonisation.*

To a solution of acid (1 eq) in CH_2Cl_2 (~1 mL per 0.2 mmol of acid) were added *i*-Pr_2NEt (1.5 eq based on acid) and pivaloyl chloride (1.5 eq based on acid) at rt. The reaction mixture was allowed to stir at rt for 10 minutes. The requisite Lewis base (1-20 mol%), Michael acceptor (1 eq) and *i*-Pr_2NEt (2.5 eq) were then added at the required temperature in that order. The reaction mixture was stirred at the required temperature until complete by TLC and was subsequently quenched by addition of HCl (1 M in H_2O). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture. Note: All racemic samples were obtained *via* this general procedure using DHPB **108** as catalyst.

Optimisation studies on compound 147

methyl 2-oxo-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(±)-**147**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), DHPB **108** (7.60 mg, 0.04 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 1 h at rt gave crude lactone (±)-**147** (95:5 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (±)-**147** (96:4 dr) as a white solid (39.0 mg, 64%); mp 118-120 °C; Chiral HPLC Chiralpak AD-H (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 15.0 min, t_R(3*S*,4*S*): 28.2 min; ν_{max} (KBr)/cm^{-1} 3085, 3031, 3007, 2955 (C-H), 1764 (C=O lactone), 1733 (C=O ester), 1660, 1496; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.92 (3H, s, CH_3), 3.96 (1H, d, *J* 8.7, C(3)*H*), 4.08 (1H, dd, *J* 8.7, 4.0, C(4)*H*), 6.71 (1H, d, *J* 4.0, C(5)*H*), 7.06-7.08

(2H, m, Ar*H*), 7.12-7.14 (2H, m, Ar*H*), 7.24-7.36 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 45.4 (*C*(4)), 52.5 (*C*(3)), 52.8 (*C*H_3), 117.8 (*C*(5)), 127.5 (*ArC*), 127.9 (*ArC*), 128.0 (*ArC*), 128.3 (*ArC*), 128.8 (*ArC*), 129.1 (*ArC*), 135.4 (*ArC*), 139.1 (*ArC*), 142.0 (*C*(6)), 160.7 (*C*$O_2$$CH_3$), 166.8 (*C*(2)); *m*/*z* (NSI^+) 326 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{19}H_{20}NO_4^+$ ($[M+NH_4]^+$) requires 326.1387; found 326.1389 (+0.7 ppm).

Asymmetric Catalyst Screen:
All reactions at rt for 3 h.

Tetramisole hydrochloride (2*S*)-**106** (9.63 mg, 0.04 mmol, 20 mol%) gave crude lactone (3*S*,4*S*)-**147** (94:6 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*S*,4*S*)-**147** (98:2 dr) as a white solid (37.0 mg, 60%); $[\alpha]_D^{20}$+196.0 (*c* 0.05, CH_2Cl_2); 86% *ee*.

i-Pr isothiourea catalyst (2*S*)-**148** (9.28 mg, 0.04 mmol, 20 mol%) gave crude lactone (3*S*,4*S*)-**147** (96:4 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*S*,4*S*)-**147** (98:2 dr) as a white solid (34.0 mg, 55%); $[\alpha]_D^{20}$+183.2 (*c* 0.2, CH_2Cl_2); 83% *ee*.

HBTM-2.1 (2*S*,3*R*)-**112** (12.3 mg, 0.04 mmol, 20 mol%) gave crude lactone (3*R*,4*R*)-**147** (96:4 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (98:2 dr) as a white solid (32.0 mg, 52%); $[\alpha]_D^{20}$-179.0 (*c* 0.5, CH_2Cl_2); 91% *ee*.

Temperature Screen:
All reactions with HBTM-2.1 (2*S*,3*R*)-**112** (12.3 mg, 0.04 mmol, 20 mol%)

Reaction for 3 h at −10 °C gave crude lactone (3*R*,4*R*)-**147** (95:5 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (98:2 dr) as a white solid (34.0 mg, 55%); 93% *ee*.

Reaction for 3 h at −30 °C gave crude lactone (3*R*,4*R*)-**147** (94:6 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (98:2 dr) as a white solid (37.0 mg, 60%); 97% *ee*.

Reaction for 3 h at −50 °C gave crude lactone (3*R*,4*R*)-**147** (96:4 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (98:2 dr) as a white solid (34.0 mg, 55%); 95% *ee*.

Reaction for 3 h at −78 °C gave crude lactone (3*R*,4*R*)-**147** (98:2 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (98:2 dr) as a white solid (37.0 mg, 60%); 96% *ee*.

Catalyst Loading Screen:

HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) for 16 h at −30 °C gave crude lactone (3*R*,4*R*)-**147** (95:5 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (98:2 dr) as a white solid (42.0 mg, 68%); 97% *ee*.

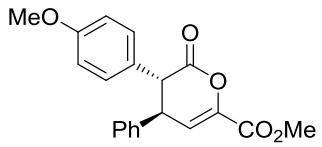
HBTM-2.1 (2*S*,3*R*)-**112** (3.08 mg, 0.01 mmol, 5 mol%) for 24 h at −30 °C gave crude lactone (3*R*,4*R*)-**147** (95:5 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (98:2 dr) as a white solid (42.0 mg, 68%); 96% *ee*.

HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 2 mol%) for 72 h at −30 °C gave crude lactone (3*R*,4*R*)-**147** (94:6 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (98:2 dr) as a white solid (34.0 mg, 55%); 96% *ee*.

Scale-up:

Following general procedure C, phenylacetic acid (0.27 g, 2.00 mmol), ketoester **143** (0.38 g, 2.00 mmol) and *i*-Pr_2NEt (0.52 mL, 3.00 mmol) in CH_2Cl_2 (10 mL), pivaloyl chloride (0.37 mL, 3.00 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (61.7 mg, 0.2 mmol, 10 mol%) and *i*-Pr_2NEt (0.87 mL, 5.00 mmol) for 16 h at −30 °C gave crude lactone (3*R*,4*R*)-**147** (90:10 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**147** (91:9 dr) as a white solid (0.40 g, 66%); 99% *ee*.

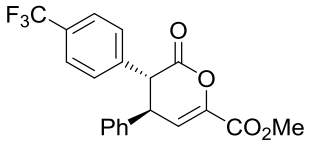
(3*R*,4*R*)-methyl 3-(4-methoxyphenyl)-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**159**

Following general procedure C, 4-methoxyphenylacetic acid (33.2 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**159** (92:8 dr). Chromatographic purification (eluent EtOAc:petrol 20:80) gave lactone (3*R*,4*R*)-**159** (98:2 dr) as a white solid (51.1 mg, 76%); mp 118-120 °C; $[\alpha]_D^{20}$-212.0 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 24.9 min, t_R(3*S*,4*S*): 43.7 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3080, 3029, 2958 (C-H), 2839, 1778 (C=O lactone), 1745 (C=O ester), 1656, 1616, 1587, 1519; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, OC*H*$_3$), 3.79-3.81 (4H, m, C(3)*H* and CO_2CH_3), 3.95 (1H, dd, *J* 8.8, 3.9 C(4)*H*), 6.61 (1H, d, *J* 3.9, C(5)*H*), 6.72-6.76 (2H, m, C(3)Ar(3,5)*H*), 6.92-6.98 (4H, m, Ar*H*), 7.16-7.22 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 45.4 (*C*(4)), 51.7 (*C*(3) or CO_2CH_3), 52.8 (*C*(3) or CO_2CH_3), 55.3 (OCH_3), 114.3 (C(3)*ArC*(3,5)), 117.9 (*C*(5)), 127.3 (C(3)*ArC*(1)), 127.5 (*ArC*), 127.8 (C(4)*ArC*(4)), 129.1 (*ArC*), 129.4 (*ArC*), 139.3 (C(4)*ArC*(1)), 142.0 (*C*(6)), 159.2 (C(3)*ArC*(4)), 160.8 (CO_2CH_3), 167.1 (*C*(2)); *m*/*z* (NSI^+) 356 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{20}H_{22}NO_5^+$ ($[M+NH_4]^+$) requires 356.1492; found 356.1494 (+0.4 ppm).

(3*R*,4*R*)-methyl 2-oxo-4-phenyl-3-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyran-6-carboxylate

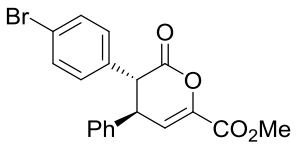


(3*R*,4*R*)-**160**

Following general procedure C, 2-(4-(trifluoromethyl)phenyl)acetic acid (40.8 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17

mg, 0.02 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 72 h at –30 °C gave crude lactone (3*R*,4*R*)-**160** (85:15 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**160** (98:2 dr) as a white solid (36.5 mg, 49%); mp 130-132 °C; $[\alpha]_D^{20}$-100.0 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 14.8 min, t_R(3*S*,4*S*): 18.4 min, 71% *ee*; ν_{max} (KBr)/cm^{-1} 3097, 3045, 2961 (C-H), 1765 (C=O lactone), 1737 (C=O ester), 1667, 1619; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, C*H*$_3$), 3.89 (1H, d, *J* 10.3, C(3)*H*), 3.98 (1H, dd, *J* 10.3, 3.4 C(4)*H*), 6.62 (1H, d, *J* 3.4, C(5)*H*), 6.90-6.95 (2H, m, Ar*H*), 7.11 (2H, d, *J* 8.1, C(3)Ar(2,6)*H*), 7.16-7.22 (3H, m, Ar*H*), 7.46 (2H, d, *J* 8.2, C(3)Ar(3,5)*H*); δ_C (125 MHz, $CDCl_3$) 45.4 (*C*(4)), 52.4 (*C*(3) or *C*H_3), 52.9 (*C*(3) or *C*H_3), 118.1 (*C*(5)), 123.9 (q, *J* 271, *C*F_3), 125.7 (q, *J* 3.4, C(3)*ArC*(3,5)), 127.5 (*ArC*), 128.2 (C(4)*ArC*(4)), 129.1 (*ArC*), 129.2 (*ArC*), 130.2 (q, *J* 32.6, C(3)*ArC*(4)), 138.5 (C(3)*ArC*(1)), 139.2 (C(4)*ArC*(1)), 142.1 (*C*(6)), 160.5 (*C*O_2CH$_3$), 166.3 (*C*(2)); *m*/*z* (NSI^+) 394 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{20}H_{19}FNO_4^+$ ($[M+NH_4]^+$) requires 394.1261; found 394.1262 (+0.3 ppm).

(3*R*,4*R*)-methyl 3-(4-bromophenyl)-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

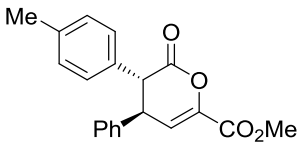


(3*R*,4*R*)-**161**

Following general procedure C, 4-bromophenylacetic acid (43.0 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**161** (90:10 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**161** (98:2 dr) as a white solid (48.1 mg, 62%); mp 110-112 °C; $[\alpha]_D^{20}$-156.0 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 22.0 min, t_R(3*S*,4*S*): 31.5 min, 93% *ee*; ν_{max} (KBr)/cm^{-1} 3089, 3029, 2954 (C-H), 1782 (C=O lactone), 1747 (C=O ester), 1660; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.79 (1H, d, *J* 10.1, C(3)*H*), 3.82 (3H, s, C*H*$_3$), 3.94 (1H, dd, *J* 10.1, 3.5 C(4)*H*), 6.60 (1H, d, *J* 3.5, C(5)*H*), 6.86-6.88 (2H, m,

C(3)Ar(2,6)*H*), 6.92-6.94 (2H, m, C(4)Ar(2,6)*H*), 7.17-7.22 (3H, m, C(4)Ar(3,5)*H* and C(4)Ar(4)*H*), 7.31-7.34 (2H, m, C(3)Ar(3,5)*H*); δ_C (100 MHz, $CDCl_3$) 45.3 (*C*(4)), 52.0 (*C*(3)), 52.9 (*C*H_3), 118.1 (*C*(5)), 122.1 (C(3)*ArC*(4)), 127.5 (*ArC*), 128.0 (C(4)*ArC*(4)), 129.2 (*ArC*), 130.2 (*ArC*), 131.9 (*ArC*), 134.2 (C(3)*ArC*(1)), 138.7 (C(4)*ArC*(1)), 142.0 (*C*(6)), 160.6 (*C*O_2CH_3), 166.5 (*C*(2)); *m*/*z* (NSI^+) 404 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{19}H_{19}{}^{79}BrNO_4{}^+$ ($[M+NH_4]^+$) requires 404.0492; found 404.0494 (+0.5 ppm).

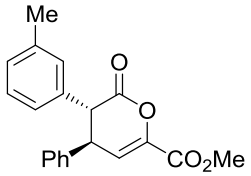
(3*R*,4*R*)-methyl 2-oxo-4-phenyl-3-(*p*-tolyl)-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**162**

Following general procedure C, *p*-tolyl acetic acid (30.0 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −30 °C gave crude lactone (3*R*,4*R*)-**162** (95:5 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**162** (97:3 dr) as a white solid (52.1 mg, 81%); mp 144-146 °C; $[\alpha]_D^{20}$-223.2 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 16.3 min, t_R(3*S*,4*S*): 23.4 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3056, 3028, 2956 (C-H), 2924, 2854, 1784 (C=O lactone), 1744 (C=O ester), 1519; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, 4-C*H*$_3$C$_6$H$_4$), 3.81 (3H, s, C*H*$_3$), 3.84 (1H, d, *J* 8.5, C(3)*H*), 3.97 (1H, dd, *J* 8.5, 4.0, C(4)*H*), 6.60 (1H, d, *J* 4.0, C(5)*H*), 6.92-6.94 (2H, m, C(3)Ar(3,5)*H*), 6.97-7.03 (4H, m, Ar*H*), 7.17-7.23 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.1 (4-*C*$H_3C_6H_4$), 45.3 (*C*(4)), 52.0(*C*(3)), 52.8 (CO_2*C*H_3), 117.8 (*C*(5)), 127.5 (*ArC*), 127.9 (C(4)*ArC*(4)), 128.1 (*ArC*), 129.1 (*ArC*), 129.5 (*ArC*), 132.4 (C(3)*ArC*(1)), 137.7 (C(3)*ArC*(4)), 139.3 (C(4)*ArC*(1)), 142.0 (*C*(6)), 160.8 (*C*O_2CH_3), 167.0 (*C*(2)); *m*/*z* (NSI^+) 340 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{20}H_{22}NO_4{}^+$ ($[M+NH_4]^+$) requires 340.1543; found 340.1548 (+1.4 ppm).

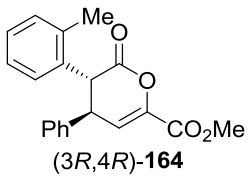
(3*R*,4*R*)-methyl 2-oxo-4-phenyl-3-(*m*-tolyl)-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**163**

Following general procedure C, m-tolyl acetic acid (30.0 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**163** (95:5 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**163** (98:2 dr) as a white solid (43.3 mg, 67%); mp 118-120 °C; $[\alpha]_D^{20}$-184.8 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 12.5 min, t_R(3*S*,4*S*): 16.9 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3084, 3029, 2962 (C-H), 2923, 2871, 1780 (C=O lactone), 1745 (C=O ester), 1664, 1606; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, 3-CH_3C$_6$H$_4$), 3.81 (3H, s, CH_3), 3.84 (1H, d, *J* 8.2, C(3)*H*), 3.98 (1H, dd, *J* 8.2, 4.2 C(4)*H*), 6.60 (1H, d, *J* 4.2, C(5)*H*), 6.83-6.85 (2H, m, Ar*H*), 6.97-7.00 (3H, m, Ar*H*), 7.09 (1H, t, *J* 7.6, C(3)Ar(5)*H*), 7.16-7.22 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (3-CH_3C$_6$H$_4$), 45.3 (*C*(4)), 52.3 (*C*(3) or CO_2CH_3), 52.8 (*C*(3) or CO_2CH_3), 117.7 (*C*(5)), 125.2 (*ArC*), 127.5 (*ArC*), 127.9 (*ArC*), 128.7 (*ArC*), 128.8 (*ArC*), 129.0 (*ArC*), 129.1 (*ArC*), 135.4 (C(3)*ArC*(1)), 138.6 (C(3)*ArC*(3)), 139.2 (C(4)*ArC*(1)), 142.0 (*C*(6)), 160.8 (CO_2CH_3), 166.9 (*C*(2)); *m*/*z* (NSI^+) 340 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{20}H_{22}NO_4^+$ ($[M+NH_4]^+$) requires 340.1543; found 340.1545 (+0.5 ppm).

(3*R*,4*R*)-methyl 2-oxo-4-phenyl-3-(*o*-tolyl)-3,4-dihydro-2*H*-pyran-6-carboxylate

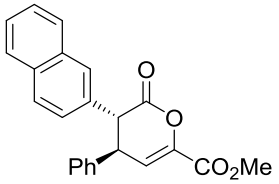


(3*R*,4*R*)-**164**

Following general procedure C, *o*-tolyl acetic acid (30.0 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**164** (95:5 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone

(3*R*,4*R*)-**164** (98:2 dr) as a white solid (42.3 mg, 66%); mp 152-154 °C; $[\alpha]_D^{20}$-116.0 (*c* 0.15, CH_2Cl_2); Chiral HPLC Chiralpak AS-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 29.9 min, t_R(3*S*,4*S*): 33.3 min, 87% *ee*; ν_{max} (KBr)/cm^{-1} 3086, 3032, 2956 (C-H), 2925, 1764 (C=O lactone), 1732 (C=O ester), 1659; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 2.04 (3H, s, 2-CH_3C$_6$H$_4$), 3.94 (3H, s, CH_3), 4.05 (1H, dd, *J* 9.8, 3.5 C(4)*H*) 4.14 (1H, d, *J* 9.8, C(3)*H*), 6.71 (1H, d, *J* 3.5, C(5)*H*), 7.02-7.04 (2H, m, Ar*H*), 7.08-7.10 (1H, m, Ar*H*), 7.14-7.28 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 19.6 (2-CH_3C$_6$H$_4$), 45.3 (*C*(4)), 48.7 (*C*(3)), 52.8 (CO_2CH_3), 118.1 (*C*(5)), 126.6 (*ArC*), 127.6 (*ArC*), 127.9 (*ArC*), 127.9 (*ArC*), 127.9 (*ArC*), 128.9 (*ArC*), 130.7 (*ArC*), 134.2 (C(3)*ArC*(1)), 136.5 (C(3)*ArC*(2)), 139.3 (C(4)*ArC*(1)), 142.0 (*C*(6)), 160.8 (CO_2CH_3), 166.9 (*C*(2)); *m*/*z* (NSI^+) 340 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{20}H_{22}NO_4^+$ ($[M+NH_4]^+$) requires 340.1543; found 340.1546 (+0.8 ppm).

(3*R*,4*R*)-methyl 3-(naphthalen-2-yl)-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

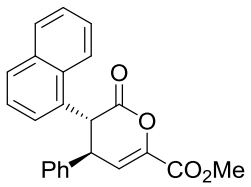


(3*R*,4*R*)-**165**

Following general procedure C, 1-naphthyl acetic acid (37.2 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**165** (93:7 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**165** (98:2 dr) as a white solid (52.4 mg, 73%); mp 170-172 °C; $[\alpha]_D^{20}$-212.4 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 18.2 min, t_R(3*S*,4*S*): 25.8 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3059, 3027, 2955 (C-H), 1774 (C=O lactone), 1745 (C=O ester), 1655, 1603; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, CH_3), 4.03 (1H, d, *J* 8.8, C(3)*H*), 4.12 (1H, dd, *J* 8.8, 3.9, C(4)*H*), 6.64 (1H, d, *J* 3.9, C(5)*H*), 6.98-7.00 (2H, m, Ar*H*), 7.13-7.19 (3H, m, Ar*H*), 7.21 (1H, dd, *J* 8.6, 1.9, Ar*H*), 7.35-7.42 (3H, m, Ar*H*) 7.63-7.65 (1H, m, Ar*H*), 7.71-7.74 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 45.2 (*C*(4)), 52.6 (*C*(3) or *C*H_3), 52.8 (*C*(3) or *C*H_3), 117.9 (*C*(5)), 125.7 (*ArC*), 126.4 (*ArC*),

126.4 (*ArC*), 127.5 (*ArC*), 127.7 (*ArC*), 127.7 (*ArC*), 127.9 (*ArC*), 127.9 (*ArC*), 128.8 (*ArC*), 129.1 (*ArC*), 132.7 (*ArC*), 132.8 (*ArC*), 133.2 (*ArC*), 139.1 (C(4)*ArC*(1), 142.0 (*C*(6)), 160.7 (CO_2CH_3), 166.8 (*C*(2)); *m*/*z* (NSI^+) 376 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{23}H_{22}NO_4^+$ ($[M+NH_4]^+$) requires 376.1543; found 376.1546 (+0.7 ppm).

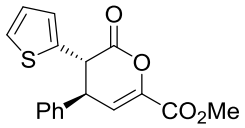
(3*R*,4*R*)-methyl 3-(naphthalen-1-yl)-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**166**

Following general procedure C, 1-naphthyl acetic acid (37.2 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**166** (96:4 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**166** (97:3 dr) as a white solid (51.6 mg, 72%); mp 152-154 °C; $[\alpha]_D^{20}$-129.6 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 14.1 min, t_R(3*S*,4*S*): 15.5 min, 86% *ee*; ν_{max} (KBr)/cm^{-1} 3084, 2956 (C-H), 1770 (C=O lactone), 1739 (C=O ester), 1664, 1599; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, CH_3), 4.15 (1H, dd, *J* 6.7, 4.7, C(4)*H*), 4.61 (1H, d, *J* 6.7, C(3)*H*), 6.59 (1H, d, *J* 4.7, C(5)*H*), 7.00-7.02 (2H, m, Ar*H*), 7.13 (1H, d, *J* 7.0, Ar*H*), 7.17-7.22 (3H, m, Ar*H*), 7.29 (1H, t, *J* 7.7, Ar*H*), 7.41-7.48 (2H, m, Ar*H*), 7.71-7.82 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 45.2 (*C*(4)), 49.3 (*C*(3)), 52.9 (CH_3), 117.5 (*C*(5)), 123.0 (*ArC*), 125.3 (*ArC*), 125.9 (*ArC*), 125.9 (*ArC*), 126.7 (*ArC*), 127.3 (*ArC*), 128.0 (*ArC*), 129.0 (*ArC*), 129.3 (*ArC*), 129.5 (*ArC*), 130.6 (*ArC*), 131.9 (*ArC*), 134.2 (*ArC*), 139.6 (C(4)*ArC*(1)), 141.8 (*C*(6)), 160.8 (CO_2CH_3), 166.6 (*C*(2)); *m*/*z* (NSI^+) 376 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{23}H_{22}NO_4^+$ ($[M+NH_4]^+$) requires 376.1543; found 376.1547 (+1.0 ppm).

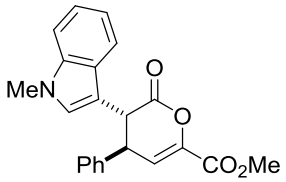
(3*S*,4*R*)-methyl 2-oxo-4-phenyl-3-(thiophen-2-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*S*,4*R*)-**167**

Following general procedure C, 2-(thiophen-2-yl)acetic acid (28.4 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*S*,4*R*)-**167** (80:20 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*S*,4*R*)-**167** (95:5 dr) as a white solid (55.4 mg, 88%); mp 118-120 °C; $[\alpha]_D^{20}$-200.4 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*R*): 13.3 min, t_R(3*R*,4*S*): 30.1 min, 91% *ee*; ν_{max} (KBr)/cm^{-1} 3110, 2953 (C-H), 2919, 1769 (C=O lactone), 1736 (C=O ester), 1656; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.91 (3H, s, CO_2CH_3), 4.13 (1H, dd, *J* 6.7, 4.7 C(4)*H*), 4.30 (1H, d, *J* 6.7, C(3)*H*), 6.73 (1H, d, *J* 4.7, C(5)*H*), 6.88 (1H, dt, *J* 3.5, 0.9, C(3)Ar(3)*H*), 6.94 (1H, dd, *J* 5.1, 3.5, C(3)Ar(4)*H*), 7.14-7.17 (2H, m, Ar*H*), 7.27 (1H, dd, *J* 5.1, 1.2, C(3)Ar(5)*H*), 7.31-7.37 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 45.9 (*C*(4)), 47.8 (*C*(3)), 52.9 (CO_2CH_3), 116.9 (*C*(5)), 125.7 (C(3)*ArC*(5)), 127.0 (*ArC*), 127.0 (*ArC*), 127.3 (*ArC*), 128.2 (*ArC*), 129.3 (*ArC*), 137.0 (C(3)*ArC*(2)), 138.6 (C(4)*ArC*(1)), 142.2 (*C*(6)), 160.6 (CO_2CH_3), 165.5 (*C*(2)); *m*/*z* (CI^+) 332 ($[M+NH_4]^+$, 100%); HRMS (CI^+) $C_{17}H_{18}NO_4S^+$ ($[M+NH_4]^+$) requires 332.0951; found 332.0945 (-1.8 ppm).

(3*R*,4*R*)-methyl 3-(1-methyl-1*H*-indol-3-yl)-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

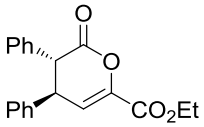


(3*R*,4*R*)-**168**

Following general procedure C, 2-(1-methyl-1*H*-indol-3-yl)acetic acid (37.8 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –30 °C gave crude

lactone (3*R*,4*R*)-**168** (91:9 dr). Chromatographic purification (eluent EtOAc:petrol 25:75) gave lactone (3*R*,4*R*)-**168** (98:2 dr) as a yellow solid (48.0 mg, 66%); mp 48-50 °C; $[\alpha]_D^{20}$-286.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 13.1 min, t_R(3*S*,4*S*): 26.6 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3060, 3028, 2953 (C-H), 1774 (C=O lactone), 1736 (C=O ester), 1663; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.75 (3H, s, NCH_3), 3.92 (3H, s, CO_2CH_3), 4.23 (1H, app t, *J* 5.1, C(4)*H*), 4.34 (1H, d, *J* 4.8, C(3)*H*), 6.73 (1H, dd, *J* 5.3, 0.8, C(5)*H*), 6.90 (1H, s, C(3)Ar(2)*H*), 7.16-7.20 (3H, m, Ar*H*), 7.27-7.38 (5H, m, Ar*H*), 7.64 (1H, dt, *J* 8.0, 0.9, C(3)Ar(4)*H*); δ_C (100 MHz, $CDCl_3$) 32.9 (NCH_3), 44.4 (*C*(3) or *C*(4)), 44.6 (*C*(3) or *C*(4)), 52.8 (CO_2CH_3), 108.8 (C(3)*ArC*(3)), 109.7 (C(3)*ArC*(7)), 116.8 (*C*(5)), 118.9 (*ArC*), 119.8 (*ArC*), 122.3 (*ArC*), 126.3 (C(3)*ArC*(3a)), 126.7 (*ArC*), 127.2 (*ArC*), 128.0 (*ArC*), 129.3 (*ArC*), 137.0 (*ArC*), 139.5 (*ArC*), 142.1 (*C*(6)), 161.0 (CO_2CH_3), 166.3 (*C*(2)); *m*/*z* (NSI^+) 362 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{22}H_{20}NO_4^+$ ($[M+H]^+$) requires 362.1398; found 362.1391 (-1.9 ppm).

(3*R*,4*R*)-ethyl 2-oxo-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

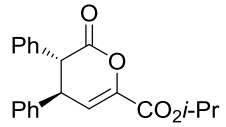


(3*R*,4*R*)-**189**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate[171] (40.8 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**189** (85:15 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**189** (98:2 dr) as a white solid (47.7 mg, 74%); mp 146-148 °C; $[\alpha]_D^{20}$-199.6 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 20.0 min, t_R(3*S*,4*S*): 48.1 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3084, 3067, 2988, 2941 (C-H), 1773 (C=O lactone), 1732 (C=O ester), 1660, 1606; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, CH_2CH_3), 3.85 (1H, d, *J* 8.8, C(3)*H*), 3.98 (1H, dd, *J* 8.8, 3.9, C(4)*H*), 4.24-4.32 (2H, m, CH_2CH_3), 6.60 (1H, d, *J* 3.9, C(5)*H*), 6.95-6.98 (2H, m, Ar*H*), 7.01-7.04 (2H, m, Ar*H*), 7.16-7.23 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 45.5 (*C*(4)), 52.5 (*C*(3)), 62.1 (CH_2CH_3), 117.6 (*C*(5)), 127.5 (*ArC*), 127.9 (*ArC*), 128.0

(*ArC*), 128.4 (Ar*C*), 128.8 (*ArC*), 129.1 (*ArC*), 135.5 (C(3)*ArC*(1)), 139.2 (C(4)*ArC*(1)), 142.3 (*C*(6)), 160.3 (CO_2CH_3), 166.9 (*C*(2)); *m*/*z* (NSI^+) 340 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{20}H_{22}NO_4^+$ ($[M+NH_4]^+$) requires 340.1543; found 340.1546 (+0.8 ppm).

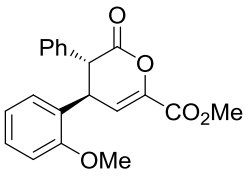
(3*R*,4*R*)-isopropyl 2-oxo-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**190**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **546** (43.6 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −30 °C gave crude lactone (3*R*,4*R*)-**190** (87:13 dr). Chromatographic purification (eluent EtOAc:petrol 10:90) gave lactone (3*R*,4*R*)-**190** (97:3 dr) as a white solid (51.7 mg, 77%); mp 128-130 °C; $[\alpha]_D^{20}$-185.6 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 16.6 min, t_R(3*S*,4*S*): 46.6 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3066, 3030, 2992, 2937 (C-H), 1773 (C=O lactone), 1728 (C=O ester), 1660, 1607; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.37 (6H, dd, *J* 6.3, 1.2, CH(C*H*$_3$)CH_3 and CH(CH_3)C*H*$_3$), 3.94 (1H, d, *J* 9.1, C(3)*H*), 4.06 (1H, dd, *J* 9.1, 3.8, C(4)*H*), 5.23 (1H, sept, *J* 6.3, C*H*(CH_3)$_2$), 6.67 (1H, d, *J* 3.8, C(5)*H*), 7.05-7.08 (2H, m, Ar*H*), 7.10-7.13 (2H, m, Ar*H*), 7.26-7.33 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (CH(*C*H$_3$)CH_3), 21.8 (CH(CH_3)*C*H$_3$), 45.5 (*C*(4)), 52.5 (*C*(3)), 70.0 (*C*H(CH_3)$_2$), 117.4 (*C*(5)), 127.6 (*ArC*), 127.8 (*ArC*), 127.9 (*ArC*), 128.4 (Ar*C*), 128.8 (*ArC*), 129.0 (*ArC*), 135.5 (C(3)*ArC*(1)), 139.3 (C(4)*ArC*(1)), 142.5 (*C*(6)), 159.8 (*C*$O_2$$CH_3$), 167.1 (*C*(2)); *m*/*z* (ES^+) 359 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{21}H_{20}NaO_4^+$ ($[M+Na]^+$) requires 359.1259; found 359.1254 (-1.4 ppm).

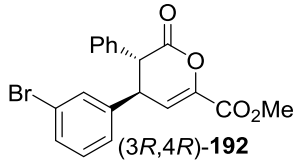
(3*R*,4*R*)-methyl 4-(2-methoxyphenyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**191**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%), keto ester **178** (44.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −30 °C gave crude lactone (3*R*,4*R*)-**191** (89:11 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**191** (96:4 dr) as a white solid (58.9 mg, 87%); mp 78-80 °C; $[\alpha]_D^{20}$-188.8 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 15.0 min, t_R(3*S*,4*S*): 22.3 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3095, 3029, 2957 (C-H), 1778 (C=O lactone), 1740 (C=O ester), 1660, 1617, 1588; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.71 (3H, s, OC*H*$_3$), 3.80 (3H, s, CO_2CH_3), 4.05 (1H, d, *J* 4.6, C(3)*H*), 4.19 (1H, t, *J* 4.9, C(4)*H*), 6.47 (1H, dd, *J* 5.3, 0.7, C(5)*H*), 6.79-6.83 (2H, m, C(4)Ar(3)*H* and C(4)Ar(5)*H*), 6.97 (1H, dd, *J* 7.5, 1.7, C(4)Ar(6)*H*), 7.15-7.26 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 41.5 (*C*(4)), 50.3 (*C*(3)), 52.9 (CO_2CH_3), 55.0 (OCH_3), 111.0 (C(4)*ArC*(3)), 116.3 (*C*(5)), 121.0 (C(4)*ArC*(5)), 127.1 (C(4)*ArC*(1)), 127.6 (*ArC*), 127.8 (Ar*C*), 128.5 (*ArC*), 128.9 (*ArC*), 129.3 (*ArC*), 137.1 (C(3)*ArC*(1)), 141.8 (*C*(6)), 156.9 (C(4)*ArC*(2)), 161.0 (CO_2CH_3), 167.0 (*C*(2)); *m*/*z* (NSI^+) 356 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{20}H_{22}O_5N^+$ ($[M+NH_4]^+$) requires 356.1492; found 356.1493 (+0.1 ppm).

(3*R*,4*R*)-methyl 4-(3-bromophenyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

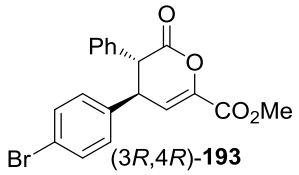


(3*R*,4*R*)-**192**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **548** (53.8 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −30 °C gave crude lactone (3*R*,4*R*)-**192** (97:3 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**192** (98:2 dr) as a white solid (49.7 mg, 64%); mp 110-112 °C; $[\alpha]_D^{20}$-176.8 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (50% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 22.1 min, t_R(3*S*,4*S*): 30.2 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3086,

3061, 3028, 2960 (C-H), 1779 (C=O lactone), 1741 (C=O ester), 1660, 1570; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.80-3.83 (4H, m, C(3)*H* and CH_3), 3.96 (1H, dd, *J* 9.0, 3.8, C(4)*H*), 6.57 (1H, d, *J* 3.8, C(5)*H*), 6.85 (1H, d, *J* 7.7, C(4)Ar(6)*H*), 7.00-7.07 (3H, m, C(4)Ar(5)*H* and Ar*H*), 7.13 (1H, t, *J* 1.7, C(4)Ar(2)*H*), 7.19-7.25 (3H, m, Ar*H*), 7.29-7.31 (1H, m, C(4)Ar(4)*H*); δ_C (100 MHz, $CDCl_3$) 45.1 (*C*(4)), 52.3 (*C*(3) or *C*H_3), 52.9 (*C*(3) or *C*H_3), 116.9 (*C*(5)), 123.0 (C(4)*ArC*(3)), 126.3 (*ArC*), 128.2 (*ArC*), 128.3 (*ArC*), 129.0 (*ArC*), 130.6 (*ArC*), 130.6 (*ArC*), 131.1 (*ArC*), 134.9 (C(3)*ArC*(1)), 141.3 (C(4)*ArC*(1)), 142.4 (*C*(6)), 160.6 (*C*$O_2$$CH_3$), 166.4 (*C*(2)); *m*/*z* (ES^+) 409 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{19}H_{15}{}^{79}BrNaO_4{}^+$ ($[M+Na]^+$) requires 409.0051; found 409.0040 (-2.8 ppm).

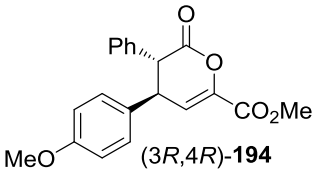
(3*R*,4*R*)-methyl 4-(4-bromophenyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**193**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **547** (53.8 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**193** (94:6 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**193** (98:2 dr) as a white solid (55.1 mg, 71%); mp 68-70 °C; $[\alpha]_D^{20}$-189.2 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (50% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 21.2 min, t_R(3*S*,4*S*): 26.4 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3088, 3031, 2955 (C-H), 1782 (C=O lactone), 1745 (C=O ester), 1660; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.89 (1H, d, *J* 9.4, C(3)*H*), 3.93 (3H, s, CH_3), 4.07 (1H, dd, *J* 9.4, 3.7, C(4)*H*), 6.67 (1H, d, *J* 3.7, C(5)*H*), 6.92-6.95 (2H, m, C(4)Ar(2,6)*H*), 7.09-7.12 (2H, m, Ar*H*), 7.30-7.34 (3H, m, Ar*H*) 7.40-7.43 (2H, m, C(4)Ar(3,5)*H*); δ_C (75 MHz, $CDCl_3$) 45.3 (*C*(4)), 52.8 (*C*(3) or *C*H_3), 53.3 (*C*(3) or *C*H_3), 117.7 (*C*(5)), 122.3 (C(4)*ArC*(4)), 128.5 (C(3)*ArC*(4)), 128.8 (*ArC*), 129.3 (*ArC*), 129.7 (*ArC*), 132.6 (C(4)*ArC*(3,5)), 135.5 (C(3)*ArC*(1)), 138.6 (C(4)*ArC*(1)), 142.7 (*C*(6)), 161.0 (*C*$O_2$$CH_3$), 166.9 (*C*(2)); *m*/*z* (ES^+) 409 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{19}H_{15}{}^{79}BrNaO_4{}^+$ ($[M+Na]^+$) requires 409.0051; found 409.0059 (+1.8 ppm).

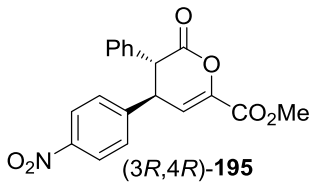
(3*R*,4*R*)-methyl 4-(4-methoxyphenyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**194**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **549** (44.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 40 h at −30 °C gave crude lactone (3*R*,4*R*)-**194** (92:8 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**194** (92:8 dr) as a white solid (50.0 mg, 74%); mp 98-100 °C; $[\alpha]_D^{20}$-191.6 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (50% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 22.7 min, t_R(3*S*,4*S*): 29.0 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3095, 3031, 2954 (C-H), 1778 (C=O lactone), 1736 (C=O ester), 1660, 1614, 1586, 1513; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, OC*H*$_3$), 3.81-3.83 (4H, m, C(3)*H* and CO_2CH_3), 3.94 (1H, dd, *J* 8.6, 4.0, C(4)*H*), 6.60 (1H, d, *J* 4.0, C(5)*H*), 6.70-6.73 (2H, m, C(4)Ar(3,5)*H*), 6.86-6.90 (2H, m, C(4)Ar(2,6)*H*), 7.02-7.04 (2H, m, Ar*H*) 7.19-7.24 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.7 (*C*(4)), 52.7 (*C*(3) or CO_2CH_3), 52.8 (*C*(3) or CO_2CH_3), 55.3 (O*C*H$_3$), 114.4 (C(4)*ArC*(3,5)), 118.2 (*C*(5)), 127.9 (C(3)*ArC*(4)), 128.3 (*ArC*), 128.6 (*ArC*), 128.8 (*ArC*), 131.1 (C(4)*ArC*(1)), 135.5 (C(3)*ArC*(1)), 141.8 (*C*(6)), 159.1 (C(4)*ArC*(4)), 160.8 (CO_2CH_3), 166.9 (*C*(2)); *m*/*z* (ES^+) 361 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{20}H_{18}NaO_5^+$ ($[M+Na]^+$) requires 361.1052; found 361.1045 (-1.9 ppm).

(3*R*,4*R*)-ethyl 4-(4-nitrophenyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

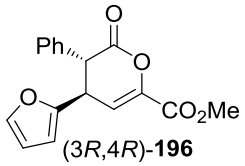


(3*R*,4*R*)-**195**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), (*E*)-methyl 4-(4-nitrophenyl)-2-oxobut-3-enoate[171] (49.8 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30

mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**195** (91:9 dr). Chromatographic purification (eluent EtOAc:petrol 20:80) gave lactone (3*R*,4*R*)-**195** (91:9 dr) as a light yellow solid (46.4 mg, 63%); mp 116-118 °C; $[\alpha]_D^{20}$-143.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (50% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 34.2 min, t_R(3*S*,4*S*): 41.7 min, 90% *ee*; ν_{max} (KBr)/cm^{-1} 3083, 3032, 2997 (C-H), 1775 (C=O lactone), 1727 (C=O ester), 1668, 1597, 1518 (N=O), 1353 (N=O); Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.1, CH_2CH_3), 3.79 (1H, d, *J* 10.4, C(3)*H*), 4.12 (1H, dd, *J* 10.4, 3.4, C(4)*H*), 4.27-4.33 (2H, m, CH_2CH_3), 6.56 (1H, d, *J* 3.4, C(5)*H*), 6.96-6.99 (2H, m, Ar*H*), 7.11-7.13 (2H, m, C(4)Ar(2,6)*H*), 7.19-7.24 (3H, m, Ar*H*), 8.03-8.05 (2H, m, C(4)Ar(3,5)*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 45.3 (*C*(4)), 52.2 (*C*(3)), 62.4 (CH_2CH_3), 115.9 (*C*(5)), 124.2 (C(4)*ArC*(3,5)), 128.4 (C(3)*ArC*(4)), 128.5 (*ArC*), 128.7 (*ArC*), 129.1 (*ArC*), 134.4 (C(3)*ArC*(1)), 143.1 (*C*(6)), 146.5 (*ArC*), 147.5 (*ArC*), 159.9 ($CO_2CH_2CH_3$), 166.2 (*C*(2)); *m*/*z* (ES^+) 390 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{20}H_{17}NNaO_6^+$ ($[M+Na]^+$) requires 390.0954; found 390.0942 (-2.9 ppm).

(3*R*,4*R*)-methyl 4-(furan-2-yl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

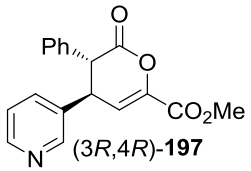


(3*R*,4*R*)-**196**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **174** (36.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**196** (98:2 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**196** (99:1 dr) as a white solid (43.0 mg, 72%); mp 80-82 °C; $[\alpha]_D^{20}$-190.0 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralcel OJ-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 49.5 min, t_R(3*R*,4*R*): 56.2 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3092, 2954 (C-H), 1770 (C=O lactone), 1732 (C=O ester), 1662, 1508; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, CH_3), 4.18-4.23 (2H, m, C(3)*H* and C(4)*H*), 6.05 (1H, d, *J* 3.3, C(5)*H*), 6.28 (1H, dd, *J* 3.3, 1.9, C(4)Ar(3)*H*), 6.66 (1H, dd, *J*

3.8, 1.4, C(4)Ar(4)*H*), 7.21-7.23 (2H, m, C(3)Ar(2,6)*H*), 7.32-7.38 (4H, m, C(3)Ar(3,5)*H*, C(3)Ar(4)*H* and C(4)Ar(5)*H*); δ_C (100 MHz, $CDCl_3$) 38.7 (*C*(4)), 49.2 (*C*(3), 52.8 (*C*$O_2$$CH_3$), 107.4 (*C*(5)), 110.5 (C(4)*ArC*(3)), 114.7 (C(4)*ArC*(4)), 127.9 (*ArC*), 128.2 (C(3)*ArC*(4)), 129.0 (*ArC*), 135.0 (C(3)*ArC*(1)), 142.3 (*C*(6)), 142.8 (C(4)*ArC*(5)), 150.7 (C(4)*ArC*(2)), 160.6 (*C*$O_2$$CH_3$), 166.4 (*C*(2)); *m*/*z* (ES^+) 321 ($[M+Na]^+$, 95%); HRMS (ES^+) $C_{17}H_{14}NaO_5^+$ ($[M+Na]^+$) requires 321.0739; found 321.0741 (+0.6 ppm).

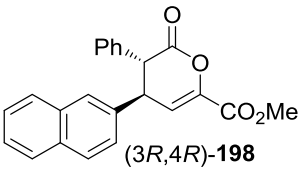
(3*R*,4*R*)-methyl 2-oxo-3-phenyl-4-(pyridin-3-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**197**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **551** (38.2 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**197** (94:6 dr). Chromatographic purification (eluent EtOAc:petrol 65:35) gave lactone (3*R*,4*R*)-**197** (93:7 dr) as a white solid (53.8 mg, 87%); mp 104-106 °C; $[\alpha]_D^{20}$-119.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 39.2 min, t_R(3*S*,4*S*): 53.1 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3086, 2992, 2955 (C-H), 1775 (C=O lactone), 1731 (C=O ester), 1662; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.80 (1H, d, *J* 9.9, C(3)*H*), 3.83 (3H, s, CH_3), 4.04 (1H, dd, *J* 9.9, 3.6, C(4)*H*), 6.59 (1H, d, *J* 3.6, C(5)*H*), 6.99-7.01 (2H, m, C(3)Ar(2,6)*H*), 7.12-7.15 (1H, m, C(4)Ar(5)*H*), 7.19-7.25 (3H, m, C(3)Ar(3,5)*H* and C(3)Ar(4)*H*), 7.29 (1H, dt, *J* 7.9, 2.1, C(4)Ar(4)*H*), 8.22 (1H, d, *J* 2.1, C(4)Ar(2)*H*), 8.42 (1H, dd, *J* 4.8, 1.5, C(4)Ar(6)*H*); δ_C (100 MHz, $CDCl_3$) 43.1 (*C*(4)), 52.3 (*C*(3) or *C*$O_2$$CH_3$), 52.9 (*C*(3) or *C*$O_2$$CH_3$), 116.7 (*C*(5)), 123.8 (C(4)*ArC*(5)), 128.3 (C(3)*ArC*(4)), 128.5 (*ArC*), 129.0 (*ArC*), 134.5 (C(3)*ArC*(1)), 134.9 (C(4)*ArC*(3)), 134.9 (C(4)*ArC*(4)), 142.8 (*C*(6)), 149.2 (C(4)*ArC*(2)), 149.4 (C(4)*ArC*(6)), 160.5 (*C*$O_2$$CH_3$), 166.3 (*C*(2)); *m*/*z* (ES^+) 310 ($[M+H]^+$, 32%); HRMS (ES^+) $C_{18}H_{16}NO_4^+$ ($[M+H]^+$) requires 310.1079; found 310.1087 (+2.4 ppm).

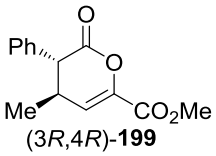
(3*R*,4*R*)-methyl 4-(naphthalen-2-yl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**198**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **550** (48.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**198** (95:5 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave lactone (3*R*,4*R*)-**198** (99:1 dr) as a white solid (59.0 mg, 82%); mp 146-148 °C; $[\alpha]_D^{20}$-259.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (50% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 25.0 min, t_R(3*S*,4*S*): 29.2 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3054, 3025, 2955 (C-H), 1788 (C=O lactone), 1736 (C=O ester), 1663, 1600; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.95 (3H, s, CH_3), 4.10 (1H, d, *J* 8.6, C(3)*H*), 4.27 (1H, dd, *J* 8.6, 4.0, C(4)*H*), 6.80 (1H, d, *J* 4.0, C(5)*H*), 7.16-7.21 (3H, m, Ar*H*), 7.27-7.34 (3H, m, Ar*H*), 7.50-7.54 (3H, m, Ar*H*), 7.76-7.85 (3H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 45.5 (*C*(4)), 52.4 (*C*(3) or *C*O_2CH_3), 52.9 (*C*(3) or *C*O_2CH_3), 117.7 (*C*(5)), 125.2 (*ArC*), 126.3 (*ArC*), 126.5 (*ArC*), 126.6 (*ArC*), 127.7 (*ArC*), 127.8 (*ArC*), 128.0 (*ArC*), 128.3 (*ArC*), 128.9 (*ArC*), 129.1 (*ArC*), 132.8 (*ArC*), 133.4 (*ArC*), 135.4 (*ArC*), 136.4 (*ArC*), 142.1 (*C*(6)), 160.8 (*C*O_2CH_3), 166.8 (*C*(2)); *m*/*z* (ES^+) 381 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{23}H_{18}NaO_4^+$ ($[M+Na]^+$) requires 381.1103; found 381.1089 (-3.7 ppm).

(3*R*,4*R*)-methyl 4-methyl-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

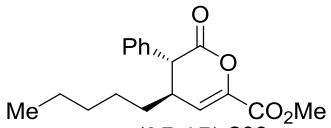


(3*R*,4*R*)-**199**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), (E)-methyl 2-oxopent-3-enoate[171] (25.6 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**199** (88:12 dr). Chromatographic purification (eluent EtOAc:petrol 15:85) gave

lactone (3*R*,4*R*)-**199** (93:7 dr) as a white solid (39.6 mg, 80%); mp 94-96 °C; $[\alpha]_D^{20}$-46.7 (*c* 0.15, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 12.7 min, t_R(3*S*,4*S*): 17.4 min, 96% *ee*; ν_{max} (KBr)/cm^{-1} 3089, 2976 (C-H), 2952, 1768 (C=O lactone), 1729 (C=O ester), 1661, 1499; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 7.1, C(4)HC*H*$_3$), 2.86-2.95 (1H, m, C(4)*H*), 3.39 (1H, d, *J* 10.4, C(3)*H*), 3.79 (3H, s, CO_2CH_3), 6.44 (1H, d, *J* 3.3, C(5)*H*), 7.11-7.13 (2H, m, Ar(2,6)*H*), 7.23-7.32 (3H, m, Ar(3,5)*H* and Ar(4)*H*)); δ_C (100 MHz, $CDCl_3$) 19.0 (C(4)*C*H$_3$), 33.3 (*C*(4)), 52.0 (*C*(3) or CO_2CH_3), 52.7 (*C*(3) or CO_2CH_3), 120.7 (*C*(5)), 128.0 (*ArC*(4)), 128.5 (*ArC*), 129.0 (*ArC*), 135.4 (*ArC*(1)), 141.1 (*C*(6)), 160.8 (*C*O$_2$CH$_3$), 167.8 (*C*(2)); *m*/*z* (ES^+) 269 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{14}H_{14}NaO_4^+$ ($[M+Na]^+$) requires 269.0790; found 269.0789 (-0.5 ppm).

(3*R*,4*R*)-methyl 2-oxo-4-pentyl-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



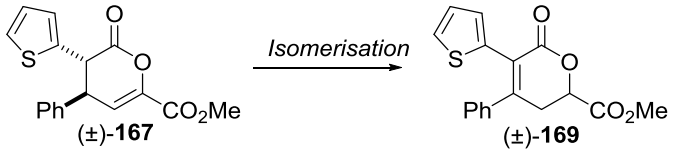
(3*R*,4*R*)-**200**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), (*E*)-methyl 2-oxonon-3-enoate[171] (36.8 mg, 0.20 mmol) and *i*-Pr$_2$NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr$_2$NEt (87 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**200** (80:20 dr). Chromatographic purification (eluent EtOAc:petrol 10:90) gave lactone (3*R*,4*R*)-**200** (90:10 dr) as a white solid (46.1 mg, 76%); mp 48-50 °C; $[\alpha]_D^{20}$-87.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 9.7 min, t_R(3*S*,4*S*): 13.2 min, 95% *ee*; ν_{max} (KBr)/cm^{-1} 2929, 2860 (C-H), 1777 (C=O lactone), 1741 (C=O ester), 1661; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.79 (3H, t, *J* 7.0, (CH$_2$)$_4$C*H*$_3$), 1.12-1.41 (8H, m, 4C*H*$_2$), 2.76-2.83 (1H, m, C(4)*H*), 3.58 (1H, d, *J* 8.6, C(3)*H*), 3.79 (3H, s, CO_2CH_3), 6.51 (1H, d, *J* 4.1, C(5)*H*), 7.11-7.13 (2H, m, Ar(2,6)*H*), 7.23-7.32 (3H, m, Ar(3,5)*H* and Ar(4)*H*); δ_C (100 MHz, $CDCl_3$) 14.0 ((CH$_2$)$_4$*C*H$_3$), 22.5 (*C*H$_2$), 25.8 (*C*H$_2$), 31.5 (*C*H$_2$), 32.7 (*C*H$_2$), 38.2 (*C*(4)), 49.9 (*C*(3)), 52.7 (CO_2CH_3), 118.8 (*C*(5)), 128.0 (*ArC*(4)), 128.2 (*ArC*), 129.0 (*ArC*), 135.6 (*ArC*(1)), 141.4 (*C*(6)), 160.8 (*C*O$_2$CH$_3$), 167.8 (*C*(2)); *m*/*z* (ES^+) 325 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{18}H_{22}NaO_4^+$ ($[M+Na]^+$) requires 325.1416; found 325.1419 (+0.9 ppm).

Isomerisation studies

The Michael addition-lactonisation to form lactone (±)-**167** was carried out for 30 minutes at −78 °C with DHPB **108** as catalyst. At higher reaction temperatures, such as rt, lactone (±)-**167** showed a marked propensity to isomerise to lactone (±)-**169**. Carrying out the reaction at −78 °C, followed by addition of HCl (1 M in H_2O) to quench the reaction at −78 °C prevents the formation of lactone (±)-**169**.

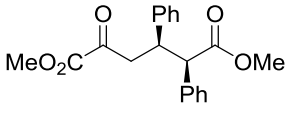
A simple NMR experiment showed that addition of DHPB to (±)-**167** in $CDCl_3$ rapidly promoted complete isomerisation to (±)-**169**.



Characterisation data for compound (±)-**169**:

Lactone (±)-**169** was obtained as a light yellow oil; ν_{max} (thin film)/cm^{-1} 3064, 2955 (C-H), 2921, 2852, 1752 (C=O lactone), 1725 (C=O ester), 1625, 1587; δ_H (400 MHz, $CDCl_3$) 3.18 (2H, d, *J* 5.3, C(5)*H*), 3.78 (3H, s, CO_2CH_3), 5.11 (1H, t, *J* 5.3, C(6)*H*), 6.73-6.75 (2H, m, C(3)Ar(3)*H*), 7.08-7.10 (2H, m, Ar*H*), 7.15-7.17 (1H, m, Ar*H*), 7.21-7.24 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 33.9 (*C*(5)), 53.2 (CO_2CH_3), 73.6 (*C*(6)), 122.6 (*C*(3)), 126.3 (*ArC*), 127.3 (*ArC*), 128.2 (*ArC*), 128.7 (*ArC*), 129.2 (*ArC*), 130.1 (*ArC*), 134.2 (C(3)*ArC*(2)), 137.9 (C(4)*ArC*(1)), 149.8 (*C*(4)), 162.9 (*C*(2)), 169.7 (CO_2CH_3); *m*/*z* (ES^+) 337 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{17}H_{14}NaO_4S^+$ ($[M+Na]^+$) requires 337.0511; found 337.0513 (+0.8 ppm).

(2*R*,3*R*)-dimethyl 5-oxo-2,3-diphenylhexanedioate



(2*R*,3*R*)-**201**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), ketoester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (51.9 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), pivaloyl chloride (37.0 μL, 0.30 mmol), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at –30 °C followed by addition of MeOH (2 mL) and stirring at rt for 1 h gave crude diester (2*R*,3*R*)-**201** (95:5 dr). Chromatographic

purification (eluent EtOAc:petrol 15:85) gave diester (2*R*,3*R*)-**201** (97:3 dr) as a colourless oil (62.3 mg, 92%); $[\alpha]_D^{20}$-108.8 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 19.3 min, t_R(3*S*,4*S*): 23.4 min, 96% *ee*; ν_{max} (thin film)/cm^{-1} 3064, 3031, 2954 (C-H), 2849, 1732 (C=O), 1603; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.14 (1H, dd, *J* 17.4, 4.3, C(4)*H*), 3.44 (1H, dd, *J* 17.4, 9.3, C(4)*H*), 3.60 (3H, s, CO_2CH_3), 3.70 (3H, s, $C(O)CO_2CH_3$), 3.79 (1H, d, *J* 10.9, C(2)*H*), 3.84-3.96 (1H, m, C(3)*H*), 6.92-7.06 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 44.0 (*C*(4)), 44.2 (*C*(3)), 52.3 (CH_3), 53.0 (CH_3), 57.3 (*C*(2), 126.8 (*ArC*), 127.4 (*ArC*), 128.2 (*ArC*), 128.3 (*ArC*), 128.4 (*ArC*), 128.5 (*ArC*), 136.4 (C(2)*ArC*(1)), 140.1 (C(3)*ArC*(1)), 161.0 ($C(O)CO_2CH_3$), 173.4 (*C*(1)), 191.7 (*C*(5)); *m*/*z* (ES^+) 363 ($[M+Na]^+$, 90%); HRMS (ES^+) $C_{20}H_{20}NaO_5^+$ ($[M+Na]^+$) requires 363.1208; found 363.1210 (+0.4 ppm).

9.2.2 References and Notes

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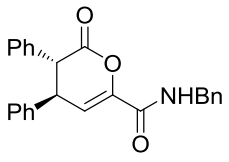
9.3 Experimental for Chapter 3

9.3.1 Experimental Procedures and Characterisation Data

General procedure D: *Intermolecular Michael addition-lactonisation.*

To a solution of acid (1 eq) in CH_2Cl_2 (~1 mL per 0.2 mmol of acid) were added *i*-Pr_2NEt (1.5 eq based on acid) and pivaloyl chloride (1.5 eq based on acid) at rt. The reaction mixture was allowed to stir at rt for 10 minutes. The requisite Lewis base (1-20 mol%), Michael acceptor (1 eq) and *i*-Pr_2NEt (2.5 eq) were then added at the required temperature in that order. The reaction mixture was stirred at the required temperature until complete by TLC and was subsequently quenched by addition of HCl (1 M in H_2O). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture. Note: All racemic samples were obtained *via* this general procedure using DHPB **108** as catalyst.

(3*R*,4*R*)-*N*-benzyl-2-oxo-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxamide

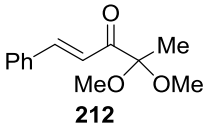


(3*R*,4*R*)-**209**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%), (*E*)-*N*-benzyl-2-oxo-4-phenylbut-3-enamide[171] (53.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at –30 °C gave crude lactone (3*R*,4*R*)-**209** (68:32 dr). Chromatographic purification (eluent EtOAc:petrol 25:75) gave lactone (3*R*,4*R*)-**209** (97:3 dr) as a white solid (47.1 mg, 61%); mp 50-52 °C; $[\alpha]_D^{20}$-158.0 (*c* 0.15, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 10.5 min, t_R(3*R*,4*R*): 13.3 min, 95% *ee*; ν_{max} (KBr)/cm^{-1} 3063, 3031, 2959, 2932 (C-H), 1774 (C=O lactone), 1731 (C=O amide), 1660, 1527; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.82 (1H, d, *J* 9.3, C(3)*H*), 3.99 (1H, dd, *J* 9.3, 3.7, C(4)*H*), 4.49 (2H, qd, *J* 13.3, 5.9, CH_2Ph),

6.65 (1H, d, *J* 3.7, C(5)*H*), 6.91-6.95 (2H, m, Ar*H*), 6.97-7.02 (2H, m, Ar*H*), 7.13-7.32 (11H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 43.7 (*C*H_2Ph), 45.1 (*C*(4)), 52.8 (*C*(3)), 114.0 (*C*(5)), 127.6 (*ArC*), 127.8 (*ArC*), 127.9 (*ArC*), 128.1 (Ar*C*), 128.2 (*ArC*), 128.4 (*ArC*), 128.8 (*ArC*) 128.9 (*ArC*), 129.0 (*ArC*), 135.4 (*ArC*), 137.2 (*ArC*), 139.4 (*ArC*), 144.0 (*C*(6)), 159.1 (*C*ONH), 167.2 (*C*(2)); *m*/*z* (NSI^+) 384 ($[M+H]^+$, 78%); HRMS (NSI^+) $C_{25}H_{22}NO_3^+$ ($[M+H]^+$) requires 384.1594; found 384.1597 (+0.7 ppm).

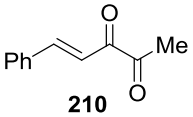
(*E*)-4,4-dimethoxy-1-phenylpent-1-en-3-one



212

To a solution of benzaldehyde (1.02 mL, 10.0 mmol) and 3,3-dimethoxybutan-2-one (1.22 mL, 9.1 mmol) in MeOH (10 mL) was added a solution of NaOH (1.6 g, 40 mmol) in H_2O (8 mL). The reaction mixture was stirred at rt for 16 h. The MeOH was removed under reduced pressure and the reaction mixture was extracted with Et_2O (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by heating at 100 °C under reduced pressure to remove volatile impurities giving **212** as a yellow oil (1.59 g, 80 %); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, CH_3), 3.24 (6H, s, 2 OCH_3), 7.20 (1H, d, *J* 16.0, C(2)*H*), 7.32-7.35 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.54-7.57 (2H, m, Ar(2,6)*H*), 7.73 (1H, d, *J* 16.0, C(1)*H*). Spectroscopic data are in accordance with the literature.[77]

(*E*)-5-phenylpent-4-ene-2,3-dione

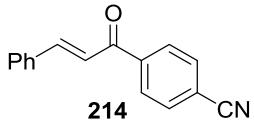


210

To a solution of *p*-toluene sulfonic acid mono hydrate (173 mg, 0.91 mmol) in acetone (50 mL) was added **212** (1.00 g, 4.55 mmol) and the reaction was allowed to stir at rt for 16 h. The acetone was removed under reduced pressure and the residue was dissolved in Et_2O. The organic fraction was washed several times with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent EtOAc:petrol 5:95) gave keto enone **210** as a yellow solid (0.42 g, 53%); mp 50-52 °C; {lit.[176] mp 48-50 °C}; δ_H (400 MHz, $CDCl_3$) 2.48 (3H, s, CH_3), 7.43-7.49 (4H, m, Ar(3,5)*H*, Ar(4)*H* and

C(4)*H*), 7.66-7.68 (2H, m, Ar(2,6)*H*), 7.87 (1H, d, *J* 16.2, C(5)*H*). Spectroscopic data are in accordance with the literature.[77]

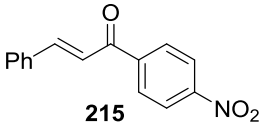
4-cinnamoylbenzonitrile



214

To a solution of NaOH (3.00 g, 75.0 mmol) in ethanol (40 mL), at 0 °C was added 4-acetylbenzonitrile (1.45 g, 10.0 mmol). The solution was warmed to rt and benzaldehyde (1.02 mL, 10.0 mmol) was added. The reaction mixture was allowed to stir for 16 h at 0 °C. The solid was then filtered, washed with H_2O, dried and recrystallised from ethanol to give enone **214** as a yellow solid (0.95 g, 41 %); mp 122-124 °C (EtOH); {lit.[176] mp 110-112 °C (EtOH)}; δ_H (500 MHz, $CDCl_3$) 7.45-7.50 (4H, m, Ar*H* and C(2)*H*), 7.66-7.68 (2H, m, Ar*H*), 7.82-7.87 (3H, m, Ar*H* and C(3)*H*), 8.10 (2H, d, *J* 8.4, Ar*H*). Spectroscopic data are in accordance with the literature.[176]

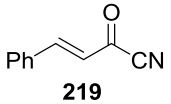
(*E*)-1-(4-nitrophenyl)-3-phenylprop-2-en-1-one



215

To a solution of NaOH (3.00 g, 75.0 mmol) in ethanol (40 mL), at 0 °C was added 1-(4-nitrophenyl)ethanone (1.65 g, 10.0 mmol). The solution was warmed to rt and benzaldehyde (1.02 mL, 10.0 mmol) was added. The reaction mixture was allowed to stir for 16 h at 0 °C. The solid was then filtered, washed with H_2O, dried and recrystallised from ethanol to give enone **215** as an orange solid (1.49 g, 59 %); mp 148-150 °C (EtOH); {lit.[177] mp 151-152 °C (EtOH)}; δ_H (400 MHz, $CDCl_3$) 7.38-7.44 (4H, m, C(3)Ar(3,5)*H*, C(3)Ar(4)*H* and C(2)*H*), 7.59-7.61 (2H, m, C(3)Ar(2,6)*H*), 7.89 (1H, d, *J* 15.7, C(3)*H*), 8.07-8.10 (2H, m, C(1)Ar(2,6)*H*), 8.28-8.31 (2H, m, C(1)Ar(3,5)*H*). Spectroscopic data are in accordance with the literature.[177]

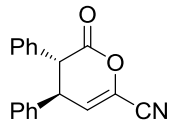
cinnamoyl cyanide



219

To a solution of cinnamoyl chloride (1.00 g, 6.00 mmol) and *n*-Bu_4NBr (194 mg, 0.60 mmol) in CH_2Cl_2 (30 mL) was added a solution of NaCN (293 mg, 6.00 mmol) in H_2O (2 mL) at 0 °C. The reaction mixture was stirred for 1 h after which time the solids were filtered off and washed with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 4:96) gave enone **219** as a light yellow solid (0.33 g, 35%); mp 110-112 °C; {lit.[178] mp 115 °C}; δ_H (500 MHz, $CDCl_3$) 6.80 (1H, dd, *J* 16.2, 0.8, C(2)*H*), 7.41-7.44 (2H, m, Ar(3,5)*H*), 7.47-7.50 (1H, m, Ar(4)*H*), 7.58 (2H, d, *J* 7.8, Ar(2,6)*H*), 7.95 (1H, d, *J* 16.2, C(3)*H*). Spectroscopic data are in accordance with the literature.[178]

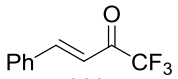
(3*R*,4*R*)-2-oxo-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carbonitrile



(3*R*,4*R*)-**223**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%), enone **219** (31.4 mg, 0.20 mmol) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 15 minutes at rt gave crude lactone (3*R*,4*R*)-**223** (79:21 dr). Chromatographic purification (eluent EtOAc:petrol 10:90) gave lactone (3*R*,4*R*)-**223** (>98:2 dr) as a white solid (36.9 mg, 67%); mp 90-92 °C; $[\alpha]_D^{20}$-204.4 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 15.2 min, t_R(3*S*,4*S*): 17.0 min, 96% *ee*; ν_{max} (KBr)/cm^{-1} 3079, 3030, 2962 (C-H), 2238 (C≡N), 1781 (C=O), 1666; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.90 (1H, d, *J* 8.9, C(3)*H*), 4.00 (1H, dd, *J* 3.9, 8.9, C(4)*H*), 6.29 (1H, d, *J* 3.9, C(5)*H*), 6.93-6.95 (2H, m, Ar*H*), 6.99-7.02 (2H, m, Ar*H*), 7.19-7.25 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 45.9 (*C*(4)), 52.5 (*C*(3)), 112.0 (*C*N), 123.5 (*C*(5), 127.3 (*C*(6)), 127.4 (*ArC*), 127.4 (*ArC*), 128.2 (Ar*C*), 128.4 (*ArC*), 129.0 (*ArC*), 129.3 (*ArC*), 134.5 (C(3)*ArC*(1)), 138.0 (C(4)*ArC*(1)), 165.0 (*C*(2)); *m*/*z* ($APCI^+$) 293 ($[M+NH_4]^+$, 100%); HRMS ($APCI^+$) $C_{18}H_{17}O_2N_2^+$ ($[M+NH_4]^+$) requires 293.1285; found 293.1292 (+2.5 ppm).

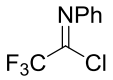
(*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one



220

To a solution of benzaldehyde (0.51 mL, 5.00 mmol), glacial acetic acid (0.5 mL, 8.73 mmol) and piperidine (0.50 mL, 5.06 mmol) in THF (40 mL) at rt was added trifluoroacetone (0.45 mL, 5.00 mmol). A further three portions of trifluoroacetone (0.45 mL, 5.00 mmol) were added every 30 minutes. After stirring for 2 h the reaction was quenched with sat. aq. NH_4Cl and extracted with Et_2O (x 3). The combined organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent CH_2Cl_2:petrol 10:90) gave enone **220** as a colourless oil (0.21 g, 21 %); δ_H (500 MHz, $CDCl_3$) 6.96 (1H, d, *J* 16.0, C(3)*H*), 7.37-7.45 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.57-7.59 (2H, m, Ar(2,6)*H*), 7.91 (1H, d, *J* 16.0, C(4)*H*); δ_F (470 MHz, $CDCl_3$) -77.6 (CF_3). Spectroscopic data are in accordance with the literature.[179]

(*Z*)-2,2,2-trifluoro-*N*-phenylacetimidoyl chloride



245

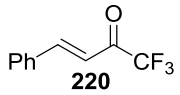
To a solution of triphenylphosphine (34.6 g, 0.13 mol), Et_3N (7.39 mL, 53.0 mmol), trifluoroacetic acid (3.37 mL, 44.0 mmol) and CCl_4 (21 mL) was stirred for 10 minutes before aniline (4.83 mL, 53.0 mmol) was added and the reaction mixture was stirred at reflux for 3 h. The reaction mixture was then concentrated *in vacuo* and the residue taken up in hexane. The precipitate was filtered and washed several times with hexane. The filtrate was concentrated *in vacuo* and the residual oil was purified by distillation to give imine **245** as a yellow oil (3.08 g, 34%); bp 50-52 °C (5 mmHg); {lit.[83] bp 55-56 °C (11 mmHg)}; δ_H (300 MHz, $CDCl_3$) 6.98-7.02 (2H, m, Ar(2,6)*H*), 7.18-7.24 (1H, m, Ar(4)*H*), 7.31-7.38 (2H, m, Ar(3,5)*H*); δ_F (282 MHz, $CDCl_3$) -72.1 (CF_3). Spectroscopic data are in accordance with the literature.[83]

General procedure E: *Formation of trifluoromethyl enones.*

To a solution of *i*-Pr_2NH (2 eq) in THF was added *n*-BuLi (2.5M in hexanes, 2 eq) at −78 °C and the solution was allowed to stir for 20 minutes. Diethyl methylphosphonate (1 eq) was added at −78 °C followed by a further 30 minutes of stirring. (*Z*)-2,2,2-

trifluoro-*N*-phenylacetimidoyl chloride (1 eq) was then added slowly followed by stirring at −78 °C for 1 h. A solution of the requisite aldehyde (1 eq) in THF was then added dropwise at −78 °C. The reaction mixture was then warmed to rt over 2 h and stirred for 16 h. HCl (2 M in H_2O, 4 eq) was added and the reaction mixture was stirred for a further 4 h before being extracted with Et_2O (x 3). The combined organic extracts were washed with sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture.

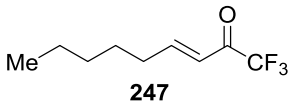
(*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one



220

Following general procedure E, *i*-Pr_2NH (5.44 mL, 40.0 mmol) and *n*-BuLi (2.5M in hexanes, 16.0 mL, 40.0 mmol) in THF (80 mL), diethyl methylphosphonate (2.96 mL, 20.0 mmol), imine **245** (4.16 g, 20.0 mmol) and benzaldehyde (2.04 mL, 20.0 mmol) in THF (20 mL) followed by HCl (2 M in H_2O, 40 mL, 80 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 5:95) gave enone **220** as a light yellow oil (3.63 g, 91%); δ_H (500 MHz, $CDCl_3$) 6.96 (1H, d, *J* 16.0, C(3)*H*), 7.37-7.45 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.57-7.59 (2H, m, Ar(2,6)*H*), 7.91 (1H, d, *J* 16.0, C(4)*H*); δ_F (470 MHz, $CDCl_3$) -77.6 (CF_3). Spectroscopic data are in accordance with the literature.[179]

(*E*)-1,1,1-trifluorononon-3-en-2-one

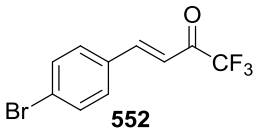


247

Following general procedure E, diisopropylamine (1.36 mL, 10.0 mmol) and *n*-BuLi (2.5M in hexanes, 4 mL, 10.0 mmol) in THF (20 mL), diethyl methylphosphonate (0.74 mL, 5.00 mmol), imine **245** (1.04 g, 5.00 mmol) and hexanal (0.61 mL, 5.00 mmol) in THF (10 mL) followed by HCl (2 M in H_2O, 10 mL, 20 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 10:90) gave enone **247** as a light yellow oil (0.74 g, 76%); ν_{max} (ATR)/cm^{-1} 2959 (C-H), 2932, 1728 (C=O), 1628; δ_H (500 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.1, CH_3), 1.33-1.37 (4H, m, 2 CH_2), 1.53-1.58 (2H, m, CH_2), 2.36 (2H, qd, *J* 7.4, 1.2, CH_2C=), 6.44 (1H, dd, *J* 15.8, 0.9, C(3)*H*), 7.36 (1H,

dt, *J* 15.3, 7.4, C(4)*H*); δ_C (125 MHz, $CDCl_3$) 14.1 (*C*H_3), 22.5 (*C*H_2CH$_3$), 27.4 (*C*H_2Et), 31.5 (=*C*H_2), 116.5 (q, *J* 290, *C*F_3), 121.5 (*C*(3)), 157.1 (*C*(4)), 180.0 (q, *J* 35.1, *C*(2)); δ_F (376 MHz, $CDCl_3$) -77.5 (C*F*$_3$); *m*/*z* (APCI$^+$) 195 ([M+H]$^+$, 70%); HRMS (APCI$^+$) $C_9H_{14}F_3O^+$ ([M+H]$^+$) requires 195.0991; found 195.0989 (-1.2 ppm).

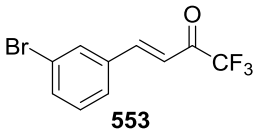
(*E*)-4-(4-bromophenyl)-1,1,1-trifluorobut-3-en-2-one



552

Following general procedure E, *i*-Pr$_2$NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 4-bromobenzaldehyde (0.46 g, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 3:97) gave enone **552** as a light yellow solid (0.52 g, 75%); mp 40-42 °C; {lit.[180] mp 55-57 °C}; δ_H (300 MHz, $CDCl_3$) 6.94 (1H, dd, *J* 16.0, 0.8, C(3)*H*), 7.41-7.45 (2H, m, Ar*H*), 7.51-7.55 (2H, m, Ar*H*), 7.83 (1H, d, *J* 16.0, C(4)*H*); δ_F (470 MHz, $CDCl_3$) -78.1 (C*F*$_3$). Spectroscopic data are in accordance with the literature.[180]

(*E*)-4-(3-bromophenyl)-1,1,1-trifluorobut-3-en-2-one

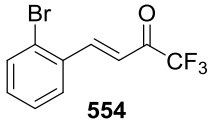


553

Following general procedure E, *i*-Pr$_2$NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 3-bromobenzaldehyde (0.46 g, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 3:97) gave enone **553** as a light yellow oil (0.43 g, 62%); ν_{max} (film)/cm^{-1} 3067, 2921 (C-H), 1722 (C=O), 1611, 1561; δ_H (400 MHz, $CDCl_3$) 6.93 (1H, dd, *J* 16.0, 0.8, C(3)*H*), 7.26 (1H, t, *J* 7.9, Ar(5)*H*), 7.48 (1H, d, *J* 7.8, Ar*H*), 7.55 (1H, ddd, *J* 8.0, 1.9, 1.0, Ar*H*), 7.71 (1H, t, *J* 1.8, Ar(2)*H*), 7.80 (1H, d, *J* 16.0, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 116.3 (q, *J* 289, *C*F_3), 117.9 (*C*(3)), 123.4 (*ArC*(3)), 127.9 (*ArC*), 130.7 (*ArC*), 131.7 (*ArC*), 135.0 (Ar*C*), 135.3

(*ArC*(1)), 148.2 (*C*(4)), 179.8 (q, *J* 35.0, *C*(2)); δ_F (376 MHz, $CDCl_3$) -78.2 (CF_3); *m*/*z* (NSI^+) 279 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{10}H_7{}^{79}BrF_3O^+$ ($[M+H]^+$) requires 278.9627; found 278.9626 (-0.3 ppm).

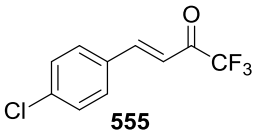
(*E*)-4-(2-bromophenyl)-1,1,1-trifluorobut-3-en-2-one



554

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 2-bromobenzaldehyde (0.29 mL, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 5:95) gave enone **554** as a light yellow oil (0.45 g, 65%); ν_{max} (film)/cm^{-1} 3070, 2923 (C-H), 1724 (C=O), 1603, 1564; δ_H (300 MHz, $CDCl_3$) 6.89 (1H, dd, *J* 16.0, 0.7, C(3)*H*), 7.18-7.34 (2H, m, Ar*H*), 7.62 (2H, ddd, *J* 15.9, 7.7, 1.7, Ar*H*), 8.29 (1H, d, *J* 16.0, C(4)*H*); δ_C (125 MHz, $CDCl_3$) 116.3 (q, *J* 289, *C*F_3), 119.1 (*C*(3)), 127.0 (*ArC*(2)), 128.0 (*ArC*), 128.2 (*ArC*), 133.0 (*ArC*), 133.3 (*ArC*(1)), 133.9 (Ar*C*), 148.3 (*C*(4)), 179.8 (q, *J* 36.0, *C*(2)); δ_F (282 MHz, $CDCl_3$) -78.0 (CF_3); *m*/*z* (NSI^+) 279 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{10}H_7{}^{79}BrF_3O^+$ ($[M+H]^+$) requires 278.9627; found 278.9626 (-0.3 ppm).

(*E*)-4-(4-chlorophenyl)-1,1,1-trifluorobut-3-en-2-one

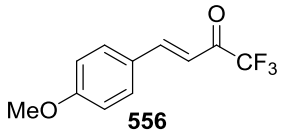


555

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 4-chlorobenzaldehyde (0.35 mg, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 5:95) gave enone **555** as a white solid (0.44 g, 76%); mp 42-44 °C; {lit.[181] mp 42-45 °C}; δ_H (300 MHz, $CDCl_3$) 6.92 (1H, dd, *J* 16.0, 0.8, C(3)*H*), 7.34-7.39 (2H, m, Ar(3,5)*H*), 7.49-7.54 (2H,

m, Ar(2,6)*H*), 7.85 (1H, d, *J* 16.0, C(4)*H*); δ_F (282 MHz, $CDCl_3$) -78.1 (CF_3). Spectroscopic data are in accordance with the literature.[181]

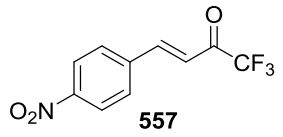
(*E*)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one



556

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 4-methoxybenzaldehyde (0.31 mL, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 30:70) gave enone **556** as a yellow solid (0.46 mg, 79%); mp 30-32 °C; {lit.[182] mp 35-37 °C}; δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 6.82 (1H, dd, *J* 15.8, 0.8, C(3)*H*), 6.87-6.90 (2H, m, Ar(3,5)*H*), 7.52-7.56 (2H, m, Ar(2,6)*H*), 7.87 (1H, d, *J* 15.8, C(4)*H*); δ_F (376 MHz, $CDCl_3$) -78.0 (CF_3). Spectroscopic data are in accordance with the literature.[180]

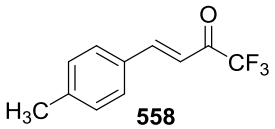
(*E*)-1,1,1-trifluoro-4-(4-nitrophenyl)but-3-en-2-one



557

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 4-nitrobenzaldehyde (378 mg, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 30:70) gave enone **557** as a yellow solid (0.43 g, 70%); mp 80-82 °C; {lit.[84] mp 98-99 °C}; δ_H (400 MHz, $CDCl_3$) 7.05 (1H, dd, *J* 16.1, 0.7, C(3)*H*), 7.72-7.76 (2H, m, Ar(2,6)*H*), 7.91 (1H, d, *J* 16.1, C(4)*H*), 8.23-8.26 (2H, m, Ar(3,5)*H*); δ_F (376 MHz, $CDCl_3$) -78.2 (CF_3). Spectroscopic data are in accordance with the literature.[84]

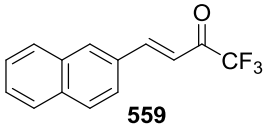
(*E*)-1,1,1-trifluoro-4-(*p*-tolyl)but-3-en-2-one



558

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 4-methylbenzaldehyde (0.30 mL, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 5:95) gave enone **558** as a light yellow solid (0.48 mg, 89%); mp 30-32 °C; {lit.[183] mp 35 °C}; δ_H (400 MHz, $CDCl_3$) 2.44 (3H, s, C*H*$_3$), 7.00 (1H, dd, *J* 15.9, 0.7, C(3)*H*), 7.28-7.30 (2H, m, Ar(3,5)*H*), 7.57 (2H, d, *J* 8.2, Ar(2,6)*H*), 7.98 (1H, d, *J* 15.9, C(4)*H*); δ_F (376 MHz, $CDCl_3$) -78.0 (C*F*$_3$). Spectroscopic data are in accordance with the literature.[183]

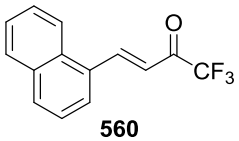
(*E*)-1,1,1-trifluoro-4-(naphthalen-2-yl)but-3-en-2-one



559

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 2-naphthaldehyde (0.39 g, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 5:95) gave enone **559** as a light yellow solid (0.48 g, 76%); mp 65-67 °C; {lit.[180] mp 62-64 °C}; δ_H (400 MHz, $CDCl_3$) 7.06 (1H, dd, *J* 15.9, 0.7, C(3)*H*), 7.47-7.54 (2H, m, Ar*H*), 7.68 (1H, dd, *J* 8.6, 1.7, Ar*H*), 7.79-7.85 (3H, m, Ar*H*), 8.01 (1H, s, Ar(1)*H*), 8.07 (1H, d, *J* 15.9, C(4)*H*); δ_F (376 MHz, $CDCl_3$) -78.0 (C*F*$_3$). Spectroscopic data are in accordance with the literature.[180]

(*E*)-1,1,1-trifluoro-4-(naphthalen-1-yl)but-3-en-2-one

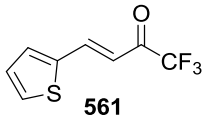


560

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL,

2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 1-naphthaldehyde (0.34 mL, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 5:95) gave enone **560** as a yellow oil (0.56 g, 82%); δ_H (400 MHz, $CDCl_3$) 7.08 (1H, d, *J* 15.7, C(3)*H*), 7.45-7.60 (3H, m, Ar*H*), 7.84-7.88 (2H, m, Ar*H*), 7.94 (1H, d, *J* 8.2, Ar*H*), 8.15 (1H, d, *J* 8.5, Ar*H*), 8.80 (1H, d, *J* 15.7, C(4)*H*); δ_F (376 MHz, $CDCl_3$) -78.0 (CF_3). Spectroscopic data are in accordance with the literature.[179]

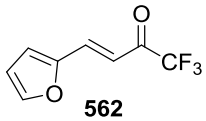
(*E*)-1,1,1-trifluoro-4-(thiophen-2-yl)but-3-en-2-one



561

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and thiophene-2-carbaldehyde (0.23 mL, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 10:90) gave enone **561** as a light yellow oil (0.46 g, 89%); δ_H (500 MHz, $CDCl_3$) 6.71 (1H, d, *J* 15.6, C(3)*H*), 7.08 (1H, dd, *J* 5.0, 3.8, Ar(4)*H*), 7.41 (1H, d, *J* 3.6, Ar(3)*H*), 7.51 (1H, d, *J* 5.0, Ar(5)*H*), 8.00 (1H, d, *J* 15.6, C(4)*H*); δ_F (282 MHz, $CDCl_3$) -78.0 (CF_3). Spectroscopic data are in accordance with the literature.[184]

(*E*)-1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one

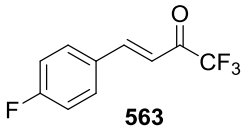


562

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and furfuraldehyde (0.21 mL, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 10:90) gave enone **562** as a yellow oil (0.27 g, 57%); δ_H (300 MHz, $CDCl_3$) 6.51 (1H, dd, *J* 3.5, 1.8, Ar(4)*H*), 6.80-6.85 (2H, m, C(3)*H* and Ar(3)*H*), 7.54-7.55 (1H, m, Ar(5)*H*), 7.62 (1H, d, *J* 15.6,

C(4)*H*); δ_F (282 MHz, $CDCl_3$) -78.1 (CF_3). Spectroscopic data are in accordance with the literature.[179]

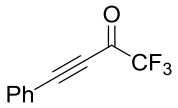
(*E*)-1,1,1-trifluoro-4-(4-fluorophenyl)but-3-en-2-one



563

Following general procedure E, *i*-Pr_2NH (0.68 mL, 5.00 mmol) and *n*-BuLi (2.5M in hexanes, 2.00 mL, 5.00 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.50 mmol), imine **245** (0.52 g, 2.50 mmol) and 4-fluorobenzaldehyde (0.27 mL, 2.50 mmol) in THF (2.5 mL) followed by HCl (2 M in H_2O, 5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH_2Cl_2:petrol 5:95) gave enone **563** as a white solid (0.41 g, 76%); mp 26-28 °C; {lit.[185] mp 39-41 °C}; δ_H (400 MHz, $CDCl_3$) 6.97 (1H, d, *J* 16.0, C(3)*H*), 7.16-7.20 (2H, m, Ar(3,5)*H*), 7.67-7.70 (2H, m, Ar(2,6)*H*), 7.96 (1H, d, *J* 16.0, C(4)*H*); δ_F (376 MHz, $CDCl_3$) -78.1 (CF_3), -106.0 (Ar*F*). Spectroscopic data are in accordance with the literature.[185]

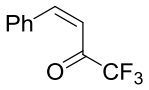
1,1,1-trifluoro-4-phenylbut-3-yn-2-one



298

To a solution of phenylacetylene (1.00 mL, 9.12 mmol) in THF (25 mL) at −78 °C was added *n*-BuLi (3.65 mL, 9.12 mmol) and the reaction mixture was stirred at −78 °C for 20 minutes. A solution of ethyl trifluoroacetate (1.09 mL, 9.12 mmol) in THF (15 mL) was added followed by boron trifluoride diethyl etherate (1.37 mL, 10.9 mmol) and the reaction mixture was stirred at −78 °C for 2 h. The reaction mixture was quenched by dropwise addition of sat. aq. NaCl and extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture. Chromatographic purification (eluent Et_2O:petrol 20:80) gave alkyne **298** as a yellow oil (1.80 g, quant.); δ_H (300 MHz, $CDCl_3$) 7.36-7.41 (2H, m, Ar(3,5)*H*), 7.48-7.54 (1H, m, Ar(4)*H*), 7.60-7.64 (2H, m, Ar(2,6)*H*); δ_F (282 MHz, $CDCl_3$) -78.3 (CF_3). Spectroscopic data are in accordance with the literature.[186]

(*Z*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one

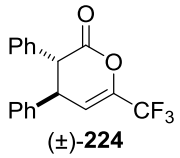


295

To a solution of alkyne **298** (1.80 g, 9.10 mmol) in THF (50 mL) at rt was added 5% Palladium on calcium carbonate (0.97 g, 0.46 mmol) and hydrogen gas was bubbled through the solution using an appended balloon for 4 h at rt. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give the crude reaction mixture. Chromatographic purification (eluent 100% petrol) gave enone **295** as a light yellow oil (0.73 g, 40%); ν_{max} (film) /cm^{-1} 3067, 2965 (C-H), 1719 (C=O), 1593, 1568; δ_H (300 MHz, $CDCl_3$) 6.52 (1H, dd, *J* 12.9, 0.7, C(3)*H*), 7.29 (1H, d, *J* 12.9, C(4)*H*), 7.42-7.50 (3H, m, Ar*H*), 7.87-7.91 (2H, m, Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 116.3 (q, *J* 290, *C*F$_3$), 116.7 (*C*(3)), 128.4 (*ArC*), 131.2 (*ArC*), 131.6 (*ArC*(4)), 133.7 (*ArC*(1)), 151.9 (*C*(4)), 179.1 (q, *J* 34.3, *C*(2)); δ_F (282 MHz, $CDCl_3$) -79.0 (C*F*$_3$); *m*/*z* (APCI$^+$) 201 ([M+H]$^+$, 100%); HRMS (APCI$^+$) $C_{10}H_8F_3O^+$ ([M+H]$^+$) requires 201.0522; found 201.0520 (-0.9 ppm).

Optimisation studies on compound 224

3,4-diphenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(±)-**224**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr$_2$NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), DHPB **108** (7.60 mg, 0.04 mmol), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr$_2$NEt (87 μL, 0.50 mmol) for 30 minutes at rt gave crude lactone (±)-**224** (86:14 dr). Chromatographic purification (eluent Et$_2$O:petrol 3.5:96.5) gave lactone (±)-**224** (96:4 dr) as a white solid (41.9 mg, 66%); mp 90-92 °C; Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 10.9 min, t_R(3*S*,4*S*): 12.2 min; ν_{max} (KBr)/cm^{-1} 3084, 3032, 2962 (C-H), 1774 (C=O), 1702, 1606; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.89 (1H, d, *J* 8.8, C(3)*H*), 3.92-3.98 (1H, m, C(4)*H*), 6.06 (1H, d, *J* 3.5, C(5)*H*), 6.94-6.96 (2H, m, Ar*H*), 6.99-7.03 (2H, m, Ar*H*), 7.17-7.24 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.8 (*C*(4)), 52.8 (*C*(3)), 110.7 (q, *J* 3.5,

C(5)), 118.5 (q, *J* 270, *C*F_3), 127.4 (*ArC*), 128.1 (*ArC*), 128.2 (*ArC*), 128.3 (*ArC*), 128.9 (*ArC*), 129.2 (*ArC*), 135.1 (C(3)*ArC*(1)), 138.8 (C(4)*ArC*(1)), 140.9 (q, *J* 38.0, *C*(6)), 165.8 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI^+) 336 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{18}H_{17}F_3NO_2^+$ ($[M+NH_4]^+$) requires 336.1206; found 336.1205 (-0.3 ppm).

Asymmetric Catalyst Screen:
All reactions for 15 minutes at rt.

Tetramisole hydrochloride (2*S*)-**106** (4.82 mg, 0.02 mmol, 10 mol%) gave crude lactone (3*S*,4*S*)-**224** (87:13 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*S*,4*S*)-**224** (97:3 dr) as a white solid (38.6 mg, 61%); 89% *ee*.

Benzotetramisole (2*R*)-**107** (5.04 mg, 0.02 mmol, 10 mol%) gave crude lactone (3*R*,4*R*)-**224** (82:18 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**224** (94:6 dr) as a white solid (48.5 mg, 76%); 77% *ee*.

HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) gave crude lactone (3*R*,4*R*)-**224** (85:15 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**224** (>98:2 dr) as a white solid (46.3 mg, 73%); 95% *ee*.

Temperature Screen:
All reactions with HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%)

Reaction for 3 h at –30 °C gave crude lactone (3*R*,4*R*)-**224** (86:14 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**224** (97:3 dr) as a white solid (50.1 mg, 79%); 96% *ee*.

Reaction for 4 h at –78 °C gave crude lactone (3*R*,4*R*)-**224** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**224** (98:2 dr) as a white solid (52.5 mg, 83%); 99% *ee*.

Catalyst Loading Screen:

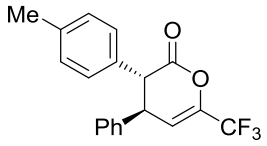
All reactions at –78 °C for 16 h.

HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%) gave crude lactone (3*R*,4*R*)-**224** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**224** (98:2 dr) as a white solid (50.8 mg, 80%); $[\alpha]_D^{20}$-227.2 (*c* 0.25, CH_2Cl_2); 99% *ee*.

HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 2 mol%) gave crude lactone (3*R*,4*R*)-**224** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**224** (98:2 dr) as a white solid (50.5 mg, 79%); 99% *ee*.

HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%) gave crude lactone (3*R*,4*R*)-**224** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**224** (98:2 dr) as a white solid (50.2 mg, 79%); 99% *ee*.

(3*R*,4*R*)-4-phenyl-3-(*p*-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

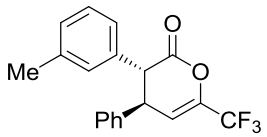


(3*R*,4*R*)-**225**

Following general procedure D, *p*-tolylacetic acid (30.0 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at –78 °C gave crude lactone (3*R*,4*R*)-**225** (93:7 dr). Chromatographic purification (eluent Et_2O:petrol 3:97) gave lactone (3*R*,4*R*)-**225** (98:2 dr) as a white solid (49.8 mg, 75%); mp 88-90 °C; $[\alpha]_D^{20}$-219.0 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 14.0 min, t_R(3*R*,4*R*): 16.4 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3083, 3030 (C-H), 1773 (C=O), 1700, 1519; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 2.23 (3H, s, C*H*$_3$), 3.87 (1H, d, *J* 8.6, C(3)*H*), 3.92-3.95 (1H, m, C(4)*H*), 6.04 (1H, d, *J* 3.7, C(5)*H*), 6.90-6.92 (2H, m, C(3)Ar(3,5)*H*), 6.95-6.98 (2H, m, C(3)Ar(2,6)*H*), 7.02-7.04 (2H, m, Ar*H*), 7.15-7.23 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.1 (*C*H$_3$), 44.7 (*C*(4)), 52.4 (*C*(3)), 110.7 (q, *J* 3.5, *C*(5)), 118.5 (q, *J* 270, *C*F$_3$), 127.4 (*ArC*), 128.0 (*ArC*),

128.0 (C(4)*ArC*(4)), 129.2 (*ArC*), 129.7 (*ArC*), 132.0 (C(3)*ArC*(1)), 138.0 (*ArC*), 138.9 (*ArC*), 140.8 (q, *J* 38.0, *C*(6)), 166.0 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (CF_3); *m*/*z* (NSI^+) 350 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{19}H_{19}F_3NO_2^+$ ($[M+NH_4]^+$) requires 350.1362; found 350.1366 (+1.0 ppm).

(3*R*,4*R*)-4-phenyl-3-(*m*-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**226**

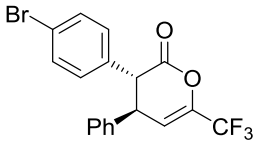
Following general procedure D, *m*-tolylacetic acid (30.0 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**226** (94:6 dr). Chromatographic purification (eluent Et_2O:petrol 3:97) gave lactone (3*R*,4*R*)-**226** (99:1 dr) as a white solid (60.1 mg, 91%); mp 52-54 °C; $[\alpha]_D^{20}$-219.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 18.4 min, t_R(3*S*,4*S*): 27.7 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3079, 3031 (C-H), 2921, 1779 (C=O), 1698, 1611; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 2.23 (3H, s, C*H*$_3$), 3.87 (1H, d, *J* 8.1, C(3)*H*), 3.92-3.96 (1H, m, C(4)*H*), 6.05 (1H, d, *J* 3.8, C(5)*H*), 6.81-6.84 (2H, m, Ar*H*), 6.97-7.02 (3H, m, Ar*H*), 7.11 (1H, t, *J* 7.6, C(3)Ar(5)*H*), 7.16-7.24 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (*C*H_3), 44.8 (*C*(4)), 52.7 (*C*(3)), 110.5 (q, *J* 3.5, *C*(5)), 118.5 (q, *J* 270, *C*F_3), 125.1 (*ArC*), 127.4 (*ArC*), 128.1 (*ArC*), 128.8 (*ArC*), 128.9 (*ArC*), 129.2 (*ArC*), 135.1 (C(3)*ArC*(1)), 138.7 (*ArC*), 138.9 (*ArC*), 140.8 (q, *J* 38.0, *C*(6)), 165.8 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.7 (CF_3); *m*/*z* (NSI^+) 350 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{19}H_{19}F_3NO_2^+$ ($[M+NH_4]^+$) requires 350.1362; found 350.1367 (+1.3 ppm).

Scale-up:

Following general procedure D, *m*-tolylacetic acid (1.13 g, 7.50 mmol), *i*-Pr_2NEt (1.96 mL, 11.3 mmol) and pivaloyl chloride (1.39 mL, 11.3 mmol) in CH_2Cl_2 (75 mL), HBTM-2.1 (2*S*,3*R*)-**112** (23.1 mg, 0.075 mmol, 1 mol%), enone **220** (1.50 g, 7.50 mmol) and *i*-Pr_2NEt (3.27 mL, 18.8 mmol) for 40 h at −78 °C gave crude lactone (3*R*,4*R*)-**226**

(94:6 dr). Chromatographic purification (eluent Et_2O:petrol 2:98) gave lactone (3*R*,4*R*)-**226** (96:4 dr) as a white solid (2.12 g, 85%); 98% *ee*.

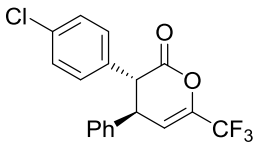
(3*R*,4*R*)-3-(4-bromophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**227**

Following general procedure D, 4-bromophenylacetic acid (43.0 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**227** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**227** (>99:1 dr) as a white solid (56.9 mg, 72%); mp 66-68 °C; $[\alpha]_D^{20}$-198.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 23.5 min, t_R(3*R*,4*R*): 25.5 min, 95% *ee*; ν_{max} (KBr)/cm^{-1} 3089, 3030, 2961 (C-H), 1784 (C=O), 1700; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.83 (1H, d, *J* 10.2, C(3)*H*), 3.88-3.95 (1H, m, C(4)*H*), 6.06 (1H, d, *J* 2.6, C(5)*H*), 6.83-6.87 (2H, m, C(3)Ar(2,6)*H*), 6.90-6.94 (2H, m, Ar*H*), 7.17-7.24 (3H, m, Ar*H*), 7.32-7.36 (2H, m, C(3)Ar(3,5)*H*); δ_C (100 MHz, $CDCl_3$) 44.7 (*C*(4)), 52.3 (*C*(3)), 111.0 (q, *J* 3.3, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 122.3 (C(3)*ArC*(4)), 127.4 (*ArC*), 128.2 (C(4)*ArC*(4)), 129.3 (*ArC*), 130.2 (Ar*C*), 132.0 (*ArC*), 133.9 (C(3)*ArC*(1)), 138.4 (C(4)*ArC*(1)), 140.7 (q, *J* 37.9, *C*(6)), 165.4 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (CF_3); *m*/*z* (NSI^+) 414 ($[M+NH_4]^+$, 61%); HRMS (NSI^+) $C_{18}H_{16}{}^{79}BrF_3NO_2{}^+$ ($[M+NH_4]^+$) requires 414.0311; found 414.0310 (-0.2 ppm).

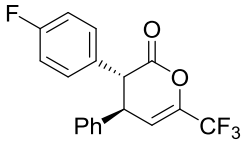
(3*R*,4*R*)-3-(4-chlorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**228**

Following general procedure D, 4-chlorophenylacetic acid (34.1 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**228** (91:9 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**228** (>99:1 dr) as a white solid (58.2 mg, 83%); mp 91-93 °C; $[\alpha]_D^{20}$-226.0 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 25.4 min, t_R(3*S*,4*S*): 40.3 min, 96% *ee*; ν_{max} (KBr)/cm^{-1} 3086, 3031 (C-H), 1771 (C=O), 1701, 1602; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.84 (1H, d, *J* 10.2, C(3)*H*), 3.89-3.93 (1H, m, C(4)*H*), 6.06 (1H, d, *J* 2.8, C(5)*H*), 6.89-6.93 (4H, m, Ar*H*), 7.17-7.23 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.7 (*C*(4)), 52.3 (*C*(3)), 111.1 (q, *J* 3.4, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 127.4 (*ArC*), 128.2 (C(4)*ArC*(4)), 129.1 (*ArC*), 129.2 (*ArC*), 129.9 (Ar*C*), 133.3 (C(3)*ArC*(1)), 134.1 (C(3)*ArC*(4)), 138.4 (C(4)*ArC*(1)), 140.9 (q, *J* 38.0, *C*(6)), 165.5 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI^+) 353 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{18}H_{13}{}^{35}ClF_3O_2{}^+$ ($[M+H]^+$) requires 353.0551; found 353.0551 (+0.1 ppm).

(3*R*,4*R*)-3-(4-fluorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

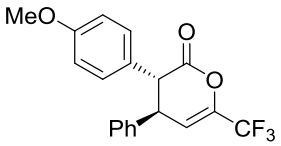


(3*R*,4*R*)-**229**

Following general procedure D, 4-fluorophenylacetic acid (30.8 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**229** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**229** (>99:1 dr) as a white solid (54.3 mg, 81%); mp 79-81 °C; $[\alpha]_D^{20}$-256.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 19.2 min, t_R(3*S*,4*S*): 39.4 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3088, 2928 (C-H), 1772 (C=O), 1702, 1611, 1518; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.83-3.94 (2H, m, C(3)*H* and C(4)*H*), 6.07 (1H, d, *J* 2.9, C(5)*H*),

6.87-6.97 (6H, m, Ar*H*), 7.17-7.24 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.9 (*C*(4)), 52.1 (*C*(3)), 111.0 (q, *J* 3.5, *C*(5)), 115.9 (d, *J* 21.5, C(3)*ArC*(3,5)), 118.4 (q, *J* 270, *C*F_3), 127.4 (*ArC*), 128.2 (C(4)*ArC*(4)), 129.2 (*ArC*), 130.2 (d, *J* 8.2, C(3)*ArC*(2,6)), 130.7 (d, *J* 3.4, C(3)*ArC*(1)), 138.5 (C(4)*ArC*(1)), 140.9 (q, *J* 38.0, *C*(6)), 162.3 (d, *J* 246, C(3)*ArC*(4)), 165.7 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (C*F*$_3$), -114.2 (Ar*F*); *m*/*z* (NSI^+) 354 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{18}H_{16}F_4NO_2^+$ ($[M+NH_4]^+$) requires 354.1112; found 354.1115 (+0.9 ppm).

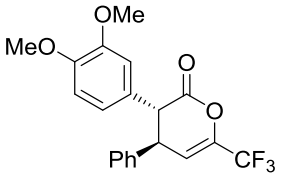
(3*R*,4*R*)-3-(4-methoxyphenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**230**

Following general procedure D, *p*-methoxyphenylacetic acid (33.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**230** (92:8 dr). Chromatographic purification (eluent Et_2O:petrol 10:90) gave lactone (3*R*,4*R*)-**230** (97:3 dr) as a white solid (58.9 mg, 85%); mp 90-92 °C; $[\alpha]_D^{20}$-199.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 28.7 min, t_R(3*S*,4*S*): 31.2 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3033, 2961 (C-H), 2840, 1784 (C=O), 1700, 1614, 1586, 1516; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, C*H*$_3$), 3.84 (1H, d, *J* 9.0, C(3)*H*), 3.89-3.93 (1H, m, C(4)*H*), 6.05 (1H, d, *J* 3.5, C(5)*H*), 6.73-6.76 (2H, m, C(3)Ar(3,5)*H*), 6.91-6.96 (4H, m, Ar*H*), 7.17-7.23 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.8 (*C*(4)), 52.0 (*C*(3)), 55.3 (*C*H$_3$), 110.8 (q, *J* 3.5, *C*(5)), 114.3 (*ArC*(3)), 118.5 (q, *J* 270, *C*F_3), 127.0 (C(3)*ArC*(1)), 127.4 (*ArC*), 128.0 (C(4)*ArC*(4)), 129.2 (*ArC*), 129.4 (*ArC*), 138.9 (C(4)*ArC*(1)), 140.8 (q, *J* 37.9, *C*(6)), 159.3 (C(3)*ArC*(4)), 166.1 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI^+) 366 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{19}H_{19}F_3NO_3^+$ ($[M+NH_4]^+$) requires 366.1312; found 366.1318 (+1.8 ppm).

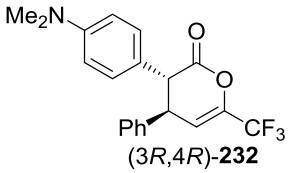
(3*R*,4*R*)-3-(3,4-dimethoxyphenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**231**

Following general procedure D, 3,4-dimethoxyphenylacetic acid (39.4 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**231** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 30:70) gave lactone (3*R*,4*R*)-**231** (92:8 dr) as a colourless oil (66.1 mg, 87%); $[\alpha]_D^{20}$-268.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 19.6 min, t_R(3*R*,4*R*): 21.1 min, 98% *ee*; ν_{max} (thin film)/cm^{-1} 3088, 3006, 2934 (C-H), 1790 (C=O), 1698, 1594, 1516; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.71 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.84 (1H, d, *J* 8.8, C(3)*H*), 3.89-3.94 (1H, m, C(4)*H*), 6.07 (1H, d, *J* 3.5, C(5)*H*), 6.48 (1H, d, *J* 2.1, C(3)Ar(2)*H*), 6.57 (1H, dd, *J* 8.3, 2.1, C(3)Ar(6)*H*), 6.70 (1H, d, *J* 8.3, C(3)Ar(5)*H*), 6.94-6.98 (2H, m, Ar*H*), 7.17-7.25 (3H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 45.0 (*C*(4)), 52.4 (*C*(3)), 55.9 (O*C*H$_3$), 55.9 (O*C*H$_3$), 110.7 (q, *J* 3.5, *C*(5)), 111.2 (*ArC*), 111.3 (*ArC*), 118.5 (q, *J* 270, *C*F$_3$), 120.6 (C(3)*ArC*(6)), 127.4 (*ArC*) 127.4 (C(3)*ArC*(1)), 128.1 (C(4)*ArC*(4)), 129.2 (*ArC*), 138.9 (C(4)*ArC*(1)), 140.9 (q, *J* 38.0, *C*(6)), 148.8 (*ArC*), 149.1 (*ArC*), 165.9 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI^+) 379 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{20}H_{18}F_3O_4^+$ ($[M+H]^+$) requires 379.1152; found 379.1149 (-0.7 ppm).

(3*R*,4*R*)-3-(4-(dimethylamino)phenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

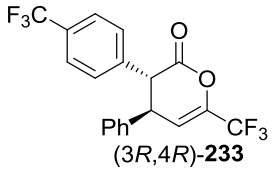


(3*R*,4*R*)-**232**

Following general procedure D, 2-(4-(dimethylamino)phenyl)acetic acid (35.8 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude

lactone (3*R*,4*R*)-**232** (95:5 dr). Chromatographic purification (eluent Et_2O:petrol 15:85) gave lactone (3*R*,4*R*)-**232** (95:5 dr) as a colourless oil (57.5 mg, 80%); $[\alpha]_D^{20}$-286.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 14.9 min, t_R(3*S*,4*S*): 16.8 min, 99% *ee*; ν_{max} (thin film)/cm^{-1} 3088, 3031, 2922 (C-H), 1790 (C=O), 1698, 1615, 1525; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 2.85 (6H, s, 2 NCH_3), 3.83 (1H, d, *J* 7.6, C(3)*H*), 3.88-3.93 (1H, m, C(4)*H*), 6.04 (1H, d, *J* 4.1, C(5)*H*), 6.53-6.58 (2H, m, C(3)Ar(3,5)*H*), 6.87-6.91 (2H, m, C(3)Ar(2,6)*H*), 6.98-7.01 (2H, m, Ar*H*), 7.15-7.25 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 40.4 (2 NCH_3), 44.8 (*C*(4)), 51.8 (*C*(3)), 110.4 (q, *J* 3.4, *C*(5)), 112.6 (C(3)*ArC*(3,5)), 118.6 (q, *J* 270, *C*F_3), 122.4 (C(3)*ArC*(1)), 127.4 (*ArC*), 127.9 (C(4)*ArC*(4)), 128.7 (*ArC*), 129.2 (*ArC*), 139.3 (C(4)*ArC*(1)), 140.8 (q, *J* 37.8, *C*(6)), 150.2 (C(3)*ArC*(4)), 166.3 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (CF_3); *m*/*z* (NSI^+) 362 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{20}H_{19}F_3NO_2^+$ ($[M+H]^+$) requires 362.1362; found 362.1362 (-0.1 ppm).

(3*R*,4*R*)-4-phenyl-6-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyran-2-one

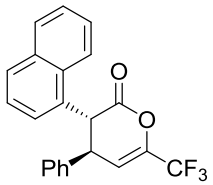


(3*R*,4*R*)-**233**

Following general procedure D, 2-(4-(trifluoromethyl)phenyl)acetic acid (40.8 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 72 h at −30 °C gave crude lactone (3*R*,4*R*)-**233** (86:14 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**233** (99:1 dr) as a white solid (46.2 mg, 60%); mp 80-82 °C; $[\alpha]_D^{20}$-153.6 (*c* 0.125, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 16.2 min, t_R(3*R*,4*R*): 18.8 min, 64% *ee*; ν_{max} (KBr)/cm^{-1} 3030, 2926 (C-H), 1780 (C=O), 1621; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.94-3.96 (2H, m, C(3)*H* and C(4)*H*), 6.09 (1H, d, *J* 2.3, C(5)*H*), 6.91-6.93 (2H, m, Ar*H*), 7.10 (2H, d, *J* 8.1, C(3)Ar(2,6)*H*), 7.19-7.22 (3H, m, Ar*H*), 7.48 (2H, d, *J* 8.1, C(3)Ar(3,5)*H*); δ_C (100 MHz, $CDCl_3$) 44.7 (*C*(4)), 52.6 (*C*(3)), 111.1 (q, *J* 3.3, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 123.8 (q, *J* 271, *C*F_3), 125.8 (q, *J* 3.6, C(3)*ArC*(3,5)),

127.4 (*ArC*), 128.3 (C(4)*ArC*(4)), 129.0 (*ArC*), 129.3 (*ArC*), 130.4 (q, *J* 32.4, C(3)*ArC*(4)), 138.1 (*ArC*), 138.8 (*ArC*), 141.0 (q, *J* 38.2, *C*(6)), 165.2 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -63.2 ($C_6H_4CF_3$), -72.6 (CF_3); *m*/*z* (NSI^+) 404 ($[M+NH_4]^+$, 82%); HRMS (NSI^+) $C_{19}H_{16}F_6NO_2^+$ ($[M+NH_4]^+$) requires 404.1080; found 404.1080 (+0.1 ppm).

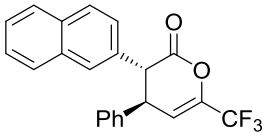
(3*R*,4*R*)-3-(naphthalen-1-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**234**

Following general procedure D, 1-naphthylacetic acid (37.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**234** (67:33 dr). Chromatographic purification (eluent Et_2O:petrol 4:96) gave lactone (3*R*,4*R*)-**234** (71:29 dr) as a colourless oil (65.0 mg, 88%); $[\alpha]_D^{20}$-303.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 18.5 min, t_R(3*R*,4*R*): 26.0 min, 97% *ee*; ν_{max} (thin film)/cm^{-1} 3087, 2962 (C-H), 1780 (C=O), 1702, 1600, 1512; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 4.09-4.13 (1H, m, C(4)*H*), 4.64 (1H, d, *J* 6.7, C(3)*H*), 6.03 (1H, d, *J* 4.5, C(5)*H*), 6.98-7.01 (2H, m, Ar*H*), 7.12 (1H, d, *J* 6.8, Ar*H*), 7.16-7.23 (3H, m, Ar*H*), 7.29 (1H, t, *J* 7.7, Ar*H*), 7.40-7.49 (2H, m, Ar*H*), 7.72-7.82 (3H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 44.3 (*C*(4)), 49.6 (*C*(3)), 110.4 (q, *J* 3.5, *C*(5)), 118.6 (q, *J* 270, CF_3), 122.8 (*ArC*), 125.3 (*ArC*), 125.8 (*ArC*), 126.0 (*ArC*), 126.9 (*ArC*), 127.2 (*ArC*), 128.2 (*ArC*), 129.2 (*ArC*), 129.4 (*ArC*), 129.6 (*ArC*), 130.5 (*ArC*), 131.5 (*ArC*), 134.3 (*ArC*), 139.2 (C(4)*ArC*(1)), 140.8 (q, *J* 38.0, *C*(6)), 165.6 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (CF_3); *m*/*z* (NSI^+) 369 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{22}H_{16}F_3O_2^+$ ($[M+H]^+$) requires 369.1097; found 369.1087 (-2.7 ppm).

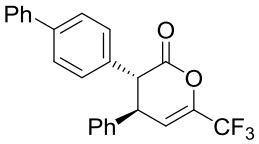
(3*R*,4*R*)-3-(naphthalen-2-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**235**

Following general procedure D, 2-naphthylacetic acid (37.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**235** (94:6 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**235** (98:2 dr) as a colourless oil (64.5 mg, 88%); $[\alpha]_D^{20}$-289.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 18.0 min, t_R(3*S*,4*S*): 27.6 min, 97% *ee*; ν_{max} (thin film)/cm^{-1} 3088, 2962 (C-H), 1791 (C=O), 1701, 1602, 1509; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 4.05 (2H, s, C(3)*H* and C(4)*H*), 6.07 (1H, s, C(5)*H*), 6.96-6.98 (2H, m, Ar*H*), 7.13-7.19 (4H, m, Ar*H*), 7.36-7.40 (3H, m, Ar*H*), 7.61-7.64 (1H, m, Ar*H*), 7.71-7.74 (2H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 44.7 (*C*(4)), 52.9 (*C*(3)), 110.8 (q, *J* 3.5, *C*(5)), 118.5 (q, *J* 270, *C*F_3), 125.5 (*ArC*), 126.5 (*ArC*), 126.5 (*ArC*), 127.4 (*ArC*), 127.7 (*ArC*), 127.9 (*ArC*), 128.1 (*ArC*), 128.9 (*ArC*), 129.2 (*ArC*), 132.3 (*ArC*), 132.8 (*ArC*), 133.2 (*ArC*), 138.7 (C(4)*ArC*(1)), 140.9 (q, *J* 38.0, *C*(6)), 165.8 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI^+) 386 ($[M+NH_4]^+$, 56%); HRMS (NSI^+) $C_{22}H_{19}F_3NO_2^+$ ($[M+NH_4]^+$) requires 386.1362; found 386.1364 (+0.4 ppm).

(3*R*,4*R*)-3-([1,1'-biphenyl]-4-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

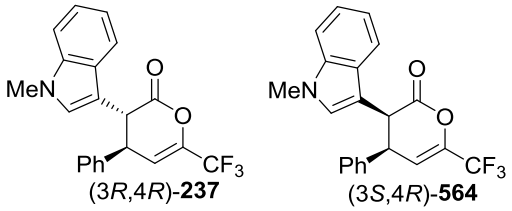


(3*R*,4*R*)-**236**

Following general procedure D, biphenylacetic acid (42.4 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**236** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**236** (98:2 dr) as a white solid (70.4 mg, 89%); mp 81-83 °C; $[\alpha]_D^{20}$-

297.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 14.0 min, t_R(3*R*,4*R*): 16.8 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3085, 3031 (C-H), 1771 (C=O), 1705, 1600; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.92-4.01 (2H, s, C(3)*H* and C(4)*H*), 6.08 (1H, d, *J* 3.4, C(5)*H*), 6.96-6.99 (2H, m, Ar*H*), 7.06-7.09 (2H, m, Ar*H*), 7.15-7.37 (6H, m, Ar*H*), 7.42-7.49 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.8 (*C*(4)), 52.5 (*C*(3)), 110.8 (q, *J* 3.4, *C*(5)), 118.5 (q, *J* 270, *C*F_3), 127.1 (*ArC*), 127.4 (*ArC*), 127.6 (*ArC*), 127.6 (*ArC*), 128.1 (*ArC*), 128.7 (*ArC*), 128.8 (*ArC*), 129.2 (*ArC*), 134.0 (C(3)*ArC*(1)), 138.8 (*ArC*), 140.3 (*ArC*), 140.9 (q, *J* 38.0, *C*(6)), 141.0 (*ArC*), 165.8 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI^+) 395 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{24}H_{18}F_3O_2^+$ ($[M+H]^+$) requires 395.1253; found 395.1246 (-1.9 ppm).

(3*R*,4*R*)-3-(1-methyl-1*H*-indol-3-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**237** (3*S*,4*R*)-**564**

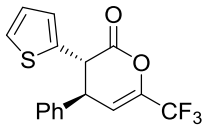
Following general procedure D, 2-(1-methyl-1*H*-indol-3-yl)acetic acid (37.8 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −30 °C gave crude lactones (3*R*,4*R*)-**237** and (3*S*,4*R*)-**564** (74:26 dr).

Major (*anti*) Diasteroisomer: Chromatographic purification (eluent Et_2O:petrol 10:90) gave lactone (3*R*,4*R*)-**237** (97:3 dr) as a yellow solid (50.2 mg, 68%); mp 126-128 °C; $[\alpha]_D^{20}$-164.0 (*c* 0.225, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 21.1 min, t_R(3*S*,4*S*): 34.9 min, 96% *ee*; ν_{max} (KBr)/cm^{-1} 3033, 2939 (C-H), 1780 (C=O), 1699, 1616, 1544; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.66 (3H, s, C*H*$_3$), 4.06-4.08 (1H, m, C(4)*H*), 4.26 (1H, d, *J* 4.8, C(3)*H*), 6.05 (1H, d, *J* 5.1, C(5)*H*), 6.78 (1H, s, C(3)Ar(2)*H*), 7.07-7.12 (3H, m, Ar*H*), 7.18-7.28 (5H, m, Ar*H*), 7.52 (1H, d, *J* 7.9, C(3)Ar(4)*H*); δ_C (100 MHz, $CDCl_3$) 32.9 (*C*H$_3$), 44.0 (*C*(4)), 44.7 (*C*(3)), 108.4 (C(3)*ArC*(3)), 109.6 (q, *J* 3.4, *C*(5)),

109.8 (*ArC*), 118.6 (*ArC*), 118.6 (q, *J* 270, *C*F_3), 119.9 (*ArC*), 122.4 (*ArC*), 126.1 (C(3)*ArC*(3a)), 126.6 (*ArC*), 127.1 (*ArC*), 128.1 (*ArC*), 129.4 (*ArC*), 137.0 (C(3)*ArC*(7a)), 139.1 (C(4)*ArC*(1)), 141.1 (q, *J* 37.7, *C*(6)), 165.2 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI$^+$) 389 ([M+NH_4]$^+$, 100%); HRMS (NSI$^+$) $C_{21}H_{20}F_3N_2O_2^+$ ([M+NH_4]$^+$) requires 389.1471; found 389.1474 (+0.7 ppm).

Minor (*syn*) Diasteroisomer: Chromatographic purification (eluent Et_2O:petrol 10:90) gave lactone (3*S*,4*R*)-**564** (>99:1 dr) as a yellow oil (19.1 mg, 26%); $[\alpha]_D^{20}$+47.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*S*): 16.0 min, t_R(3*S*,4*R*): 20.0 min, 28% *ee*; ν_{max} (KBr)/cm^{-1} 3032, 2934 (C-H), 1791 (C=O), 1700, 1616, 1550; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.55 (3H, s, C*H*$_3$), 4.00 (1H, td, *J* 6.4, 1.4, C(4)*H*), 4.64 (1H, d, *J* 6.7, C(3)*H*), 6.23 (1H, d, *J* 6.0, C(5)*H*), 6.40 (1H, s, C(3)Ar(2)*H*), 6.86-6.71 (2H, m, Ar*H*), 7.00 (1H, ddd, *J* 7.9, 6.9, 1.1, Ar*H*), 7.05-7.09 (2H, m, Ar*H*), 7.12-7.16 (2H, m, Ar*H*), 7.19-7.23 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 32.8 (*C*H_3), 42.7 (*C*(4)), 42.9 (*C*(3)), 104.8 (C(3)*ArC*(3)), 109.5 (*ArC*), 111.5 (q, *J* 3.4, *C*(5)), 117.7 (*ArC*), 118.7 (q, *J* 270, *C*F_3), 119.4 (*ArC*), 121.8 (*ArC*), 127.2 (C(3)*ArC*(3a)), 128.2 (*ArC*), 128.2 (*ArC*), 128.6 (*ArC*), 128.8 (*ArC*), 135.6 (C(3)*ArC*(7a)), 136.2 (C(4)*ArC*(1)), 141.8 (q, *J* 37.7, *C*(6)), 166.0 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.4 (C*F*$_3$); *m*/*z* (NSI$^+$) 372 ([M+H]$^+$, 18%); HRMS (NSI$^+$) $C_{21}H_{17}F_3NO_2^+$ ([M+H]$^+$) requires 372.1206; found 372.1211 (+1.4 ppm).

(3*S*,4*R*)-4-phenyl-3-(thiophen-2-yl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

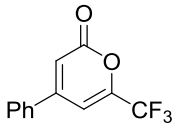


(3*R*,4*R*)-**238**

Following general procedure D, 2-(thiophen-2-yl)acetic acid (28.4 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**238** (87:13 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**238** (96:4 dr) as a white solid (48.4 mg, 75%); mp 51-53 °C; $[\alpha]_D^{20}$-248.0 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*R*): 5.8 min, t_R(3*R*,4*S*): 8.4 min, 89% *ee*; ν_{max} (KBr)/cm^{-1}

3084, 2921 (C-H), 1775 (C=O), 1702; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.98-4.01 (1H, m, C(4)*H*), 4.24 (1H, d, *J* 6.8, C(3)*H*), 6.09 (1H, d, *J* 4.5, C(5)*H*), 6.78 (1H, dt, *J* 3.5, 0.9, C(3)Ar(3)*H*), 6.85 (1H, dd, *J* 5.1, 3.6, C(3)Ar(4)*H*), 7.03-7.06 (2H, m, Ar*H*), 7.18-7.29 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 45.3 (*C*(4)), 48.1 (*C*(3)), 109.9 (q, *J* 3.5, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 125.9 (*ArC*), 127.0 (*ArC*), 127.1 (*ArC*), 127.2 (*ArC*), 128.4 (*ArC*), 129.4 (*ArC*), 136.5 (*ArC*), 138.2 (*ArC*), 141.1 (q, *J* 38.2, *C*(6)), 164.4 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.7 (C*F*$_3$); *m*/*z* (NSI^+) 342 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{16}H_{15}F_3NO_2S^+$ ($[M+NH_4]^+$) requires 342.0770; found 342.0775 (+1.4 ppm).

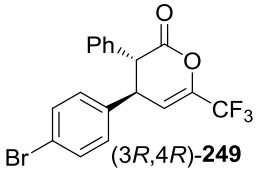
4-phenyl-6-(trifluoromethyl)-2*H*-pyran-2-one



242

Following general procedure D, 2-(phenylthio)acetic acid (67.3 mg, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74 mg, 0.60 mmol) in CH_2Cl_2 (2 mL), acceptor **220** (40.0 mg, 0.20 mmol), DHPB **108** (7.60 mg, 0.04 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 15:85) **242** as a light yellow solid (23.0 mg, 48%); mp 48-50 °C; ν_{max} (ATR)/cm^{-1} 3113, 3078 (C-H), 1738 (C=O), 1667, 1560; δ_H (400 MHz, $CDCl_3$) 6.59 (1H, d, *J* 0.8, C(3)*H*), 6.90 (1H, d, *J* 0.7, C(5)*H*), 7.44-7.49 (3H, m, Ar(3,5)*H* and Ar(4)*H*), 7.52-7.54 (2H, m, Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 104.8 (q, *J* 3.7, *C*(5)), 113.8 (*C*(3)), 118.1 (q, *J* 271, *C*F_3), 126.7 (*ArC*), 129.6 (*ArC*), 131.6 (*ArC*(4)), 134.2 (*ArC*(1)), 148.5 (q, *J* 38.9, *C*(6)), 153.3 (*C*(4)), 159.4 (*C*=O); *m*/*z* (NSI^+) 241 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{12}H_8F_3O_2^+$ ($[M+H]^+$) requires 241.0471; found 241.0474 (+1.3 ppm).

(3*R*,4*R*)-4-(4-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

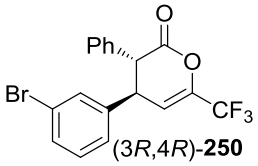


(3*R*,4*R*)-**249**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-

2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **552** (55.8 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**249** (88:12 dr). Chromatographic purification (eluent Et_2O:petrol 4.5:95.5) gave lactone (3*R*,4*R*)-**249** (99:1 dr) as a white solid (54.0 mg, 68%); mp 58-60 °C; $[\alpha]_D^{20}$-252.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 26.9 min, t_R(3*S*,4*S*): 30.8 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3088, 3033, 2926 (C-H), 1780 (C=O), 1703; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.82 (1H, d, *J* 9.6, C(3)*H*), 3.91-3.96 (1H, m, C(4)*H*), 6.02 (1H, dd, *J* 3.4, 0.5, C(5)*H*), 6.80-6.83 (2H, m, C(4)Ar(2,6)*H*), 6.97-7.00 (2H, m, Ar*H*), 7.21-7.26 (3H, m, Ar*H*), 7.30-7.34 (2H, m, C(4)Ar(3,5)*H*); δ_C (100 MHz, $CDCl_3$) 44.3 (*C*(4)), 52.6 (*C*(3)), 110.2 (q, *J* 3.4, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 122.1 (C(4)*ArC*(4)), 128.3 (C(3)*ArC*(4)), 128.3 (*ArC*), 129.0 (*ArC*), 129.1 (*ArC*), 132.3 (*ArC*), 134.6 (C(3)*ArC*(1)), 137.8 (C(4)*ArC*(1)), 141.2 (q, *J* 38.1, *C*(6)), 165.4 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.7 (C*F*$_3$); *m*/*z* (NSI^+) 414 ($[M+NH_4]^+$, 62%); HRMS (NSI^+) $C_{18}H_{16}{}^{79}BrF_3NO_2^+$ ($[M+NH_4]^+$) requires 414.0311; found 414.0311 (+0.0 ppm).

(3*R*,4*R*)-4-(3-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

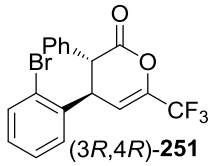


(3*R*,4*R*)-**250**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **553** (55.8 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**250** (80:20 dr). Chromatographic purification (eluent Et_2O:petrol 4.5:95.5) gave lactone (3*R*,4*R*)-**250** (99:1 dr) as a white solid (51.0 mg, 64%); mp 70-72 °C; $[\alpha]_D^{20}$-227.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 24.3 min, t_R(3*S*,4*S*): 47.5 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3083, 2960 (C-H), 1774 (C=O), 1702, 1592, 1570; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.85 (1H, d, *J* 9.3, C(3)*H*), 3.89-3.96 (1H, m, C(4)*H*), 6.02 (1H, dd, *J* 3.2, C(5)*H*), 6.84 (1H, dd, *J* 6.6, 1.2, C(4)Ar(6)*H*), 6.98-7.01 (2H, m, Ar*H*), 7.06 (1H, t, *J*

7.8, C(4)Ar(5)*H*), 7.11 (1H, t, *J* 1.8, C(4)Ar(2)*H*), 7.21-7.26 (3H, m, Ar*H*), 7.31 (1H, ddd, *J* 8.0, 1.9, 1.0, C(4)Ar(4)*H*); δ_C (100 MHz, $CDCl_3$) 44.4 (*C*(4)), 52.6 (*C*(3)), 109.9 (q, *J* 3.5, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 123.1 (C(4)*ArC*(3)), 126.1 (*ArC*), 128.3 (*ArC*), 128.4 (*ArC*), 129.1 (*ArC*), 130.5 (*ArC*), 130.7 (*ArC*), 131.3 (*ArC*), 134.5 (C(3)*ArC*(1)), 141.0 (C(4)*ArC*(1), 141.3 (q, *J* 38.2, *C*(6)), 165.3 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.7 (C*F*$_3$); *m*/*z* (NSI^+) 414 ($[M+NH_4]^+$, 68%); HRMS (NSI^+) $C_{19}H_{16}{}^{79}BrF_3NO_2{}^+$ ($[M+NH_4]^+$) requires 414.0311; found 414.0313 (+0.5 ppm).

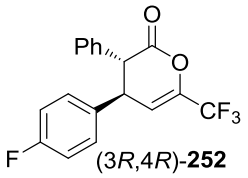
(3*R*,4*R*)-4-(2-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**251**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **554** (55.8 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**251** (87:13 dr). Chromatographic purification (eluent Et_2O:petrol 3:97) gave lactone (3*R*,4*R*)-**251** (95:5 dr) as a white solid (68.0 mg, 86%); mp 78-80 °C; $[\alpha]_D^{20}$-214.0 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 8.8 min, t_R(3*S*,4*S*): 18.5 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3083, 3037, 2926 (C-H), 1778 (C=O), 1709, 1567; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 4.12 (1H, d, *J* 5.6, C(3)*H*), 4.49-4.52 (1H, m, C(4)*H*), 5.99 (1H, d, *J* 5.1, C(5)*H*), 7.07-7.11 (2H, m, Ar*H*), 7.20-7.29 (6H, m, Ar*H*), 7.51 (1H, dd, *J* 8.1, 1.1, C(4)Ar(3)*H*); δ_C (125 MHz, $CDCl_3$) 43.6 (*C*(4)), 50.9 (*C*(3)), 109.0 (q, *J* 3.4, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 124.1 (C(4)*ArC*(2)), 127.7 (*ArC*), 128.3 (*ArC*), 128.4 (*ArC*), 128.5 (*ArC*), 129.1 (*ArC*), 129.9 (*ArC*), 133.9 (C(4)*ArC*(3)), 134.8 (C(3)*ArC*(1)), 136.9 (C(4)*ArC*(1), 141.8 (q, *J* 38.0, *C*(6)), 165.2 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI^+) 414 ($[M+NH_4]^+$, 85%); HRMS (NSI^+) $C_{19}H_{16}{}^{79}BrF_3NO_2{}^+$ ($[M+NH_4]^+$) requires 414.0311; found 414.0314 (+0.7 ppm).

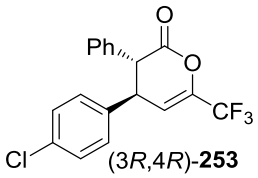
(3*R*,4*R*)-4-(4-fluorophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**252**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **563** (43.6 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**252** (86:14 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**252** (>99:1 dr) as a white solid (57.2 mg, 85%); mp 80-82 °C; $[\alpha]_D^{20}$-302.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 10.9 min, t_R(3*S*,4*S*): 22.3 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3086, 3037, 2926 (C-H), 1774 (C=O), 1703, 1605, 1512; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.82 (1H, d, *J* 9.5, C(3)*H*), 3.93-3.97 (1H, m, C(4)*H*), 6.04 (1H, dd, *J* 3.5, 0.5, C(5)*H*), 6.86-6.93 (4H, m, Ar*H*), 6.97-7.00 (2H, m, Ar*H*), 7.20-7.25 (3H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 44.1 (*C*(4)), 53.0 (*C*(3)), 110.6 (q, *J* 3.3, *C*(5)), 116.1 (d, *J* 21.4, C(4)*ArC*(3,5)), 118.4 (q, *J* 270, *C*F_3), 128.2 (C(3)*ArC*(4)), 128.3 (*ArC*), 129.0 (*ArC*), 129.1 (d, *J* 8.3, C(4)*ArC*(2,6)), 134.5 (d, *J* 3.0, C(4)*ArC*(1)), 134.7 (C(3)*ArC*(1)), 141.1 (q, *J* 38.0, *C*(6)), 162.3 (d, *J* 246, C(4)*ArC*(4)), 165.6 (*C*(2)); δ_F (470 MHz, $CDCl_3$) -72.2 (C*F*$_3$), -113.7 (Ar*F*); *m*/*z* (NSI$^+$) 354 ($[M+NH_4]^+$, 100%); HRMS (NSI$^+$) $C_{18}H_{16}F_4NO_2^+$ ($[M+NH_4]^+$) requires 354.1112; found 354.1115 (+0.9 ppm).

(3*R*,4*R*)-4-(4-chlorophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

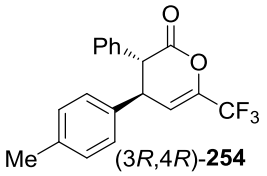


(3*R*,4*R*)-**253**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **555** (46.9 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**253** (88:12 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**253**

(>99:1 dr) as a white solid (52.4 mg, 74%); mp 64-66 °C; $[\alpha]_D^{20}$-353.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 10.2 min, t_R(3*S*,4*S*): 30.3 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3086, 3034 (C-H), 1774 (C=O), 1702, 1597; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.82 (1H, d, *J* 9.6, C(3)*H*), 3.93-3.96 (1H, m, C(4)*H*), 6.02 (1H, d, *J* 3.3, C(5)*H*), 6.86-6.88 (2H, m, Ar*H*), 6.97-7.00 (2H, m, Ar*H*), 7.15-7.26 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.2 (*C*(4)), 52.7 (*C*(3)), 110.3 (q, *J* 3.3, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 128.3 (*ArC*(4)), 128.3 (*ArC*), 128.8 (*ArC*), 129.0 (*ArC*), 129.3 (*ArC*), 134.0 (C(4)*ArC*(4)), 134.6 (C(3)*ArC*(1)), 137.2 (C(4)*ArC*(1)), 141.2 (q, *J* 38.2, *C*(6)), 165.5 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.7 (C*F*$_3$); *m*/*z* (NSI^+) 370 ($[M+NH_4]^+$, 95%); HRMS (NSI^+) $C_{18}H_{16}{}^{35}ClF_3NO_2^+$ ($[M+NH_4]^+$) requires 370.0816; found 370.0818 (+0.5 ppm).

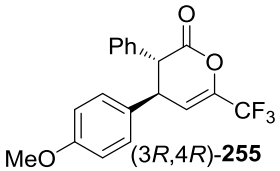
(3*R*,4*R*)-3-phenyl-4-(*p*-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**254**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **558** (42.8 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**254** (95:5 dr). Chromatographic purification (eluent Et_2O:petrol 3:97) gave lactone (3*R*,4*R*)-**254** (98:2 dr) as a white solid (61.8 mg, 93%); mp 60-62 °C; $[\alpha]_D^{20}$-256.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 7.2 min, t_R(3*S*,4*S*): 11.5 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3098, 3033, 2940 (C-H), 1778 (C=O), 1701, 1635, 1516; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, C*H*$_3$), 3.86-3.93 (2H, m, C(3)*H* and C(4)*H*), 6.03 (1H, d, *J* 3.3, C(5)*H*), 6.84 (2H, d, *J* 8.1, Ar(3)*H*), 6.99-7.04 (4H, m, Ar*H*), 7.18-7.25 (3H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.1 (*C*H$_3$), 44.4 (*C*(4)), 52.8 (*C*(3)), 110.9 (q, *J* 3.3, *C*(5)), 118.5 (q, *J* 270, *C*F_3), 127.2 (*ArC*), 128.1 (C(3)*ArC*(4)), 128.2 (*ArC*), 128.9 (*ArC*), 129.8 (*ArC*), 135.2 (*ArC*), 135.7 (*ArC*), 137.9 (*ArC*), 140.7 (q, *J* 38.0, *C*(6)), 165.9 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.6 (C*F*$_3$); *m*/*z* (NSI^+) 350 ($[M+NH_4]^+$, 95%); HRMS (NSI^+) $C_{19}H_{19}F_3NO_2^+$ ($[M+NH_4]^+$) requires 350.1362; found 350.1368 (+1.6 ppm).

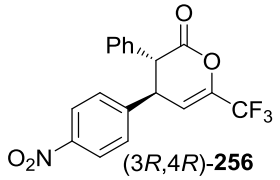
(3*R*,4*R*)-4-(4-methoxyphenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**255**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **556** (46.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**255** (94:6 dr). Chromatographic purification (eluent Et_2O:petrol 7.5:92.5) gave lactone (3*R*,4*R*)-**255** (96:4 dr) as a colourless oil (65.0 mg, 93%); $[\alpha]_D^{20}$-345.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 19.4 min, t_R(3*S*,4*S*): 24.4 min, 98% *ee*; ν_{max} (thin film)/cm^{-1} 3090, 3033, 2938 (C-H), 1780 (C=O), 1700, 1612, 1585, 1514; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.68 (3H, s, OCH_3), 3.85 (1H, d, *J* 8.8, C(3)*H*), 3.88-3.91 (1H, m, C(4)*H*), 6.03 (1H, d, *J* 3.4, C(5)*H*), 6.71-6.73 (2H, m, C(4)Ar(3,5)*H*), 6.85-6.87 (2H, m, C(4)Ar(2,6)*H*), 7.00-7.02 (2H, m, Ar*H*), 7.18-7.24 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.0 (*C*(4)), 53.0 (*C*(3)), 55.3 (O*C*H_3), 111.1 (q, *J* 3.4, *C*(5)), 114.5 (C(4)*ArC*(3,5)), 118.5 (q, *J* 270, *C*F_3), 128.1 (C(3)*ArC*(4)), 128.3 (*ArC*), 128.5 (*ArC*), 128.9 (*ArC*), 130.7 (C(4)*ArC*(1), 135.2 (C(3)*ArC*(1)), 140.7 (q, *J* 38.0, *C*(6)), 159.2 (C(4)*ArC*(4)), 165.9 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.6 (CF_3); *m*/*z* (NSI^+) 366 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{19}H_{19}F_3NO_3^+$ ($[M+NH_4]^+$) requires 366.1312; found 366.1316 (+1.2 ppm).

(3*R*,4*R*)-4-(4-nitrophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

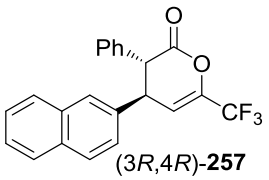


(3*R*,4*R*)-**256**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **557** (49.0 mg, 0.20 mmol) and *i*-

Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**256** (73:27 dr). Chromatographic purification (eluent Et_2O:petrol 25:75) gave lactone (3*R*,4*R*)-**256** (>99:1 dr) as a white solid (47.4 mg, 65%); mp 102-104 °C; $[\alpha]_D^{20}$-216.2 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 15.0 min, t_R(3*S*,4*S*): 29.9 min, 86% *ee*; ν_{max} (KBr)/cm^{-1} 3089, 2925, 2854 (C-H), 1778 (C=O), 1707, 1608, 1518 (N=O), 1342 (N=O); Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 3.84 (1H, d, *J* 10.4, C(3)*H*), 4.09-4.14 (1H, m, C(4)*H*), 6.05 (1H, d, *J* 3.0, C(5)*H*), 6.96-6.98 (2H, m, Ar*H*), 7.10-7.13 (2H, m, C(4)Ar(2,6)*H*), 7.21-7.25 (3H, m, Ar*H*), 8.03-8.07 (2H, m, C(4)Ar(3,5)*H*); δ_C (100 MHz, $CDCl_3$) 44.6 (*C*(4)), 52.4 (*C*(3)), 109.4 (q, *J* 3.4, *C*(5)), 118.3 (q, *J* 270, *C*F_3), 124.3 (C(4)*ArC*(3,5), 128.4 (*ArC*), 128.6 (C(3)*ArC*(4)), 128.6 (*ArC*), 129.2 (*ArC*), 133.9 (C(3)*ArC*(1)), 141.9 (q, *J* 38.3, *C*(6)), 145.9 (C(4)*ArC*(1)), 147.6 (C(4)*ArC*(4)), 164.9 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.7 (C*F*$_3$); *m*/*z* (NSI^+) 381 ($[M+NH_4]^+$, 74%); HRMS (NSI^+) $C_{18}H_{16}F_3N_2O_4^+$ ($[M+NH_4]^+$) requires 381.1057; found 381.1059 (+0.6 ppm).

(3*R*,4*R*)-4-(naphthalen-2-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

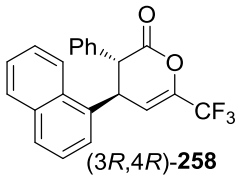


(3*R*,4*R*)-**257**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **559** (50.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**257** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**257** (98:2 dr) as a white solid (59.8 mg, 81%); mp 60-62 °C; $[\alpha]_D^{20}$-294.4 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 11.1 min, t_R(3*S*,4*S*): 26.8 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3062, 2927 (C-H), 1771 (C=O), 1700, 1634, 1601, 1509; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 4.00 (1H, d, *J* 8.9, C(3)*H*), 4.08-4.14 (1H, m, C(4)*H*), 6.12 (1H, d, *J* 3.3, C(5)*H*), 7.01-7.07 (3H, m, Ar*H*), 7.17-7.22 (3H, m, Ar*H*), 7.37-7.43 (3H, m, Ar*H*), 7.64-7.73 (3H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 44.9 (*C*(4)), 52.6 (*C*(3)), 110.7 (q, *J* 3.4, *C*(5)),

118.5 (q, *J* 270, *C*F_3), 124.9 (*ArC*), 126.5 (*ArC*), 126.5 (*ArC*), 126.7 (*ArC*), 127.7 (*ArC*), 127.8 (*ArC*), 128.2 (*ArC*), 128.3 (*ArC*), 129.0 (*ArC*), 129.2 (*ArC*), 132.8 (*ArC*), 133.3 (*ArC*), 135.0 (*ArC*), 136.0 (*ArC*), 140.8 (q, *J* 37.9, *C*(6)), 165.8 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.5 (C*F*$_3$); *m*/*z* (NSI$^+$) 386 ([M+NH_4]$^+$, 75%); HRMS (NSI$^+$) $C_{22}H_{19}F_3NO_2^+$ ([M+NH_4]$^+$) requires 386.1362; found 386.1365 (+0.7 ppm).

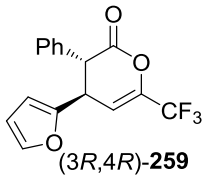
(3*R*,4*R*)-4-(naphthalen-1-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**258**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **560** (50.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**258** (94:6 dr). Chromatographic purification (eluent Et_2O:petrol 4:96) gave lactone (3*R*,4*R*)-**258** (99:1 dr) as a white solid (66.7 mg, 91%); mp 118-120 °C; $[\alpha]_D^{20}$-284.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 8.5 min, t_R(3*S*,4*S*): 10.3 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3094, 3038, 2875 (C-H), 1774 (C=O), 1708, 1596, 1513; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 4.20 (1H, d, *J* 5.3, C(3)*H*), 4.75-4.77 (1H, m, C(4)*H*), 6.15 (1H, d, *J* 5.0, C(5)*H*), 7.16-7.28 (6H, m, Ar*H*), 7.35 (1H, t, *J* 7.7, Ar*H*), 7.42-7.48 (2H, m, Ar*H*), 7.73 (1H, d, *J* 8.2, Ar*H*), 7.77-7.83 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 40.0 (*C*(4)), 51.5 (*C*(3)), 109.8 (q, *J* 3.3, *C*(5)), 118.5 (q, *J* 270, *C*F_3), 122.1 (*ArC*), 124.7 (*ArC*), 125.6 (*ArC*), 126.1 (*ArC*), 127.0 (*ArC*), 127.6 (*ArC*), 128.4 (*ArC*), 129.0 (*ArC*), 129.3 (*ArC*), 129.6 (*ArC*), 130.4 (*ArC*), 133.7 (*ArC*), 134.4 (*ArC*), 135.6 (*ArC*), 141.5 (q, *J* 37.9, *C*(6)), 165.4 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.5 (C*F*$_3$); *m*/*z* (NSI$^+$) 386 ([M+NH_4]$^+$, 57%); HRMS (NSI$^+$) $C_{22}H_{19}F_3NO_2^+$ ([M+NH_4]$^+$) requires 386.1362; found 386.1366 (+0.9 ppm).

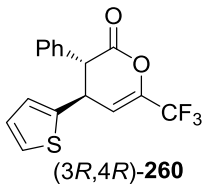
(3*R*,4*R*)-4-(furan-2-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**259**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **562** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**259** (89:11 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**259** (>99:1 dr) as a white solid (47.3 mg, 77%); mp 61-63 °C; $[\alpha]_D^{20}$-267.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 6.3 min, t_R(3*R*,4*R*): 7.4 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3033, 2940, 2879 (C-H), 1780 (C=O), 1703, 1635, 1510; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 4.04-4.09 (1H, m, C(4)*H*), 4.16 (1H, d, *J* 7.1, C(3)*H*), 5.94 (1H, d, *J* 3.3, C(5)*H*), 6.03 (1H, d, *J* 4.4, C(4)Ar(3)*H*), 6.18 (1H, dd, *J* 3.3, 1.9, C(4)Ar(4)*H*), 7.09-7.12 (2H, m, Ar*H*), 7.24-7.31 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 38.3 (*C*(4)), 49.5 (*C*(3)), 107.6 (C(4)*ArC*(3)), 107.8 (q, *J* 3.5, *C*(5)), 110.5 (C(4)*ArC*(4)), 118.4 (q, *J* 270, *C*F_3), 127.8 (*ArC*), 128.4 (C(3)*ArC*(4)), 129.1 (*ArC*), 134.7 (C(3)*ArC*(1)), 141.2 (q, *J* 38.1, *C*(6)), 143.0 (C(4)*ArC*(5)), 150.4 (C(4)*ArC*(2)), 165.4 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.9 (C*F*$_3$); *m*/*z* (NSI^+) 326 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{16}H_{15}F_3NO_3^+$ ($[M+NH_4]^+$) requires 326.0999; found 326.1003 (+1.4 ppm).

(3*R*,4*R*)-3-phenyl-4-(thiophen-2-yl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

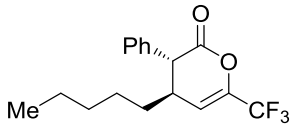


(3*R*,4*R*)-**260**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **561** (41.2 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**260** (88:12 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**260**

(98:2 dr) as a white solid (55.6 mg, 86%); mp 58-60 °C; $[\alpha]_D^{20}$-258.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 6.8 min, t_R(3*R*,4*R*): 9.1 min, 95% *ee*; ν_{max} (KBr)/cm^{-1} 3088, 3034, 2923, 2865 (C-H), 1774 (C=O), 1703; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 4.00 (1H, d, *J* 8.1, C(3)*H*), 4.24-4.27 (1H, m, C(4)*H*), 6.11 (1H, d, *J* 4.1, C(5)*H*), 6.65-6.66 (1H, m, C(4)Ar(3)*H*), 6.81 (1H, dd, *J* 5.1, 3.5, C(4)Ar(4)*H*), 7.06-7.09 (2H, m, Ar*H*), 7.13 (1H, dd, *J* 5.1, 1.1, C(4)Ar(5)*H*), 7.23-7.29 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 39.8 (*C*(4)), 53.3 (*C*(3)), 110.2 (q, *J* 3.5, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 125.4 (*ArC*), 125.7 (*ArC*), 127.3 (*ArC*), 128.1 (*ArC*), 128.4 (C(3)*ArC*(4)), 129.1 (*ArC*), 134.7 (C(3)*ArC*(1)), 140.8 (q, *J* 38.2, *C*(6)), 141.1 (C(4)*ArC*(2)), 165.3 (*C*(2)); δ_F (376 MHz, $CDCl_3$) -72.8 (C*F*$_3$); *m*/*z* (NSI^+) 342 ($[M+NH_4]^+$, 97%); HRMS (NSI^+) $C_{16}H_{15}F_3NO_2S^+$ ($[M+NH_4]^+$) requires 342.0770; found 342.0775 (+1.4 ppm).

(3*R*,4*R*)-4-pentyl-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

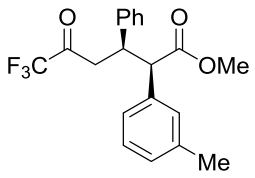


(3*R*,4*R*)-**261**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **247** (38.8 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**261** (78:22 dr). Chromatographic purification (eluent Et_2O:petrol 2:98) gave lactone (3*R*,4*R*)-**261** (86:14 dr) as a colourless oil (45.7 mg, 73%); $[\alpha]_D^{20}$-73.0 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak IB (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*R*,4*R*): 7.0 min, t_R(3*S*,4*S*): 7.7 min, 98% *ee*; ν_{max} (ATR)/cm^{-1} 2957, 2932 (C-H), 1786 (C=O), 1713; Data for major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 0.89 (3H, *J* 7.0, C*H*$_3$), 1.21-1.50 (8H, m, 4C*H*$_2$), 2.85-2.87 (1H, m, C(4)*H*), 3.72 (1H, d, *J* 8.6, C(3)*H*), 6.03 (1H, d, *J* 3.8, C(5)*H*), 7.21-7.22 (2H, m, Ar*H*), 7.35-7.43 (3H, m, Ar*H*); Selected data for minor diastereoisomer δ_H (500 MHz, $CDCl_3$) 4.08 (1H, d, *J* 6.5, C(3)*H*), 6.12 (1H, d, *J* 5.0, C(5)*H*); Data for major diastereoisomer: δ_C (100 MHz, $CDCl_3$) 13.9 (*C*H_3), 22.4 (*C*H_2), 25.6 (*C*H_2), 31.4 (*C*H_2), 32.6 (*C*H_2), 37.6 (*C*(4)), 50.1 (*C*(3)), 111.2 (q, *J* 3.3, *C*(5)), 118.5 (q, *J* 270, *C*F_3), 128.1 (*ArC*), 128.2 (C(3)*ArC*(4)), 129.1 (*ArC*), 135.4 (C(3)*ArC*(1)), 140.1 (q, *J* 37.9, *C*(6)), 166.9 (*C*(2)); Selected data for minor diastereoisomer: δ_C (100

MHz, $CDCl_3$) 26.4 (*C*H_2), 29.5 (*C*H_2), 31.6 (*C*H_2), 36.9 (*C*(4)), 48.9 (*C*(3)), 112.4 (q, *J* 3.3, *C*(5)), 128.7 (*ArC*), 129.4 (*ArC*), 166.4 (*C*(2)); *m*/*z* ($APCI^+$) 313 ($[M+H]^+$, 100%); HRMS ($APCI^+$) $C_{17}H_{20}F_3O_2^+$ ($[M+H]^+$) requires 313.1410; found 313.1408 (-0.6 ppm).

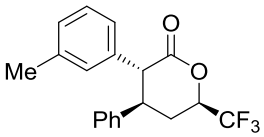
(2*R*,3*R*)-methyl 6,6,6-trifluoro-5-oxo-3-phenyl-2-(*m*-tolyl)hexanoate



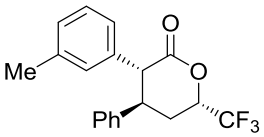
(2*R*,3*R*)-**263**

Following general procedure D, *m*-tolylacetic acid (30.0 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at –78 °C, followed by addition of MeOH (2 mL) and stirring at rt for 1 h gave crude ester (2*R*,3*R*)-**263** (92:8 dr). Chromatographic purification (eluent Et_2O:petrol 10:90) gave ester (2*R*,3*R*)-**263** (92:8 dr) as a white solid (52.6 mg, 72%); mp 58-60 °C; $[\alpha]_D^{20}$-130.4 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*,3*S*): 4.4 min, t_R(2*R*,3*R*): 5.1 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3031, 2958, 1761 (C=O ketone), 1732 (C=O ester), 1605; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 2.15 (3H, s, CH_3), 3.08 (1H, dd, *J* 18.3, 3.8, C(4)*H*), 3.29 (1H, dd, *J* 18.4, 9.4, C(4)*H*), 3.60 (3H, s, CO_2CH_3), 3.76 (1H, d, *J* 10.3, C(2)*H*), 3.82-3.90 (1H, m, C(3)*H*), 6.80-6.84 (3H, m, Ar*H*), 6.93-7.09 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (*C*H_3), 40.6 (*C*(4)), 43.4 (*C*(3)), 52.3 (CO_2CH_3), 56.9 (*C*(2), 115.3 (q, *J* 290,*C*F_3), 125.5 (*ArC*), 127.1 (*ArC*), 128.0 (*ArC*), 128.0 (*ArC*), 128.3 (*ArC*), 128.4 (*ArC*), 129.1 (*ArC*), 136.0 (*ArC*), 138.1 (*ArC*), 139.6 (*ArC*), 173.2 (*C*(1)), 189.2 (q, *J* 35.2, *C*(5)); δ_F (282 MHz, $CDCl_3$) -80.0 (CF_3); *m*/*z* (NSI^+) 382 ($[M+NH_4]^+$, 50%); HRMS (NSI^+) $C_{20}H_{23}F_3NO_3^+$ ($[M+NH_4]^+$) requires 382.1625; found 382.1627 (+0.6 ppm).

(3*R*,4*R*,6*R*)-4-phenyl-3-(*m*-tolyl)-6-(trifluoromethyl)tetrahydro-2*H*-pyran-2-one and (3*R*,4*R*,6*S*)-4-phenyl-3-(*m*-tolyl)-6-(trifluoromethyl)tetrahydro-2*H*-pyran-2-one



(3*R*,4*R*,6*R*)-**264**



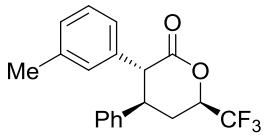
(3*R*,4*R*,6*S*)-**265**

To a solution of lactone (3*R*,4*R*)-**226** (96:4 dr) (100 mg, 0.30 mmol) in EtOAc (5 mL) was added 10% Pd/C (31.9 mg, 0.03 mmol). Hydrogen gas (1 balloon) was bubbled through the solution and the reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered through Celite and washed several times with CH_2Cl_2. Concentration *in vacuo* gave crude lactones (3*R*,4*R*,6*R*)-**264** and (3*R*,4*R*,6*S*)-**265** (53:47 dr). Chromatographic purification (eluent Et_2O:petrol 20:80) gave:

Lactone (3*R*,4*R*,6*R*)-**264** (>99:1 dr) as a white solid (51.6 mg, 51%); mp 96-98 °C; $[\alpha]_D^{20}$-252.7 (*c* 0.15, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*,6*R*): 14.6 min, t_R(3*S*,4*S*,6*S*): 41.8 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3071, 3031, 2921 (C-H), 1743 (C=O), 1612; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 2.16 (3H, s, C*H*$_3$), 2.23-2.37 (2H, m, C(5)H*H* and C(5)*H*H), 3.26 (1H, td, *J* 11.8, 3.9, C(4)*H*), 3.72 (1H, d, *J* 11.5, C(3)*H*), 4.88 (1H, ddq, *J* 12.2, 6.8, 3.2, C(6)*H*), 6.65-6.70 (2H, m, Ar*H*), 6.91-6.94 (3H, m, Ar*H*), 7.01 (1H, t, *J* 7.5, C(3)Ar(5)*H*), 7.10-7.20 (3H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.4 (*C*H_3), 29.4 (*C*(5), 45.1 (*C*(4)), 55.5 (*C*(3)), 76.0 (q, *J* 33.8, *C*(6)), 122.6 (q, *J* 278, *C*F_3), 125.7 (*ArC*), 127.1 (*ArC*), 127.6 (*ArC*), 128.5 (*ArC*), 128.5 (*ArC*), 128.9 (*ArC*), 129.3 (*ArC*), 136.7 (*ArC*), 138.4 (*ArC*), 140.0 (*ArC*), 169.4 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -79.8 (C*F*$_3$); *m*/*z* (ES^+) 357 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{19}H_{17}F_3NaO_2^+$ ($[M+Na]^+$) requires 357.1078; found 357.1087 (+2.5 ppm).

Lactone (3*R*,4*R*,6*S*)-**265** (>99:1 dr) as a colourless oil (45.6 mg, 45%); $[\alpha]_D^{20}$-100.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*,6*S*): 17.8 min, t_R(3*S*,4*S*,6*R*): 36.4 min, 97% *ee*; ν_{max} (thin film)/cm^{-1} 3031, 2923 (C-H), 1756 (C=O), 1606; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 2.16-2.26 (4H, s, C*H*$_3$ and C(5)*H*), 2.37-2.46 (1H, m, C(5)*H*), 3.46 (1H, q, *J* 6.6, C(4)*H*), 3.93 (1H, d, *J* 8.0, C(3)*H*), 4.70-4.76 (1H, ddq, 6.8, 5.6, 4.6, C(6)*H*), 6.77-6.80 (2H, m, Ar*H*), 6.91-7.25 (7H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.4 (*C*H_3), 27.3 (*C*(5), 42.5 (*C*(4)), 52.5 (*C*(3)), 74.1 (q, *J* 33.0, *C*(6)), 123.3 (q, *J* 279, *C*F_3), 125.5 (*ArC*), 126.9 (*ArC*), 127.6 (*ArC*), 128.4 (*ArC*), 128.6 (*ArC*), 129.1 (*ArC*), 129.2 (*ArC*), 137.0 (*ArC*), 138.4 (*ArC*), 140.6 (*ArC*), 169.6 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -77.7 (C*F*$_3$); *m*/*z* (ES^+) 357 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{19}H_{17}F_3NaO_2^+$ ($[M+Na]^+$) requires 357.1078; found 357.1076 (-0.6 ppm).

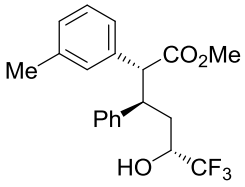
(3*R*,4*R*,6*R*)-4-phenyl-3-(*m*-tolyl)-6-(trifluoromethyl)tetrahydro-2*H*-pyran-2-one



(3*R*,4*R*,6*R*)-**264**

To a solution of lactone (3*R*,4*R*)-**226** (96:4 dr) (100 mg, 0.30 mmol) in EtOAc (3 mL) was added 5% $Rh(PPh_3)_3Cl$ (14.0 mg, 0.015 mmol). The reaction mixture was heated at 80 °C under a 50 bar pressure of Hydrogen gas for 16 h. The reaction mixture was filtered through Celite and washed several times with CH_2Cl_2. Concentration *in vacuo* gave crude lactone (3*R*,4*R*,6*R*)-**264** (96:4 dr). Chromatographic purification (eluent Et_2O:petrol 20:80) gave lactone (3*R*,4*R*,6*R*)-**264** (>99:1 dr) as a white solid (96.3 mg, 96%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*,6*R*): 14.6 min, t_R(3*S*,4*S*,6*S*): 41.8 min, 98% *ee*.

(2*R*,3*R*,5*R*)-methyl 6,6,6-trifluoro-5-hydroxy-3-phenyl-2-(*m*-tolyl)hexanoate

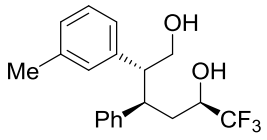


(2*R*,3*R*,5*R*)-**268**

To a solution of lactone (3*R*,4*R*,6*R*)-**264** (50.0 mg, 0.15 mmol) (>99:1 dr) in methanol (5 mL) was added DMAP (3.66 mg, 0.03 mmol). The reaction mixture was stirred at 40 °C for 5 h before being concentrated *in vacuo* to give crude alcohol (2*R*,3*R*,5*R*)-**268** (>99:1 dr). Chromatographic purification (eluent Et_2O:petrol 20:80) gave alcohol (2*R*,3*R*,5*R*)-**268** (>99:1 dr) as a white solid (49.3 mg, 90%); mp 78-80 °C; $[\alpha]_D^{20}$-169.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*,3*S*,5*S*): 7.4 min, t_R(2*R*,3*R*,5*R*): 12.8 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3431 (O-H), 3030, 2958 (C-H), 1728 (C=O), 1700, 1608; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.91-2.03 (2H, m, C(4)*H*), 2.12 (3H, s, CH_3), 2.53 (1H, d, *J* 7.0, O*H*), 3.43-3.48 (1H, m, C(5)*H*), 3.56-3.63 (4H, m, C(3)*H* and CH_3), 3.70 (1H, d, *J* 7.9 C(2)*H*), 6.80-6.84 (3H, m, Ar*H*), 6.89-6.94 (3H, m, Ar*H*), 6.98-7.02 (1H, m, Ar*H*), 7.05-7.09 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (*C*H_3), 34.4 (*C*(4)), 44.6 (*C*(3)), 52.4 (*C*H_3), 57.8 (*C*(2)), 68.3 (q, *J* 31.0, *C*(5)), 125.1 (q, *J* 280,*C*F_3), 125.5 (*ArC*), 126.9 (*ArC*), 128.0 (*ArC*), 128.1 (*ArC*), 128.4 (*ArC*), 128.5 (*ArC*), 129.1 (*ArC*), 136.6 (*ArC*), 137.9 (*ArC*),

139.5 (*ArC*), 174.0 (*C*(1); δ_F (376 MHz, $CDCl_3$) -80.5 (CF_3); *m*/*z* (EI^+) 366 ($[M]^+$, 12%); HRMS (EI^+) $C_{20}H_{21}F_3O_3^+$ ($[M]^+$) requires 366.1443; found 366.1451 (+2.2 ppm).

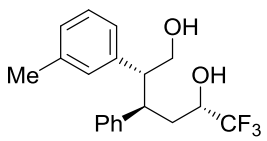
(2*R*,3*R*,5*R*)-6,6,6-trifluoro-3-phenyl-2-(*m*-tolyl)hexane-1,5-diol



(2*R*,3*R*,5*R*)-**269**

To a solution of lactone (3*R*,4*R*,6*R*)-**264** (50.0 mg, 0.15 mmol) (>99:1 dr) in THF (1 mL) at 0 °C was added $LiAlH_4$ (2 M in THF, 0.23 mL, 0.45 mmol) and the reaction mixture was allowed to stir for 10 minutes at rt. The reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ and extracted with Et_2O (x 3). The combined organic extracted were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude diol (2*R*,3*R*,5*R*)-**269** (>99:1 dr). Chromatographic purification (eluent Et_2O) gave diol (2*R*,3*R*,5*R*)-**269** (>99:1 dr) as a colourless oil (41.5 mg, 82%); $[\alpha]_D^{20}$-17.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*,3*R*,5*R*): 6.1 min, t_R(2*S*,3*S*,5*S*): 7.5 min, 98% *ee*; ν_{max} (thin film)/cm^{-1} 3334 (O-H), 3030, 2925 (C-H), 1606, 1589; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 1.67 (1H, br s, O*H*), 1.84-1.93 (1H, m, C(4)*H*), 2.06 (1H, ddd, *J* 14.2, 10.9, 3.5, C(4)*H*), 2.15 (3H, s, CH_3), 2.83 (1H, br s, O*H*), 2.93-3.00 (1H, m, C(2)*H*), 3.32-3.43 (2H, m, C(3)*H* and C(5)*H*), 3.83 (2H, d, *J* 6.3, C(1)H*H* and C(1)*H*H), 6.64-6.67 (2H, m, Ar*H*), 6.83-6.87 (3H, m, Ar*H*), 6.98 (1H, t, *J* 7.7, C(3)Ar(5)*H*), 7.01-7.12 (3H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.4 (*C*H_3), 33.1 (*C*(4)), 42.2 (*C*(3)), 53.4 (*C*(2), 64.6 (*C*(1), 68.3 (q, *J* 31.0, *C*(5)), 125.3 (q, *J* 280,*C*F_3), 126.1 (*ArC*), 126.7 (*ArC*), 127.6 (*ArC*), 128.0 (*ArC*), 128.2 (*ArC*), 128.9 (*ArC*), 129.8 (*ArC*), 137.7 (*ArC*), 139.5 (*ArC*), 140.1 (*ArC*); δ_F (282 MHz, $CDCl_3$) -80.5 (CF_3); *m*/*z* (ES^+) 361 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{19}H_{21}F_3NaO_2^+$ ($[M+Na]^+$) requires 361.1391; found 361.1398 (+1.9 ppm).

(2*R*,3*R*,5*S*)-6,6,6-trifluoro-3-phenyl-2-(*m*-tolyl)hexane-1,5-diol



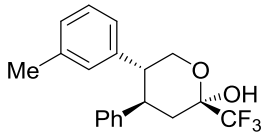
(2*R*,3*R*,5*S*)-**270**

To a solution of lactone (3*R*,4*R*,6*S*)-**265** (50.0 mg, 0.15 mmol) (>99:1 dr) in THF (1 mL) at 0 °C was added $LiAlH_4$ (2 M in THF, 0.23 mL, 0.45 mmol) and the reaction mixture was allowed to stir for 10 minutes at rt. The reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ and extracted with Et_2O (x 3). The combined organic extracted were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude diol (2*R*,3*R*,5*S*)-**270** (>99:1 dr). Chromatographic purification (eluent Et_2O:petrol 60:40) gave diol (2*R*,3*R*,5*R*)-**270** (>99:1 dr) as a white solid (42.3 mg, 83%); mp 102-104 °C; $[\alpha]_D^{20}$-19.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*,3*S*,5*R*): 8.2 min, t_R(2*R*,3*R*,5*S*): 9.3 min, 96% *ee*; ν_{max} (KBr)/cm^{-1} 3412 (O-H), 2924 (C-H), 2854; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.92-2.00 (1H, m, C(4)*H*), 2.13-2.20 (4H, m, C(4)*H* and CH_3), 3.11 (1H, q, *J* 6.9, C(3)*H*), 3.29 (1H, q, *J* 7.1, C(2)*H*), 3.78 (1H, dd, *J* 10.7, 6.7, C(1)*H*), 3.84-3.94 (2H, m, C(1)*H* and C(5)*H*), 6.57-6.59 (2H, m, Ar*H*), 6.86-6.90 (3H, m, Ar*H*), 6.97-7.00 (1H, m, C(3)Ar(5)*H*), 7.05-7.13 (3H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.4 (*C*H_3), 33.8 (*C*(4)), 43.5 (*C*(3)), 51.7 (*C*(2), 64.9 (*C*(1), 69.1 (q, *J* 30.5, *C*(5)), 125.3 (q, *J* 281,*C*F_3), 126.1 (*ArC*), 126.8 (*ArC*), 127.7 (*ArC*), 128.0 (*ArC*), 128.1 (*ArC*), 129.0 (*ArC*), 129.9 (*ArC*), 137.7 (*ArC*), 138.8 (*ArC*), 140.7 (*ArC*); δ_F (376 MHz, $CDCl_3$) -80.0 (C*F*$_3$); *m*/*z* (ES^+) 361 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{19}H_{21}F_3NaO_2^+$ ($[M+Na]^+$) requires 361.1391; found 361.1380 (-3.2 ppm).

General procedure F: *$LiAlH_4$ Mediated Rearrangements.*

To a solution of lactone (1 eq) in THF at rt was added $LiAlH_4$ (2 M in THF, 4 eq) and the reaction mixture was allowed to stir for 10 minutes at rt. The reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ and extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude the crude reaction mixture. Note: Racemic samples for HPLC analysis were obtained *via* the same general procedure using racemic dihydropyranones as starting materials.

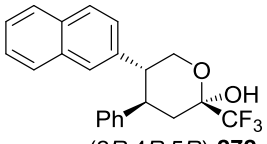
(2*R*,4*R*,5*R*)-4-phenyl-5-(*m*-tolyl)-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol



(2*R*,4*R*,5*R*)-**271**

Following general procedure F, lactone (3*R*,4*R*)-**226** (100 mg, 0.30 mmol) (96:4 dr) and $LiAlH_4$ (2 M in THF, 0.60 mL, 1.2 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2*R*,4*R*,5*R*)-**271** (96:4 dr). Chromatographic purification (eluent Et_2O:petrol 10:90) gave pyran (2*R*,4*R*,5*R*)-**271** (>99:1 dr) as a colourless oil (77.1 mg, 80%); $[\alpha]_D^{20}$-38.3 (*c* 1.0, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*,4*R*,5*R*): 5.8 min, t_R(2*S*,4*S*,5*S*): 7.3 min, 97% *ee*; ν_{max} (thin film)/cm^{-1} 3418 (O-H), 3030, 2941 (C-H), 1705, 1608. 1591; Data for major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 1.94 (1H, t, *J* 13.1, C(3)*H*), 2.12-2.15 (4H, m, C(3)*H* and CH_3), 2.74 (1H, br s, O*H*), 3.08 (1H, td, *J* 11.7, 4.6, C(5)*H*), 3.43 (1H, td, 12.2, 3.8, C(4)*H*), 3.86 (1H, dd, *J* 11.4, 4.7, C(6)*H*), 4.00 (1H, t, *J* 11.5, C(6)*H*), 6.81-6.83 (3H, m, Ar*H*), 6.96-7.03 (4H, m, Ar*H*), 7.07-7.10 (2H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.4 (*C*H_3), 35.3 (*C*(3)), 40.7 (*C*(4)), 47.2 (*C*(5), 67.2 (*C*(6), 94.5 (q, *J* 32.0, *C*(2)), 122.7 (q, *J* 284,*C*F_3), 125.2 (*ArC*), 126.6 (*ArC*), 127.6 (*ArC*), 127.8 (*ArC*), 128.3 (*ArC*), 128.5 (*ArC*), 128.9 (*ArC*), 138.0 (*ArC*), 138.5 (*ArC*), 142.0 (C(4)*ArC*(1)); δ_F (470 MHz, $CDCl_3$) -87.1 (C*F*$_3$); *m*/*z* (ES^+) 359 ($[M+Na]^+$, 100%); HRMS (ES^-) $C_{19}H_{18}F_3O_2^+$ ($[M-H]^+$) requires 335.1259; found 335.1258 (-0.4 ppm).

(2*R*,4*R*,5*R*)-5-(naphthalen-2-yl)-4-phenyl-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol

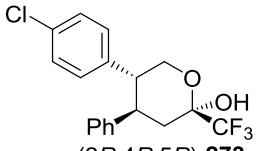


(2*R*,4*R*,5*R*)-**272**

Following general procedure F, lactone (3*R*,4*R*)-**235** (39.8 mg, 0.11 mmol) (98:2 dr) and $LiAlH_4$ (2 M in THF, 0.22 mL, 0.44 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2*R*,4*R*,5*R*)-**272** (98:2 dr). Chromatographic purification (eluent Et_2O:petrol 15:85) gave pyran (2*R*,4*R*,5*R*)-**272** (>99:1 dr) as a white solid (36.7 mg, 90%); mp 111-113 °C; $[\alpha]_D^{20}$-98.7 (*c* 0.15, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*,4*R*,5*R*): 11.9 min, t_R(2*S*,4*S*,5*S*): 17.6 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3490 (O-H), 3031, 2941 (C-H); Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 2.00 (1H, td, *J* 13.0, 2.6, C(3)*H*), 2.20 (1H, dd, *J* 13.6, 4.0, C(3)*H*), 2.75 (1H, d, *J* 2.7, O*H*), 3.30 (1H, td, *J* 11.7, 4.7, C(5)*H*), 3.58 (1H, td, 12.1, 4.0, C(4)*H*), 3.94 (1H, dd, *J* 11.4, 4.7, C(6)*H*), 4.12 (1H, t, *J* 11.5, C(6)*H*), 6.94-6.98 (1H, m, Ar*H*), 7.03-7.08 (4H, m, Ar*H*), 7.17-7.19 (1H, m, Ar*H*), 7.29-7.35 (2H, m, Ar*H*), 7.49 (1H, s,

C(5)Ar(1)*H*), 7.58-7.65 (3H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 35.4 (*C*(3)), 40.8 (*C*(4)), 47.4 (*C*(5), 67.1 (*C*(6), 94.5 (q, *J* 32.0, *C*(2)), 122.7 (q, *J* 284, *C*F_3), 125.7 (*ArC*), 126.0 (*ArC*), 126.2 (*ArC*), 126.7 (*ArC*), 127.2 (*ArC*), 127.5 (*ArC*), 127.6 (*ArC*), 127.6 (*ArC*), 128.2 (*ArC*), 128.6 (*ArC*), 132.5 (*ArC*), 133.4 (*ArC*), 136.1 (*ArC*), 141.8 (*ArC*); δ_F (376 MHz, $CDCl_3$) -87.6 (C*F*$_3$); *m*/*z* (ES^-) 371 ($[M-H]^+$, 100%); HRMS (ES^-) $C_{22}H_{18}F_3O_2^+$ ($[M-H]^+$) requires 371.1259; found 371.1272 (+3.6 ppm).

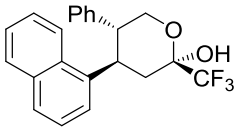
(2*R*,4*R*,5*R*)-5-(4-chlorophenyl)-4-phenyl-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol



(2*R*,4*R*,5*R*)-**273**

Following general procedure F, lactone (3*R*,4*R*)-**228** (42.2 mg, 0.12 mmol) (>99:1 dr) and $LiAlH_4$ (2 M in THF, 0.22 mL, 0.44 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2*R*,4*R*,5*R*)-**273** (>99:1 dr). Chromatographic purification (eluent Et_2O:petrol 15:85) gave pyran (2*R*,4*R*,5*R*)-**273** (>99:1 dr) as a colourless oil (40.3 mg, 94%); $[\alpha]_D^{20}$-67.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*,4*R*,5*R*): 10.7 min, t_R(2*S*,4*S*,5*S*): 18.5 min, 92% *ee*; ν_{max} (thin film)/cm^{-1} 3399 (O-H), 3031, 2940 (C-H) 1600; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.95 (1H, td, *J* 13.0, 2.1, C(3)*H*), 2.15 (1H, dd, *J* 13.5, 3.8, C(3)*H*), 2.72 (1H, d, *J* 2.2, O*H*), 3.09 (1H, td, *J* 11.7, 4.7, C(5)*H*), 3.38 (1H, td, 12.1, 3.9, C(4)*H*), 3.85 (1H, dd, *J* 11.4, 4.6, C(6)*H*), 4.00 (1H, t, *J* 11.5, C(6)*H*), 6.95-7.13 (9H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 35.2 (*C*(3)), 41.0 (*C*(4)), 46.9 (*C*(5), 66.8 (*C*(6), 94.4 (q, *J* 31.9, *C*(2)), 122.6 (q, *J* 283,*C*F_3), 126.9 (C(4)*ArC*(4)), 127.5 (*ArC*), 128.6 (*ArC*), 128.7 (*ArC*), 129.4 (*ArC*), 132.7 (C(5)*ArC*(4)), 137.1 (C(5)*ArC*(1)), 141.4 (C(4)*ArC*(1)); δ_F (376 MHz, $CDCl_3$) -87.6 (C*F*$_3$); *m*/*z* (ES^-) 355 ($[M-H]^+$, 100%); HRMS (ES^-) $C_{18}H_{15}{}^{35}ClF_3O_2^+$ ($[M-H]^+$) requires 355.0713; found 355.0716 (+0.8 ppm).

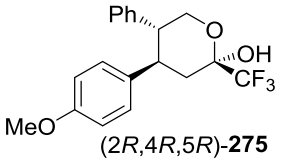
(2*R*,4*R*,5*R*)-4-(naphthalen-1-yl)-5-phenyl-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol



(2*R*,4*R*,5*R*)-**274**

Following general procedure F, lactone (3*R*,4*R*)-**258** (52.8 mg, 0.14 mmol) (99:1 dr) and $LiAlH_4$ (2 M in THF, 0.29 mL, 0.57 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2*R*,4*R*,5*R*)-**274** (99:1 dr). Chromatographic purification (eluent Et_2O:petrol 15:85) gave pyran (2*R*,4*R*,5*R*)-**274** (>99:1 dr) as a white solid (50.7 mg, 95%); mp 132-134 °C; $[\alpha]_D^{20}$+159.6 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*,4*S*,5*S*): 9.7 min, t_R(2*R*,4*R*,5*R*): 13.0 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3517 (O-H), 3065, 2948 (C-H), 1599; Data for major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 1.85 (1H, t, *J* 12.9, C(3)*H*), 2.36 (1H, dd, *J* 13.7, 3.3, C(3)*H*), 2.81 (1H, s, O*H*), 3.54 (1H, td, *J* 11.4, 4.5, C(5)*H*), 4.00 (1H, dd, *J* 11.5, 4.6, C(6)*H*), 4.10 (1H, t, *J* 11.4, C(6)*H*), 4.48 (1H, td, 12.0, 3.3, C(4)*H*), 6.96 (1H, t, *J* 7.3, Ar*H*), 7.03 (2H, t, *J* 7.5, Ar*H*) 7.11 (2H, d, *J* 7.3, Ar*H*), 7.22 (1H, t, *J* 7.6, Ar*H*), 7.27 (1H, d, *J* 6.9 Ar*H*), 7.38 (1H, t, *J* 7.5, Ar*H*), 7.47-7.50 (1H, m, Ar*H*), 7.54 (1H, d, *J* 7.9, C(3)Ar(4)*H*), 7.72 (1H, d, *J* 8.1, C(4)Ar(5)*H*), 8.17 (1H, d, *J* 8.6, C(4)Ar(8)*H*); δ_C (100 MHz, $CDCl_3$) 33.9 (*C*(4)), 36.0 (*C*(3)), 45.9 (*C*(5), 68.1 (*C*(6), 94.6 (q, *J* 32.1, *C*(2)), 122.3 (Ar*H*), 122.6 (q, *J* 283,*C*F_3), 123.8 (*ArC*), 125.5 (*ArC*), 125.5 (*ArC*), 126.4 (*ArC*), 127.0 (*ArC*), 127.1 (*ArC*), 128.0 (*ArC*), 128.6 (*ArC*), 129.1 (*ArC*), 131.4 (*ArC*), 134.0 (*ArC*), 137.7 (*ArC*) 138.4 (*ArC*); δ_F (470 MHz, $CDCl_3$) -87.0 (C*F*$_3$), -116.6 (Ar*F*); *m*/*z* (ES^-) 371 ($[M-H]^+$, 100%); HRMS (ES^-) $C_{22}H_{18}F_3O_2^+$ ($[M-H]^+$) requires 371.1259; found 371.1258 (-0.3 ppm).

(2*R*,4*R*,5*R*)-4-(4-methoxyphenyl)-5-phenyl-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol

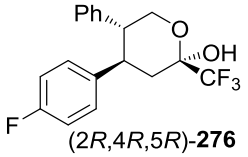


(2*R*,4*R*,5*R*)-**275**

Following general procedure F, lactone (3*R*,4*R*)-**255** (49.7 mg, 0.14 mmol) (96:4 dr) and $LiAlH_4$ (2 M in THF, 0.29 mL, 0.57 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2*R*,4*R*,5*R*)-**275** (96:4 dr). Chromatographic purification (eluent Et_2O:petrol 15:85) gave pyran (2*R*,4*R*,5*R*)-**275** (>99:1 dr) as a colourless oil (46.8 mg, 93%); $[\alpha]_D^{20}$-

39.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*,4*R*,5*R*): 12.7 min, t_R(2*S*,4*S*,5*S*): 44.4 min, 98% *ee*; ν_{max} (thin film)/cm^{-1} 3391 (O-H), 3031, 2939 (C-H), 1612, 1515; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 1.92 (1H, td, *J* 13.0, 2.5, C(3)*H*), 2.12 (1H, dd, *J* 13.5, 4.0, C(3)*H*), 2.77 (1H, d, *J* 2.6, O*H*), 3.06 (1H, td, *J* 11.7, 4.7, C(5)*H*), 3.34-3.43 (1H, m, C(4)*H*), 3.62 (3H, s, OCH_3), 3.87 (1H, dd, *J* 11.4, 4.8, C(6)*H*), 4.02 (1H, t, *J* 11.5, C(6)*H*), 6.60-6.65 (2H, m, C(4)Ar(3,5)*H*), 6.91-6.96 (2H, m, C(4)Ar(2,6)*H*), 7.01-7.14 (5H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 35.4 (*C*(3)), 40.0 (*C*(4)), 47.7 (*C*(5), 55.1 (O*C*H_3), 67.1 (*C*(6), 94.4 (q, *J* 32.0, *C*(2)), 113.8 (C(4)*ArC*(3,5)), 122.7 (q, *J* 284, *C*F_3), 126.9 (C(5)*ArC*(4)), 128.2 (*ArC*), 128.4 (*ArC*), 128.5 (*ArC*), 134.0 (C(4)*ArC*(1)), 138.7 (C(5)*ArC*(1)), 158.1 (C(4)*ArC*(4)); δ_F (282 MHz, $CDCl_3$) -87.6 (C*F*$_3$), -116.6 (Ar*F*); *m*/*z* (ES^-) 351 ($[M-H]^+$, 100%); HRMS (ES^-) $C_{19}H_{18}F_3O_3^+$ ($[M-H]^+$) requires 351.1208; found 351.1204 (-1.1 ppm).

(2*R*,4*R*,5*R*)-4-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol

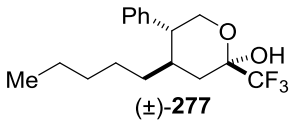


(2*R*,4*R*,5*R*)-**276**

Following general procedure F, lactone (3*R*,4*R*)-**252** (40.3 mg, 0.12 mmol) (>99:1 dr) and $LiAlH_4$ (2 M in THF, 0.22 mL, 0.44 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2*R*,4*R*,5*R*)-**276** (>99:1 dr). Chromatographic purification (eluent Et_2O:petrol 15:85) gave pyran (2*R*,4*R*,5*R*)-**276** (>99:1 dr) as a colourless oil (37.9 mg, 93%); $[\alpha]_D^{20}$-52.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*,4*R*,5*R*): 8.4 min, t_R(2*S*,4*S*,5*S*): 26.0 min, 98% *ee*; ν_{max} (thin film)/cm^{-1} 3419 (O-H), 3032, 2941 (C-H), 1704, 1606; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.93 (1H, td, *J* 13.0, 2.4, C(3)*H*), 2.13 (1H, dd, *J* 13.4, 3.9, C(3)*H*), 2.72 (1H, d, *J* 2.5, O*H*), 3.04 (1H, td, *J* 11.7, 4.7, C(5)*H*), 3.42 (1H, ddd, 14.5, 9.8, 4.4, C(4)*H*), 3.88 (1H, dd, *J* 11.4, 4.7, C(6)*H*), 4.04 (1H, t, *J* 11.5, C(6)*H*), 6.77-6.79 (2H, m, C(4)Ar(3,5)*H*), 6.96-7.13 (7H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 35.2 (*C*(3)), 40.3 (*C*(4)), 47.8 (*C*(5), 66.9 (*C*(6), 94.4 (q, *J* 32.1, *C*(2)), 115.3 (d, *J* 21.1, C(4)*ArC*(3,5)), 122.6 (q, *J* 283,*C*F_3), 127.1 (C(5)*ArC*(4)), 128.1 (*ArC*), 128.6 (*ArC*), 128.9 (d, *J* 7.8, C(4)*ArC*(2,6)), 137.5 (d, *J*, 3.0, C(4)*ArC*(1)), 138.3 (C(5)*ArC*(1)), 161.5

(d, *J* 243, C(4)*ArC*(4)); δ_F (376 MHz, $CDCl_3$) -87.6 (CF_3), -116.6 (Ar*F*); *m*/*z* (ES^-) 339 ($[M-H]^+$, 100%); HRMS (ES^-) $C_{18}H_{15}F_4O_2^+$ ($[M-H]^+$) requires 339.1008; found 339.1014 (+1.8 ppm).

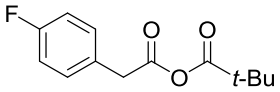
4-pentyl-5-phenyl-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol



(±)-**277**

Following general procedure F, lactone (±)-**261** (50.0 mg, 0.27 mmol) (90:10 dr) and $LiAlH_4$ (2 M in THF, 0.54 mL, 1.1 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (±)-**277** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 10:90) gave pyran (±)-**277** (>99:1 dr) as a colourless oil (41.0 mg, 80%); ν_{max} (ATR)/cm^{-1} 3408 (O-H), 2957, 2932 (C-H), 1602; δ_H (500 MHz, $CDCl_3$) 0.84 (3H, t, *J* 7.11, CH_3), 0.96-1.31 (8H, m, 4CH_2), 1.51 (1H, app t, *J* 12.7, C(3)H*H*), 2.18 (1H, dd, *J* 13.3, 3.9, C(3)*H*H), 2.22-2.29 (1H, m, C(4)*H*), 2.61 (1H, td, *J* 11.6, 4.7, C(5)*H*), 2.68 (1H, br s, O*H*), 3.80 (1H, dd, *J* 11.3, 4.7, C(6)H*H*), 3.95 (1H, t, *J* 11.6, C(6)*H*H), 7.22 (2H, d, *J* 7.2, C(5)Ar(2,6)*H*), 7.29 (1H, t, *J* 7.3, C(5)Ar(4)*H*), 7.36 (2H, t, *J* 7.5, C(5)Ar(3,5)*H*); δ_C (125 MHz, $CDCl_3$) 14.0 (*C*H_3), 22.5 (*C*H_2), 25.5 (*C*H_2), 31.8 (*C*H_2), 32.0 (*C*H_2), 33.0 (*C*H_2), 33.5 (*C*(4)), 48.1 (*C*(5)), 66.9 (*C*(6), 94.5 (q, *J* 31.8, *C*(2)), 122.8 (q, *J* 284,*C*F_3), 127.1 (C(5)*ArC*(4)), 128.2 (*ArC*), 128.7 (*ArC*), 139.5 (C(5)*ArC*(1)); *m*/*z* ($APCI^+$) 316 ($[M]^+$, 100%); HRMS ($APCI^+$) $C_{17}H_{27}F_3NO_2^+$ ($[M+NH_4]^+$) requires 334.1988; found 334.1986 (-0.7 ppm).

2-(4-fluorophenyl)acetic pivalic anhydride

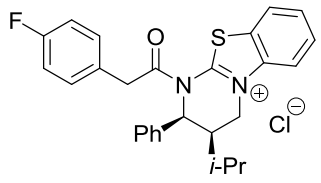


282

To a solution of 4-fluorophenylacetic acid (0.10 g, 0.65 mmol) in CH_2Cl_2 (3 mL) at rt was added *i*-Pr_2NEt (0.17 mL, 0.98 mmol) and pivaloyl chloride (0.12 mL, 0.98 mmol). The reaction mixture was allowed to stir for 15 minutes before being concentrated *in vacuo*. The crude reaction mixture was treated with petrol (10 mL) and then filtered to remove inorganic salts. The filtrate was concentrated in vacuo to give mixed anhydride **282** as a yellow oil (0.15 g, 97%) which was characterised crude without further

purification: δ_H (400 MHz, CD_2Cl_2) 1.09 (9H, s, C(C*H*$_3$)$_3$), 3.66 (2H, s, C*H*$_2$), 6.93-6.99 (2H, m, Ar(3,5)*H*), 7.15-7.20 (2H, m, Ar(2,6)*H*); δ_F (376 MHz, CD_2Cl_2) -116.2 (Ar*F*).

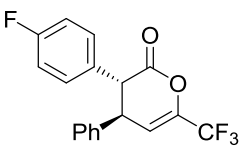
(2*S*,3*R*)-1-(2-(4-fluorophenyl)acetyl)-3-isopropyl-2-phenyl-1,2,3,4-tetrahydrobenzo[4,5]thiazolo[3,2-a]pyrimidin-5-ium chloride



(2*S*,3*R*)-**293**

To a solution of 4-fluorophenylacetyl chloride (0.10 g, 0.58 mmol) in CH_2Cl_2 (2 mL) was added isothiourea (2*S*,3*R*)-**112** (0.18 g, 0.58 mmol) and the reaction mixture was allowed to stir at rt for 10 minutes before being filtered to give salt (2*S*,3*R*)-**293** as a light yellow solid (0.26 g, 92%); mp 102-104 °C (*Decomp*); ν_{max} (KBr)/cm^{-1} 2925 (C-H), 1712 (C=O), 1603, 1535, 1511; δ_H (400 MHz, CD_2Cl_2) 0.95 (3H, d, *J* 6.7, C*H*$_3$), 1.42 (3H, d, *J* 6.6, C*H*$_3$), 1.65-1.74 (1H, m, C*H*(CH$_3$)$_2$), 3.13-3.21 (1H, m, C(3)*H*), 3.66 (1H, d, *J* 17.7, C*H*H), 3.95 (1H, app. t, *J* 13.0, C(4)*H*H), 4.79 (1H, dd, *J* 13.3, 4.4, C(4)H*H*), 5.51 (1H, d, *J* 17.8, CH*H*), 6.60 (1H, d, *J* 4.2, C(2)*H*), 6.95-6.99 (2H, m, 4-FAr(3,5)*H*), 7.15-7.18 (2H, m, Ar*H*), 7.19-7.23 (2H, m, 4-FAr(2,6)*H*), 7.42-7.48 (3H, m, Ar*H*), 7.66-7.70 (1H, m, Ar*H*), 7.81 (1H, td, *J* 7.9, 1.0), 8.02 (1H, d, *J* 8.4, Ar*H*), 8.10 (1H, d, *J* 7.6, Ar*H*); δ_C (125 MHz, CD_2Cl_2) 19.6 (*C*H$_3$), 21.9 (*C*H$_3$), 26.8 (*C*H(CH$_3$)$_2$), 39.8 (*C*(3)), 40.6 (*C*H$_2$), 44.8 (*C*(4)), 61.5 (*C*(2)), 114.2 (*ArC*), 115.4 (d, *J* 21.3, 4-F*ArC*(3,5)), 123.4 (*ArC*), 126.2 (*ArC*), 127.1 (*ArC*), 127.7 (d, *J* 3.0, 4-F*ArC*(1)), 127.9 (*ArC*), 129.6 (*ArC*), 129.9 (*ArC*), 129.9 (*ArC*), 131.9 (d, *J* 8.0, 4-F*ArC*(2,6)), 134.6 (*ArC*), 136.1 (*ArC*), 160.7 (*C*=N), 162.2 (d, *J* 245, 4-F*ArC*(4)), 173.7 (*C*=O); δ_F (376 MHz, CD_2Cl_2) -116.3 (Ar*F*); *m*/*z* (ES$^+$) 445 ([M]$^+$, 100%); HRMS (ES$^+$) $C_{27}H_{26}FN_2OS^+$ ([M]$^+$) requires 445.1750; found 445.1743 (-1.4 ppm).

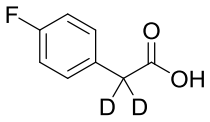
(3*R*,4*R*)-3-(4-fluorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**229**

Following general procedure D, 4-fluorophenylacetic acid (30.8 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (2 mL), acyl ammonium (2*S*,3*R*)-**293** (4.81 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**229** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**229** (>99:1 dr) as a white solid (59.3 mg, 88%) with identical spectroscopic properties to those given previously; $[\alpha]_D^{20}$-256.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 19.2 min, t_R(3*S*,4*S*): 39.4 min, 99% *ee*.

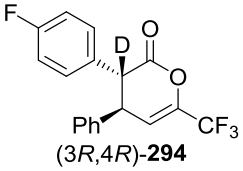
2-d^2-(4-fluorophenyl)acetic acid



285

To a solution of 4-fluorophenylacetic acid (1.00 g, 6.49 mmol) in D_2O (6 mL) was added K_2CO_3 (3.59 g, 26.0 mmol) and the reaction mixture was heated at reflux for 16 h. The crude reaction mixture was acidified by careful addition of HCl (8 M in H_2O) and extracted with CH_2Cl_2 (x 3). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The whole process was repeated a further 3 times to give acid **285** as a white solid (0.57 g, 56%) which was 99% deuterated according to ^{1}H NMR; mp 83-84 °C; ν_{max} (ATR)/cm^{-1} 3200-2520 (CO_2H), 2922 (C-H), 1692 (C=O), 1608, 1512; δ_H (300 MHz, $CDCl_3$) 7.02-7.10 (2H, m, Ar(3,5)*H*), 7.25-7.32 (2H, m, Ar(2,6)*H*), 11.9 (1H, s, O*H*); δ_C (75 MHz, $CDCl_3$) 116.0 (d, *J* 21.4, *ArC*(3,5)), 129.3 (*ArC*(1)), 131.4 (d, *J* 8.0, *ArC*(2,6)), 163.0 (d, *J* 244, *ArC*(4)), 178.7 (*C*=O); *m*/*z* (ES^+) 155 ($[M-H]^+$, 100%); HRMS (NSI^+) $C_8H_4D_2FO_2^+$ ($[M-H]^+$) requires 155.0483; found 155.0484 (+0.7 ppm).

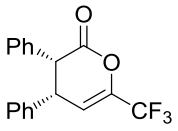
(3*R*,4*R*)-3-(4-fluorophenyl)-4-phenyl-6-(trifluoromethyl)-3-deutero-4-hydro-2*H*-pyran-2-one



(3*R*,4*R*)-**294**

Following general procedure D, acetic acid **285** (31.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.08 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**294** (90:10 dr) with 30% proton incorporation observed at C(3). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**294** (>99:1 dr) as a white solid (49.0 mg, 73%).

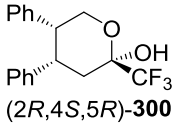
(3*R*,4*S*)-3,4-diphenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*S*)-**299**

Following general procedure D, phenylacetic acid (27.2 mg, 0.20 mmol), *i*-Pr_2NEt (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in CH_2Cl_2 (1 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **295** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (87.0 μL, 0.50 mmol) for 1 h at −78 °C gave crude lactone (3*R*,4*S*)-**299** (85:15 dr). Chromatographic purification (eluent Et_2O:petrol 3:97) gave lactone (3*R*,4*S*)-**299** (91:9 dr) as a white solid (47.3 mg, 74%); mp 100-102 °C; $[\alpha]_D^{20}$+370.0 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*S*,4*R*): 6.5 min, t_R(3*R*,4*S*): 9.2 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3094, 2922 (C-H), 1790 (C=O), 1705; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 3.86-3.91 (1H, m, C(4)*H*), 4.23 (1H, d, *J* 7.1, C(3)*H*), 6.23 (1H, dd, *J* 5.9, 0.6, C(5)*H*), 6.63-6.66 (2H, m, Ar*H*), 6.69-6.72 (2H, m, Ar*H*), 7.05-7.23 (6H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 44.4 (*C*(4)), 51.0 (*C*(3)), 111.3 (q, *J* 3.4, *C*(5)), 118.6 (q, *J* 270, *C*F_3), 128.0 (*ArC*), 128.1 (*ArC*), 128.4 (*ArC*), 128.5 (Ar*C*), 128.8 (*ArC*), 129.6 (*ArC*), 132.6 (4ry *ArC*), 134.7 (4ry *ArC*), 141.6 (q, *J* 38, *C*(6)), 165.5 (*C*(2)); δ_F (282 MHz, $CDCl_3$) -72.5 (C*F*$_3$); *m*/*z* ($APCI^+$) 319 ($[M+H]^+$, 100%); HRMS ($APCI^+$) $C_{18}H_{14}F_3O_2^+$ ($[M+H]^+$) requires 319.0940; found 319.0944 (+1.1 ppm).

(2*R*,4*S*,5*R*)-4,5-diphenyl-2-(trifluoromethyl)tetrahydro-2*H*-pyran-2-ol



(2*R*,4*S*,5*R*)-**300**

Following general procedure F, lactone (3*R*,4*S*)-**299** (84 mg, 0.26 mmol) (92:8 dr) and $LiAlH_4$ (2 M in THF, 0.53 mL, 1.06 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2*R*,4*S*,5*R*)-**300** (92:8 dr). Chromatographic purification (eluent Et_2O:petrol 15:85) gave pyran (2*R*,4*S*,5*R*)-**300** (94:6 dr) as a white solid (65.0 mg, 76%); mp 130-132 °C; $[\alpha]_D^{20}$-232 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralcel OJ-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*,4*R*,5*S*): 13.2 min, t_R(2*R*,4*S*,5*R*): 15.5 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3526 (O-H), 3029, 2944 (C-H), 1700, 1618; Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.82 (1H, dd, *J* 13.2, 3.3, C(3)*H*H), 2.21 (1H, t, *J* 13.5, C(3)H*H*), 2.73 (1H, br s, O*H*), 2.94 (1H, t, *J* 4.0, C(5)*H*), 3.73 (1H, dt, 14.0, 4.0, C(4)*H*), 4.21 (1H, d, *J* 11.5, C(6)H*H*), 4.53 (1H, dd, *J* 11.5, 3.5, C(6)*H*H), 6.68-6.71 (2H, m, Ar*H*), 6.87-6.89 (2H, m, Ar*H*), 7.00-7.10 (6H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 26.4 (*C*(3)), 38.6 (*C*(4)), 45.2 (*C*(5), 66.8 (*C*(6), 94.7 (q, *J* 32.1, *C*(2)), 122.9 (q, *J* 284,*C*F_3), 126.6 (*ArC*), 126.7 (*ArC*), 127.6 (*ArC*), 127.9 (*ArC*), 128.1 (*ArC*), 129.7 (*ArC*), 138.8 (4ry *ArC*), 141.3 (4ry *ArC*); δ_F (376 MHz, $CDCl_3$) -87.8 (CF_3); *m*/*z* (APCI$^+$) 340 ($[M+NH_4]^+$, 100%); HRMS (APCI$^+$) $C_{18}H_{21}F_3NO_2^+$ ($[M+NH_4]^+$) requires 340.1519; found 340.1517 (-0.6 ppm).

9.3.2 Kinetic Studies

General Experimental Procedure For Kinetic Studies

To an NMR tube was added the required amount of 4-fluorophenylacetic acid, 1-fluoro-4-nitrobenzene, *i*-Pr_2NEt, pivaloyl chloride and CD_2Cl_2. Subsequently, at −78 °C was added the required amount of HBTM-2.1 (2*S*,3*R*)-**112**, enone **220** and *i*-Pr_2NEt. The reaction was followed dynamically by ^{19}F NMR at −78 °C.

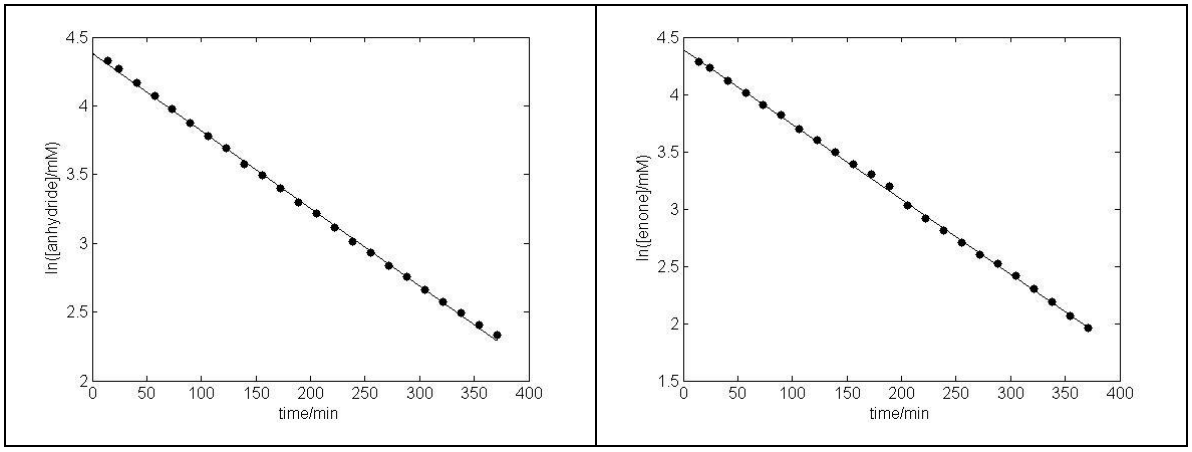
Data from NMR experiments

Concentrations are calculated based on 20 mM internal standard of 4-fluoronitrobenzene. See Table 10 in Section 3.6.1 for initial conditions. Plots of ln([mixed anhydride **282**]/mM) and ln([trifluoromethyl enone **220**]/mM) vs. time are included for each run.

Run 1

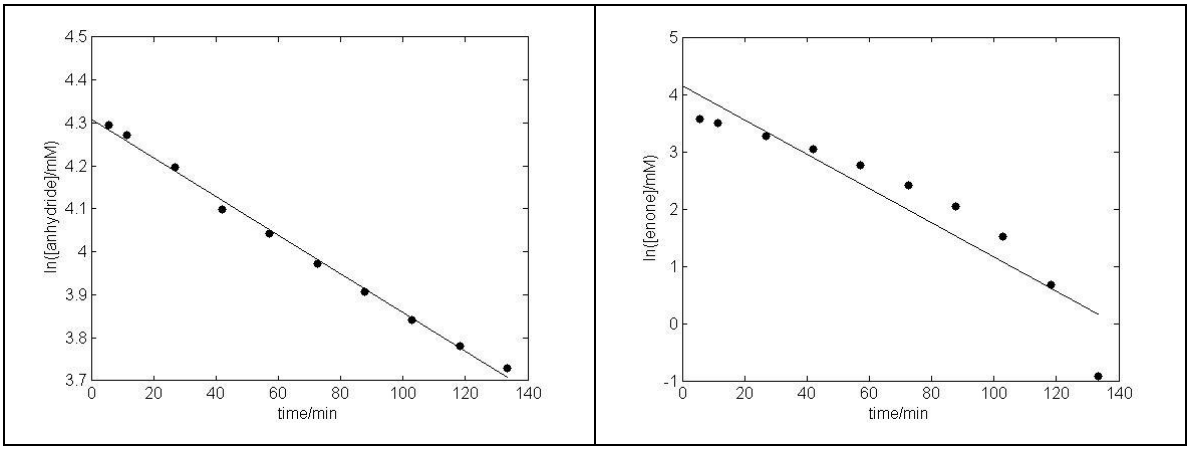
Time/minutes	[mixed anhydride **282**]/mM	[trifluoromethyl enone **220**]/mM
14.40	75.9	72.33

24.02	71.3	68.67
40.52	64.6	61.67
57.03	58.5	55.33
73.55	53.2	49.67
90.07	48.2	45.67
106.58	43.9	40.33
123.00	40.0	36.67
139.60	35.7	32.93
156.10	32.9	29.77
172.65	29.9	27.13
189.17	27.1	24.47
205.67	24.9	20.67
222.20	22.6	18.47
238.70	20.4	16.6
255.22	18.7	14.93
271.73	17.1	13.5
288.23	15.8	12.5
304.75	14.3	11.17
321.27	13.1	9.97
337.80	12.1	8.93
354.32	11.1	7.9
370.82	10.3	7.13



Run 2

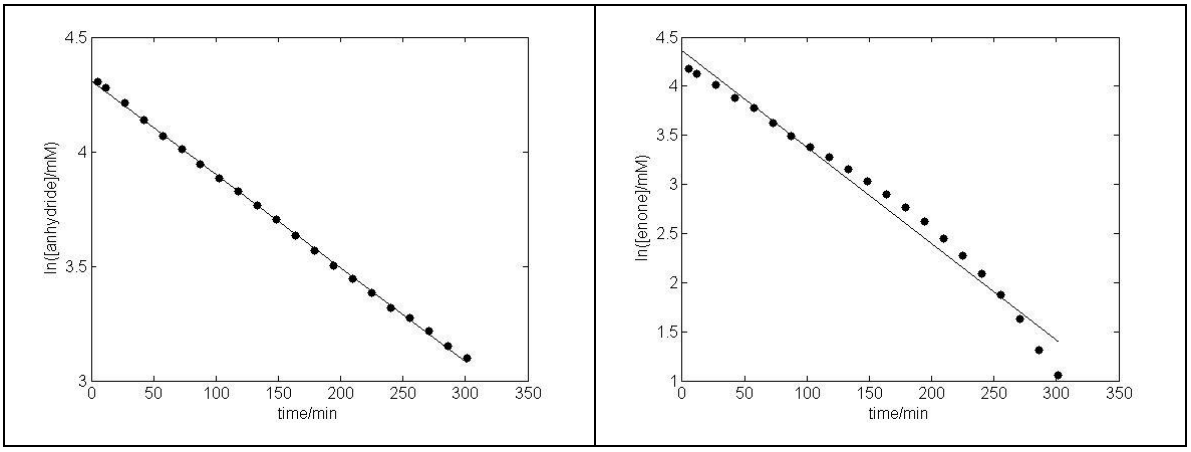
Time/minutes	[mixed anhydride **282**]/mM	[trifluoromethyl enone **220**]/mM
5.52	73.30	35.33
11.53	71.60	32.93
26.77	66.50	26.53
42.00	60.30	20.90
57.25	57.00	15.90
72.48	53.10	11.23
87.72	49.70	7.67
102.97	46.60	4.53
118.20	43.80	1.97
133.45	41.60	0.40



Run 3

Time/minutes	[mixed anhydride **282**]/mM	[trifluoromethyl enone **220**]/mM
5.07	74.10	65.00
11.52	72.20	62.00
26.75	67.50	55.33
41.98	62.60	48.67
57.22	58.40	43.67
72.45	55.20	37.67
87.70	51.70	32.97
102.92	48.70	29.37
118.17	45.90	26.37
133.40	43.10	23.37

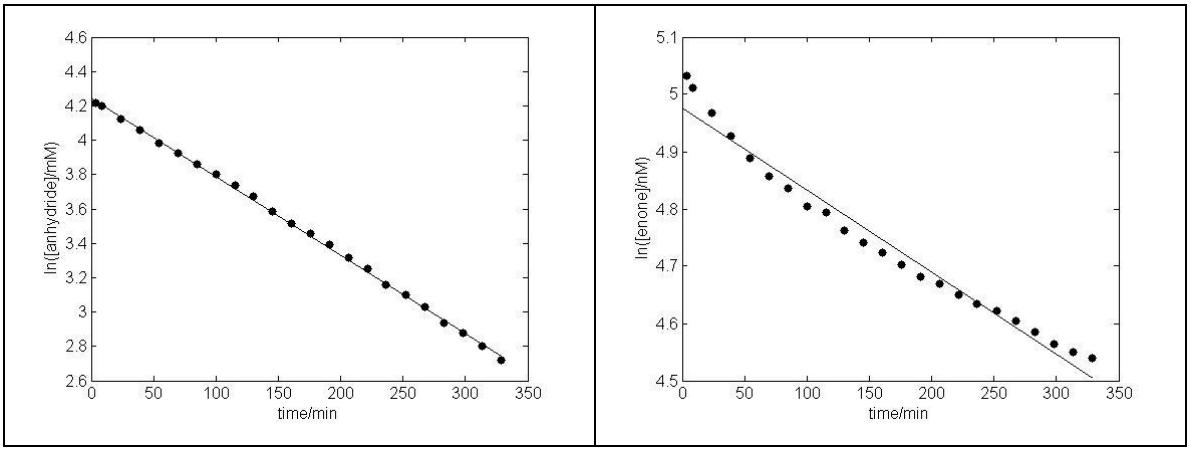
148.65	40.60	20.67
163.88	37.90	18.23
179.12	35.50	15.87
194.37	33.20	13.77
209.58	31.40	11.57
224.82	29.50	9.67
240.07	27.60	8.10
255.30	26.40	6.53
270.55	25.00	5.10
285.78	23.40	3.70
301.03	22.20	2.88
316.27	20.70	1.73
331.50	20.00	1.07
346.75	19.20	0.50
361.98	18.50	0.29
377.22	18.20	0.00



Run 4

Time/minutes	[mixed anhydride **282**]/mM	[trifluoromethyl enone **220**]/mM
3.4	67.7	153.30
8.4	66.6	150.00
23.6	61.6	143.70
38.9	58.0	138.00
54.1	53.7	132.67

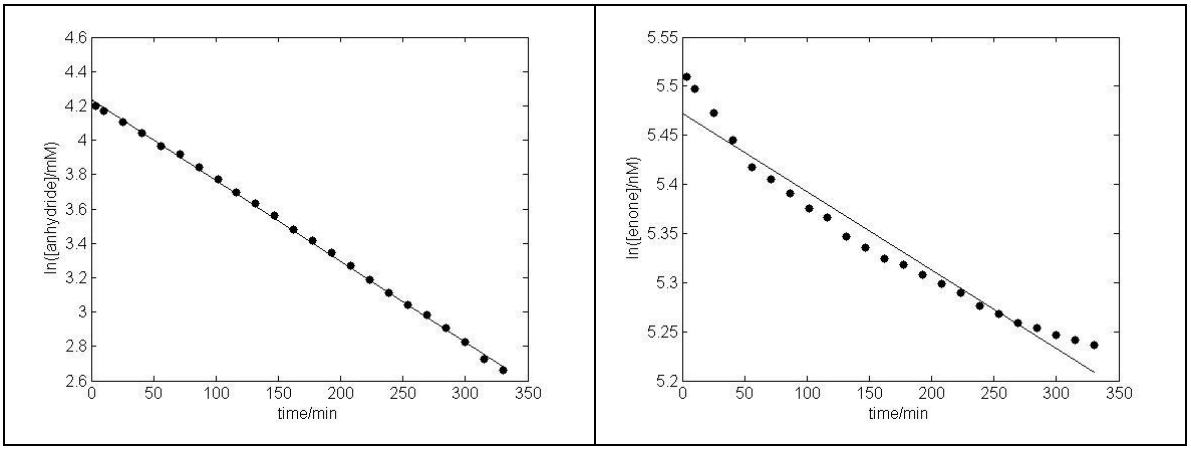
69.4	50.7	128.67
84.6	47.4	126.00
99.8	44.8	122.00
115.1	42.0	120.67
130.3	39.3	117.00
145.6	36.1	114.67
160.8	33.7	112.67
176.0	31.7	110.33
191.3	29.8	108.00
206.5	27.5	106.67
221.8	25.8	104.67
236.0	23.5	103.00
252.2	22.2	101.67
267.5	20.7	100.00
282.7	18.8	98.00
298.0	17.8	96.00
313.2	16.5	94.67
328.4	15.2	93.67



Run 5

Time/minutes	[mixed anhydride **282**]/mM	[trifluoromethyl enone **220**]/mM
4.0	66.6	247.00
9.9	64.7	244.00
25.2	60.8	238.00

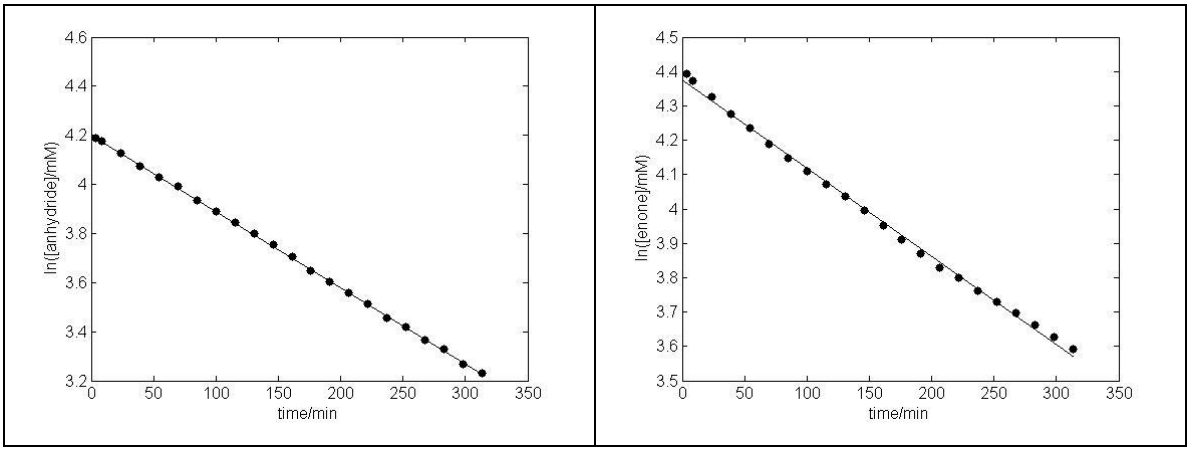
40.4	56.9	231.67
55.7	52.8	225.33
70.9	50.3	222.67
86.2	46.6	219.33
101.4	43.5	216.00
116.6	40.4	214.00
131.9	37.7	210.00
147.1	35.3	207.67
162.4	32.4	205.33
177.6	30.4	204.00
192.8	28.3	202.00
208.1	26.3	200.00
223.3	24.2	198.23
238.5	22.4	195.67
253.8	20.9	194.00
269.0	19.7	192.33
284.3	18.3	191.33
299.5	16.9	190.00
314.7	15.3	189.00
330.0	14.3	188.00



Run 6

Time (minutes)	[mixed anhydride **282**]/mM	[trifluoromethyl enone **220**]/mM
3.70	65.80	81.00

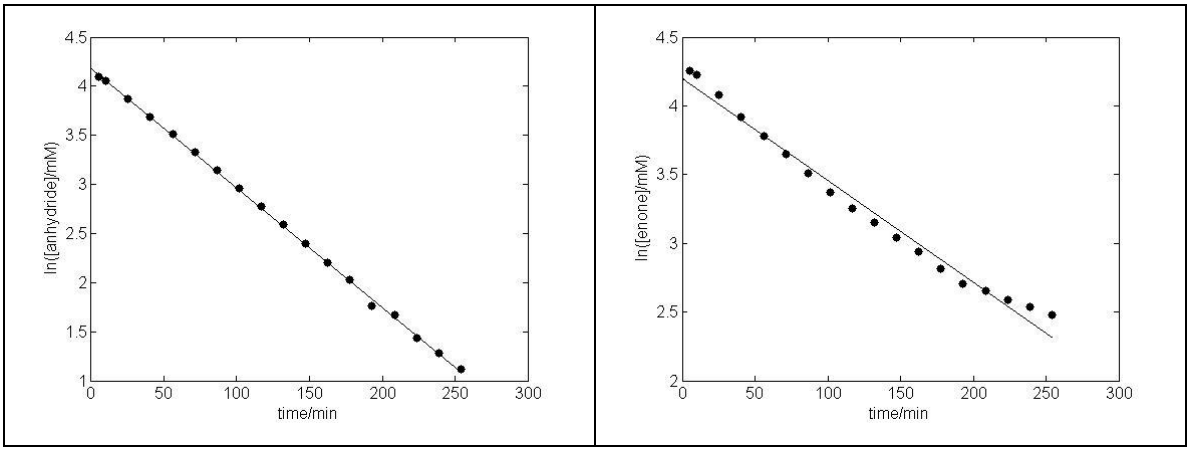
8.52	65.00	79.33
23.75	61.90	75.66
39.00	58.80	72.00
54.23	56.30	69.00
69.48	54.20	66.00
84.72	51.10	63.33
99.97	48.90	61.00
115.20	46.70	58.66
130.43	44.70	56.66
145.68	42.80	54.33
160.92	40.70	52.00
176.15	38.33	50.00
191.40	36.70	48.00
206.63	35.10	46.00
221.88	33.50	44.67
237.13	31.70	43.00
252.37	30.60	41.67
267.62	28.90	40.33
282.85	27.90	39.00
298.13	26.30	37.66
313.33	25.30	36.33



Run 7

Time/minutes	[mixed anhydride **282**]/mM	[trifluoromethyl enone **220**]/mM

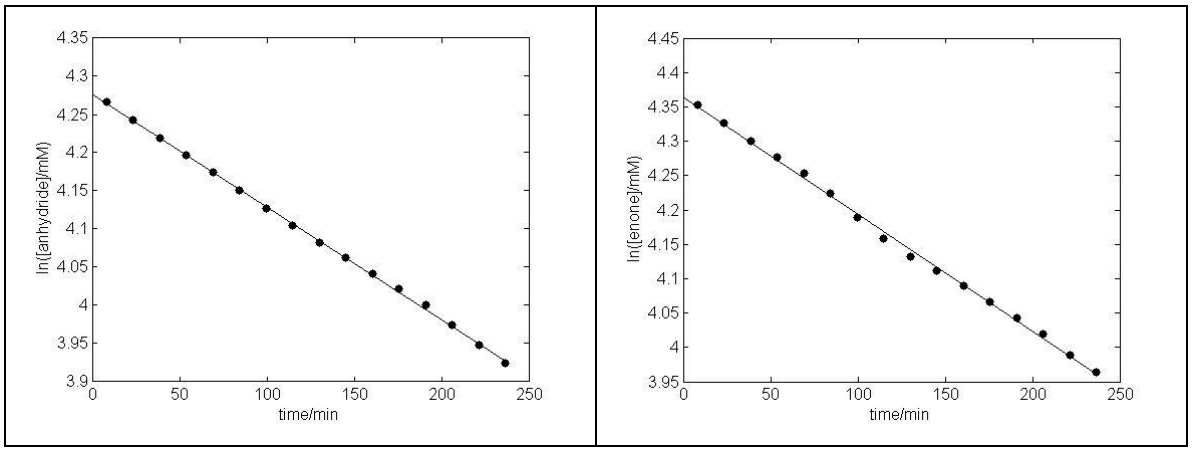
5.18	60.3	70.67
10.13	57.4	68.33
25.38	48	59.00
40.62	40	50.33
55.87	33.4	43.67
71.12	27.8	38.33
86.35	23.3	33.33
101.60	19.2	29.00
116.85	16	25.97
132.08	13.3	23.33
147.30	11	21.00
162.53	9.09	18.87
177.78	7.61	16.67
193.02	5.8	15.00
208.28	5.33	14.20
223.53	4.19	13.33
238.77	3.6	12.60
254.02	3.05	11.90



Run 8

Time/minutes	[mixed anhydride **282**]/mM	[trifluoromethyl enone **220**]/mM
8.1	71.3	77.7
23.3	69.6	75.7
38.6	68.0	73.7

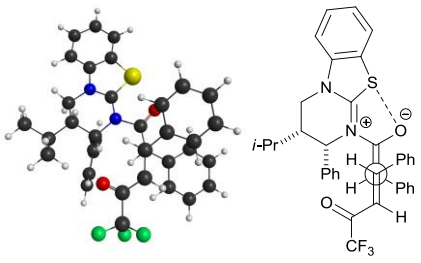
53.8	66.5	72.0
69.1	65.0	70.3
84.3	63.5	68.3
99.6	62.0	66.0
114.8	60.6	64.0
130.0	59.3	62.3
145.3	58.1	61.0
160.5	56.9	59.7
175.7	55.8	58.3
191.0	54.6	57.0
206.3	53.2	55.7
221.5	51.8	54.0
236.7	50.6	52.7



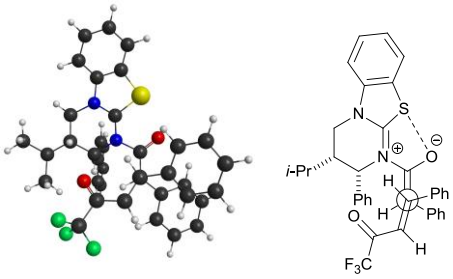
9.3.3 Computational Studies

Diastereoisomeric transition states TS C1 – TS C9

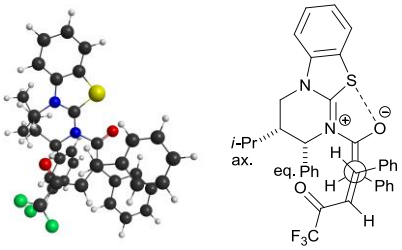
TS C1 towards (3*R*,4*R*)-**224**



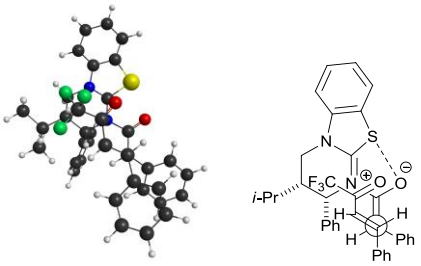
TS C2 towards (3*R*,4*R*)-**224**



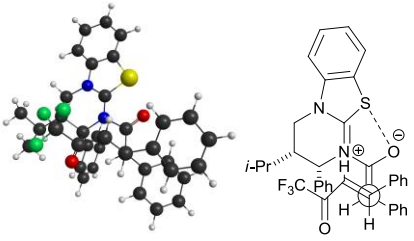
TS C3 towards (3*R*,4*R*)-**224**



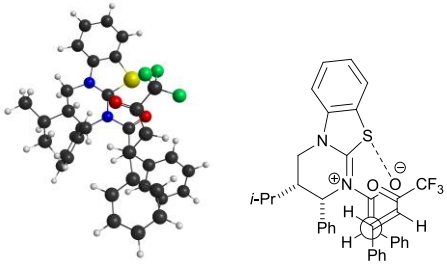
TS C4 towards (3*R*,4*R*)-**224**



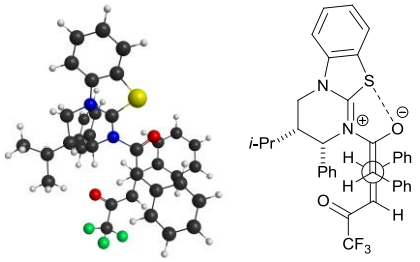
TS C5 towards (3*R*,4*S*)-**299**



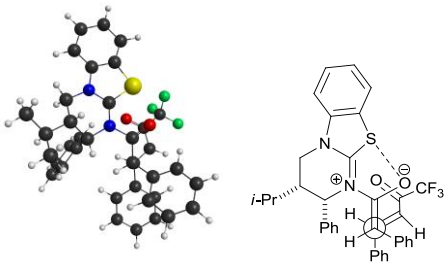
TS C6 towards (3*R*,4*S*)-**299**



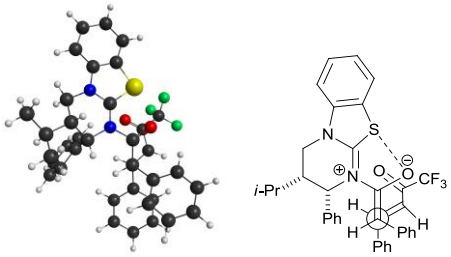
TS C7 towards (3*S*,4*S*)-**224**



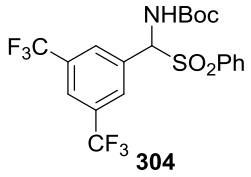
TS C8 towards (3*S*,4*R*)-**299**



TS C9 towards (3*S*,4*R*)-**299**



***tert*-butyl ((3,5-bis(trifluoromethyl)phenyl)(phenylsulfonyl)methyl)carbamate**

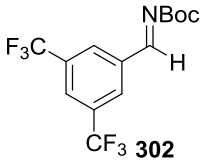


304

To a stirred solution of *tert*-butyl carbamate (4.22 g, 36.0 mmol) in THF (20 mL) under argon was added H_2O (40 mL), sodium benzenesulfinate (5.91 g, 36.0 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (6.05 mL, 36.7 mmol) sequentially followed by formic acid (7.90 mL, 0.21 mol). The reaction mixture was stirred under nitrogen for 18 h at rt. The resulting precipitate was filtered and washed with H_2O. Trituration with hexane/CH_2Cl_2 (91/9) gave sulfone **304** as a white solid (11.5 g, 66%); mp 172-174 °C; ν_{max} (ATR)/cm^{-1} 3345 (N-H), 3078 (C-H), 1699 (C=O), 1583, 1508, 1315 (S=O), 1146 (S=O); δ_H (300 MHz, $(CD_3)_2C=O$) 1.09 (9H, s, $C(CH_3)_3$), 6.32 (1H, d, *J* 11.0, C*H*), 7.54 (2H, t, *J* 7.5, $SO_2Ar(3,5)H$), 7.63 (1H, t, *J* 7.4, $SO_2Ar(4)H$), 7.82-7.90 (3H, m, $SO_2Ar(2,6)H$ and N*H*), 8.01 (1H, s, $(CF_3)_2Ar(4)H$), 8.32 (2H, s, $(CF_3)_2Ar(2,6)H$); δ_C (75 MHz, $(CD_3)_2C=O$) 28.2 ($C(CH_3)_3$), 74.1 (*C*H), 81.0 ($C(CH_3)_3$), 124.0 (heptet, *J* 3.7,

(CF_3)$_2$*ArC*(4)), 124.3 (q, *J* 270, *C*F_3), 130.1 (*ArC*), 130.5 (*ArC*), 131.3 ((CF_3)$_2$*ArC*(2,6)), 132.1 (q, *J* 33.3, (CF_3)$_2$*ArC*(3,5)), 135.2 (*ArC*), 135.2 (SO_2*ArC*(4)), 137.8 (*ArC*), 154.8 (*C*=O); *m*/*z* (ES^+) 506 ($[M+Na]^+$, 75%); HRMS (ES^+) $C_{20}H_{19}F_6NNaO_4S^+$ ($[M+Na]^+$) requires 506.0837; found 506.0841 (+0.9 ppm).

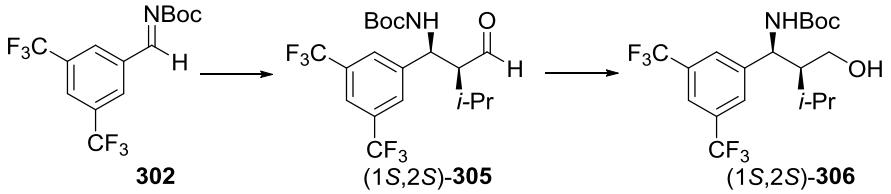
tert-butyl 3,5-bis(trifluoromethyl)benzylidenecarbamate



302

To a stirred solution of sulfone **304** (13.9 g, 28.8 mmol) in CH_2Cl_2 (460 mL) was added a solution of K_2CO_3 (88.8 g, 0.65 mol) in H_2O (460 mL). The reaction mixture was stirred at rt for 1 h. The layers were separated and the aqueous layer was extracted CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give imine **302** as a colourless oil (9.80 g, 99%) which was used immediately without purification; ν_{max} (ATR)/cm^{-1} 2984 (C-H), 1717 (C=O), 1647, 1618; δ_H (400 MHz, (CD_3)$_2$C=O) 1.58 (9H, s, C(C*H*$_3$)$_3$), 8.32 (1H, s, Ar(4)*H*), 8.58 (2H, s, Ar(2,6)*H*), 9.02 (1H, s, C*H*); δ_C (100 MHz, (CD_3)$_2$C=O) 28.0 (C(*C*H$_3$)$_3$), 83.0 (*C*(CH$_3$)$_3$), 124.1 (q, *J* 270, *C*F_3), 126.9 (heptet, *J* 3.5, *ArC*(4)), 130.4 (A*rC*(2,6)), 132.9 (q, *J* 33.6, *ArC*(3,5)), 137.9 (*ArC*(1)), 162.5 (*C*=O), 165.7 (=*C*H); *m*/*z* (NSI^+) 342 ($[M+H]^+$, 63%); HRMS (NSI^+) $C_{14}H_{14}F_6NO_2^+$ ($[M+H]^+$) requires 342.0923; found 342.0927 (+1.1 ppm).

tert-butyl ((1*S*,2*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-2-(hydroxymethyl)-3-methylbutyl)carbamate

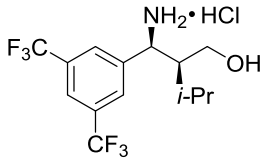


302 (1*S*,2*S*)-**305** (1*S*,2*S*)-**306**

To a stirred solution of imine **302** (8.32 g, 24.4 mmol) in anhydrous CH_3CN (240 mL) under argon was added isovaleraldehyde (5.23 mL, 48.8 mmol). The resulting solution was cooled to 0 °C. (*S*)-proline (0.56 g, 4.87 mmol) was added and the reaction mixture was stirred for 18 h at 0 °C. Distilled H_2O (80 mL) was added and the reaction mixture was allowed to warm to rt whilst maintaining vigorous stirring. Et_2O (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O

(x 3). The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting solid was triturated with hexane and filtered. The filtrate was concentrated *in vacuo* to give crude aldehyde (1*S*,2*S*)-**305** as a white solid (2.84 g, 27%) which was used directly without purification. To a stirred solution of aldehyde (1*S*,2*S*)-**305** (2.84 g, 6.65 mmol) in methanol (50 mL) under argon was added $NaBH_4$ (0.38 g, 10.0 mmol) and the reaction mixture was left to stir for 2 h at rt. Saturated aqueous $NaHCO_3$ was added and the methanol was removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (x 3). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting solid was recrystallised (Et_2O:petrol) to give alcohol (1*S*,2*S*)-**306** as a white solid (1.65 g, 16% over 2 steps); mp 110-112 °C (Et_2O:petrol); $[\alpha]_D^{20}$–8.4 (c 0.25 in $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3348 (O-H and N-H), 2970 (C-H) 1682 (C=O), 1508; δ_H (500 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.8, CH_3), 1.00 (3H, d, *J* 6.8, CH_3), 1.35 (9H, s, C(CH_3)$_3$), 1.50-1.85 (3H, m, C(2)*H*, C(3)*H* and O*H*), 3.28-3.31 (1H, m, C*H*H), 3.67-3.70 (1H, m, CH*H*), 5.11 (1H, br s, N*H*), 6.01 (1H, d, *J* 8.6, C(1)*H*), 7.71 (1H, s, Ar(4)*H*), 7.74 (2H, s, Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 22.6 (*C*H$_3$), 26.7 (*C*H$_3$), 28.2 (*C*(3)), 28.4 (C(*C*H$_3$)$_3$), 50.7 (*C*(2)), 54.9 (*C*(1)), 61.2 (*C*H$_2$), 80.1 (*C*(CH$_3$)$_3$), 121.5 (*ArC*(4)), 123.4 (q, *J* 271, *C*F$_3$), 127.5 (*ArC*(2,6)), 131.4 (q, *J* 33.0, *ArC*(3,5)), 144.1 (*ArC*(1)), 155.4 (*C*=O); *m*/*z* (NSI^+) 452 ($[M+Na]^+$, 45%); HRMS (NSI^+) $C_{19}H_{25}F_6NNaO_3^+$ ($[M+Na]^+$) requires 452.1631; found 452.1628 (-0.6 ppm).

(*S*)-2-((*S*)-amino(3,5-bis(trifluoromethyl)phenyl)methyl)-3-methylbutan-1-ol hydrochloride

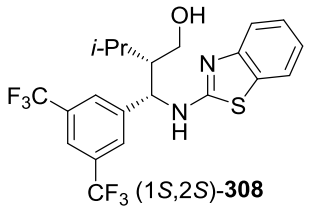


(1*S*,2*S*)-**307**

To a flask containing alcohol (1*S*,2*S*)-**306** (1.57 g, 3.65 mmol) under argon was added HCl (4 M in dioxane, 11.5 mL, 45.9 mmol) and the reaction mixture was left to stir for 4 h at rt. The reaction mixture was concentrated *in vacuo* to give amino alcohol (1*S*,2*S*)-**307** as a white solid (1.22 g, 91%); mp 218-220 °C; $[\alpha]_D^{20}$–9.2 (c 0.25 in CH_3OH); ν_{max} (ATR)/cm^{-1} 3277 (O-H and N-H), 2967 (C-H), 1588; δ_H (500 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, CH_3), 1.18 (3H, d, *J* 6.8, CH_3), 1.58 (1H, dq, *J* 13.5, 6.8, C(3)*H*), 2.10-2.15 (1H, m, C(2)*H*), 3.38 (1H, t, *J* 10.1, C(1)*H*H), 3.78 (1H, dd, *J* 11.0, 4.4, C(1)H*H*), 4.85 (1H,

d, *J* 4.8, C*H*N), 8.11 (1H, s, Ar(4)*H*), 8.21 (2H, s, Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 19.5 (*C*H_3), 22.2 (*C*H_3), 28.1 (*C*(3)), 49.8 (*C*(2)), 57.4 (*C*HN), 60.8 (*C*(1)), 124.0 (heptet, *J* 3.6, *ArC*(4)), 124.6 (q, *J* 271, *C*F_3), 130.4 (*ArC*(2,6)), 133.3 (q, *J* 33.5, *ArC*(3,5)), 139.4 (*ArC*(1)); *m*/*z* (NSI^+) 330 ($[M\text{-}Cl]^+$, 100%); HRMS (NSI^+) $C_{14}H_{18}F_6NO^+$ ($[M\text{-}Cl]^+$) requires 330.1287; found 330.1292 (+1.5 ppm).

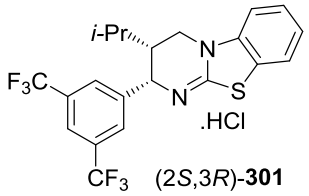
(*S*)-2-((*S*)-(benzo[d]thiazol-2-ylamino)(3,5-bis(trifluoromethyl)phenyl)methyl)-3-methylbutan-1-ol



(1*S*,2*S*)-**308**

To a sealed pressure tube containing amino alcohol (1*S*,2*S*)-**307** (1.12 g, 3.05 mmol) and *i*-Pr_2NEt (2.12 mL, 12.2 mmol) under argon at 135 °C was added 2-chlorobenzothiazole (0.41 mL, 3.23 mmol) and the reaction mixture was left to stir for 2 days at 135 °C. The reaction mixture was allowed to cool to rt. Chromatographic purification (eluent EtOH:CH_2Cl_2 2:98) gave alcohol (1*S*,2*S*)-**308** as a brown oil (1.12 g, 66%); $[\alpha]_D^{20}$–20.2 (c 0.5 in $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3281 (O-H and N-H), 2967 (C-H), 1541; δ_H (300 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.8, C*H*$_3$), 1.08 (3H, d, *J* 6.8, C*H*$_3$), 1.47 (1H, dq, *J* 13.7, 6.9, C(3)*H*), 2.10-2.16 (1H, m, C(2)*H*), 3.46 (1H, t, *J* 10.5, C(1)*H*H), 3.87 (1H, dd, *J* 10.8, 4.2, C(1)H*H*), 5.12 (1H, d, *J* 3.6, C*H*N), 6.96-7.01 (1H, m, Ar*H*), 7.15-7.21 (1H, m, Ar*H*), 7.34 (1H, dd, *J* 8.1, 0.6, Ar*H*), 7.46 (1H, dd, *J* 7.9, 0.8, Ar*H*), 7.71 (1H, s, $(CF_3)_2$Ar(4)*H*), 7.90 (2H, s, $(CF_3)_2$Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 19.9 (*C*H_3), 22.6 (*C*H_3), 26.9 (*C*(3)), 50.7 (*C*(2)), 60.6 (*C*(1)), 60.8 (*C*HN), 118.6 (*ArC*), 121.0 (*ArC*), 121.7 (heptet, *J* 3.4, $(CF_3)_2$*ArC*(4)), 121.9 (*ArC*), 123.3 (q, *J* 271, *C*F_3), 126.2 (*ArC*), 128.2 ($(CF_3)_2$*ArC*(2,6)), 129.7 (*ArC*(7a)), 131.7 (q, *J* 33.1, $(CF_3)_2$*ArC*(3,5)), 142.3 ($(CF_3)_2$*ArC*(1)), 151.3 (*ArC*(3a)), 167.0 (*C*=N); *m*/*z* (NSI^+) 463 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{21}H_{21}F_6N_2OS^+$ ($[M+H]^+$) requires 463.1273; found 463.1269 (-0.9 ppm).

(2*S*,3*R*)-2-(3,5-bis(trifluoromethyl)phenyl)-3-isopropyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine hydrochloride



(2*S*,3*R*)-**301**

To a stirred solution of alcohol (1*S*,2*S*)-**308** (1.08 g, 2.35 mmol) in toluene (20 mL) under argon was added $SOCl_2$ (0.38 mL, 5.17 mmol) and the reaction mixture was heated at reflux for 3 h with no condenser fitted. The reaction mixture was allowed to cool to rt and was quenched by addition of a few drops of methanol before being concentrated *in vacuo*. 10% aqueous NaOH solution (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (x 3). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography (eluent MeOH:petrol 2:98) gave isothiourea (2*S*,3*R*)-**301** free base. To a flask containing the free base was added HCl (4 M in dioxane, 10 mL, 40.0 mmol). After stirring at rt for 1 h the reaction mixture was concentrated *in vacuo* and the resulting solid recrystallised (EtOAc:Et_2O) to give the hydrochloride salt of isothiourea (2*S*,3*R*)-**301** as a white solid (0.32 g, 31%); mp 148-150 °C; $[\alpha]_D^{20}$+150.0 (c 0.75 in EtOAc:Et_2O); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 254 nm, 30 °C) t_R(2*R*,3*S*): 22.3 min, t_R(2*S*,3*R*): 40.5 min, 97% *ee*; ν_{max} (ATR)/cm^{-1} 2937 (C-H), 1607, 1557; δ_H (300 MHz, CD_3OD) 0.92 (3H, d, *J* 6.7, C*H*$_3$), 1.17 (3H, d, *J* 6.7, C*H*$_3$), 1.43 (1H, dq, *J* 13.7, 6.9, C*H*$(CH_3)_2$), 2.55-2.61 (1H, m, C(3)*H*), 4.00 (1H, dd, *J* 13.4, 10.6, C(4)*H*H), 4.64 (1H, dd, *J* 13.5, 4.6, C(4)H*H*), 5.56 (1H, d, *J* 4.7, C(2)*H*), 7.55 (1H, t, *J* 7.7, Ar*H*), 7.70 (1H, t, *J* 7.8, Ar*H*), 7.82 (1H, d, *J* 8.2, Ar*H*), 7.96-8.00 (3H, m, $(CF_3)_2$Ar(2,6)*H* and Ar*H*), 8.10 (1H, s, $(CF_3)_2$Ar(4)*H*); δ_C (100 MHz, CD_3OD) 19.5 (*C*H$_3$), 22.2 (*C*H$_3$), 27.8 (*C*H$(CH_3)_2$), 41.2 (*C*(3)), 44.0 (*C*(4)), 57.5 (*C*(2)), 114.3 (*ArC*), 123.8 (*ArC*), 124.0 (heptet, *J* 3.5, $(CF_3)_2$*ArC*(4)), 124.5 (*ArC*), 124.5 (q, *J* 271, *C*F_3), 127.3 (*ArC*), 129.6 ($(CF_3)_2$*ArC*(2,6)), 129.6 (*ArC*), 133.6 (q, *J* 33.4, $(CF_3)_2$*ArC*(3,5)), 139.8 (*ArC*), 141.8 ($(CF_3)_2$*ArC*(1)), 166.3 (*C*=N); *m*/*z* ($APCI^+$) 445 ($[M\text{-}Cl]^+$, 100%); HRMS ($APCI^+$) $C_{21}H_{19}F_6N_2S^+$ ($[M\text{-}Cl]^+$) requires 445.1168; found 445.1168 (+0.1 ppm). Note: Racemic sample for HPLC analysis made *via* same route using (DL)-proline for Mannich reaction to form **305**.

9.3.4 References and Notes

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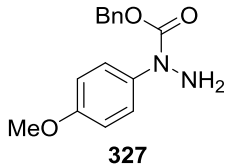
9.4 Experimental for Chapter 4

9.4.1 Experimental Procedures and Characterisation Data

General procedure G: *Cu(I) mediated N-arylation.*

To a flask under inert atmosphere was charged the requisite aryl iodide (1 eq), copper iodide (10 mol%), 1,10-phenanthroline (20 mol%), cesium carbonate (1.4 eq), benzyl carbazate (1.2 eq) and anhydrous DMF and the reaction mixture was heated at 80 °C for 1 h. Once cool the reaction mixture was filtered and concentrated *in vacuo* to give the crude reaction mixture.

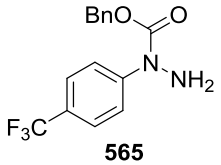
benzyl 1-(4-methoxyphenyl)hydrazinecarboxylate



327

Following general procedure G, 4-iodoanisole (10.0 g, 42.7 mmol), copper iodide (0.81 g, 4.27 mmol), 1,10-phenanthroline (1.54 g, 8.55 mmol), cesium carbonate (19.5 g, 59.8 mmol), benzyl carbazate (8.51 g, 51.3 mmol) and anhydrous DMF (45 mL) gave, after chromatographic purification (eluent Et_2O:petrol 50:50), amine **327** as a yellow solid (11.2 g, 96%); mp 69-71 °C; {lit.[187] mp 74-75 °C}; δ_H (300 MHz, $CDCl_3$) 3.73 (3H, s, OCH_3), 4.30 (2H, br s, NH_2), 5.13 (2H, s, CH_2), 6.77-6.80 (2H, m, NAr(3,5)*H*), 7.23-7.29 (7H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[187]

benzyl 1-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate



565

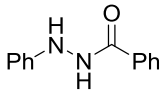
Following general procedure G, 4-iodobenzotrifluoride (1.08 mL, 7.35 mmol), copper iodide (0.14 g, 0.74 mmol), 1,10-phenanthroline (0.27 g, 1.47 mmol), cesium carbonate (3.35 g, 10.3 mmol), benzyl carbazate (1.46 g, 8.82 mmol) and anhydrous DMF (10 mL) gave, after chromatographic purification (eluent Et_2O:petrol 25:75), amine **565** as a white solid (1.02 g, 45%); mp 62-64 °C; ν_{max} (KBr)/cm^{-1} 3367 (N-H), 2956 (C-H), 1684 (C=O), 1616, 1512; δ_H (500 MHz, $CDCl_3$) 4.52 (2H, s, NH_2), 5.29 (2H, s, CH_2), 7.38-7.41 (5H, m, Ar*H*), 7.58 (2H, d, *J* 8.7, Ph(2,6)*H*), 7.74 (2H, d, *J* 7.8, NAr(3,5)*H*); δ_C (125 MHz, $CDCl_3$) 68.7 (*C*H_2), 122.4 (*ArC*), 124.2 (q, *J* 270, *C*F_3), 125.5 (q, *J* 3.5, N*ArC*(3,5)), 126.3 (q, *J* 32.1, N*ArC*(4)), 128.4 (*ArC*), 128.6 (*ArC*), 128.7 (*ArC*), 135.5 (Ph*C*(1)), 145.6 (N*ArC*(1)), 155.5 (*C*=O); *m*/*z* (CI^+) 311 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{15}H_{14}F_3N_2O_2^+$ ($[M+H]^+$) requires 311.1002; found 311.1005 (+1.0 ppm).

General procedure H: *Hydrazine acylation.*

To a solution of requisite hydrazine (1.2 eq) and Et_3N (1.2 eq) in Et_2O at 0 °C was added the requisite acid chloride (1 eq) dropwise. The reaction mixture was stirred at 0 °C for

30 minutes before being filtered. The residue was washed with H_2O and recrystallised (EtOH) to give the corresponding hydrazide.

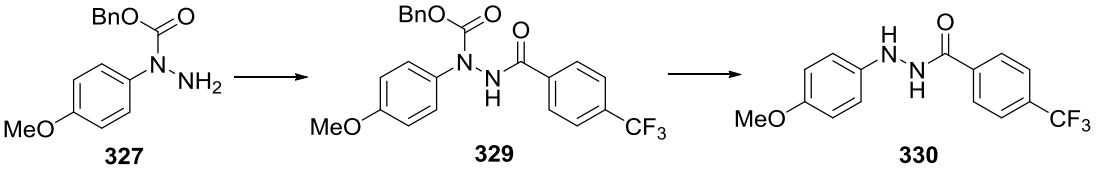
_N_'-phenylbenzohydrazide



319

Following general procedure H, phenylhydrazine (1.82 mL, 18.5 mmol), Et_3N (2.58 mL, 18.5 mmol) and benzoyl chloride (2.18 mL, 15.6 mmol) in Et_2O (35 mL) gave, after recrystallisation (EtOH), hydazide **319** as a white solid (1.60 g, 45%); mp 163-165 °C; {lit.[107] mp 171-172 °C}; δ_H (400 MHz, $CDCl_3$) 6.30 (1H, br s, ArN*H*), 6.84-6.86 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.15-7.19 (2H, m, NAr(3,5)*H*), 7.40 (2H, t, *J* 7.6, C(O)Ar(3,5)*H*), 7.49 (1H, t, *J* 7.4, C(O)Ar(4)*H*), 7.77 (2H, d, *J* 7.4, C(O)Ar(2,6)*H*), 7.94 (1H, br s, C=ON*H*). Spectroscopic data are in accordance with the literature.[189]

_N_'-(4-methoxyphenyl)-4-(trifluoromethyl)benzohydrazide

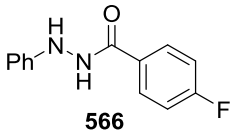


327 **329** **330**

To a solution of **327** (11.1 g, 40.8 mmol) and Et_3N (6.25 mL, 44.9 mmol) in EtOAc (100 mL) at 0 °C was added 4-trifluoromethylbenzoyl chloride (6.06 mL, 40.8 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was washed with HCl (1 M in H_2O) and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude acylated product **329** which was used without purification. To a solution of crude acylated product **329** (17.7 g, 40.8 mmol assuming 100% conversion) and 10% palladium on charcoal (4.27 g, 4.08 mmol, 10 mol%) in EtOAc (100 mL) was appended a balloon of hydrogen gas. The hydrogen gas was allowed to bubble through the reaction mixture at rt for 4 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. Recrystallisation (EtOH) gave hydrazide **330** as a white solid (7.95 g, 63% over 2 steps); mp 158-160 °C; ν_{max} (KBr)/cm^{-1} 3270 (N-H), 3068 (C-H), 1649 (C=O), 1551, 1510; δ_H (300 MHz, $(CH_3)_2S=O$) 3.67 (3H, s, OCH_3), 6.79 (4H, s, NAr(2,6)*H* and NAr(3,5)*H*), 7.69 (1H, d, *J* 2.5, ArN*H*), 7.89 (2H, d, *J* 8.2, Ar*H*), 8.11 (2H, d, *J* 8.1, Ar*H*), 10.6 (1H, d, *J* 2.2, C=ON*H*); δ_C (75

MHz, $(CH_3)_2S=O$) 55.2 (O*C*H_3), 113.9 (*ArC*), 114.3 (*ArC*), 123.9 (q, *J* 271, *C*F_3), 125.5 (q, *J* 3.7, C(O)*ArC*(3,5)), 128.2 (C(O)*ArC*(2,6)), 131.4 (q, *J* 31.7, C(O)*ArC*(4)), 136.9 (C(O)*ArC*(1)), 143.0 (N*ArC*(1)), 152.8 (N*ArC*(4)), 165.1 (*C*=O); *m*/*z* (NSI^+) 311 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{15}H_{14}F_3N_2O_2^+$ ($[M+H]^+$) requires 311.1002; found 311.1005 (+1.0 ppm).

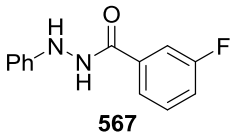
4-fluoro-*N*'-phenylbenzohydrazide



566

Following general procedure H, phenylhydrazine (0.55 mL, 5.59 mmol), Et_3N (0.78 mL, 5.59 mmol) and 4-fluorobenzoyl chloride (0.60 mL, 5.08 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **566** as a white solid (0.38 g, 32%); mp 171-173 °C; {lit.[190] mp 177-179 °C}; ν_{max} (ATR)/cm^{-1} 3271 (N-H), 3026 (C-H), 1641 (C=O), 1599, 1530; δ_H (500 MHz, $(CD_3)S=O$) 6.72-6.80 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.10-7.20 (2H, m, NAr(3,5)*H*), 7.31-7.39 (2H, m, C(O)Ar(2,6)*H*), 7.95-8.01 (3H, m, C(O)Ar(3,5)*H* and ArN*H*), 10.42 (1H, s, C(O)N*H*); δ_C (125 MHz, $(CD_3)S=O$) 112.4 (N*ArC*(2,6)), 115.5 (d, *J* 21.6, C(O)*ArC*(3,5)), 118.7 (N*ArC*(4)), 128.8 (N*ArC*(3,5)), 129.5 (d, *J* 2.6, C(O)*ArC*(1)), 130.0 (d, *J* 8.9, C(O)*ArC*(2,6)), 149.5 (N*ArC*(1)), 164.1 (d, *J* 248, C(O)*ArC*(4)), 165.3 (*C*=O); *m*/*z* (NSI^+) 231 ($[M+H]^+$, 73%); HRMS (NSI^+) $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$) requires 231.0928; found 231.099 (+0.4 ppm).

3-fluoro-*N*'-phenylbenzohydrazide

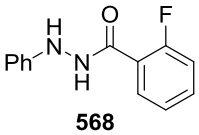


567

Following general procedure H, phenylhydrazine (0.91 mL, 9.25 mmol), Et_3N (1.29 mL, 9.25 mmol) and 3-fluorobenzoyl chloride (1.01 mL, 8.41 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **567** as a white solid (0.65 g, 34%); mp 120-122 °C; ν_{max} (KBr)/cm^{-1} 3251 (N-H), 3026 (C-H), 1646 (C=O), 1588, 1551; δ_H (300 MHz, CD_3OD) 6.79-6.88 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.16-7.22 (2H, m, NAr(3,5)*H*), 7.29-7.35 (1H, m, Ar*H*), 7.51 (1H, td, *J* 8.0, 5.7, Ar*H*), 7.62 (1H, dt, *J* 9.6, 2.0, Ar*H*), 7.71-7.74 (1H, m, Ar*H*); δ_C (75 MHz, CD_3OD) 114.3 (N*ArC*(2,6)), 115.5 (d, *J* 30.9, *ArC*), 119.9 (d, *J* 28.5, *ArC*), 121.3 (N*ArC*(4)), 124.3 (d, *J* 3.9, C(O)*ArC*(6)), 130.0

(N*ArC*(3,5)), 131.8 (d, *J* 10.6, C(O)*ArC*(5)), 136.5 (d, *J* 9.2, C(O)*ArC*(1)), 150.0 (N*ArC*(1)), 164.2 (d, *J* 326, C(O)*ArC*(3)), 168.8 (*C*=O); *m*/*z* (NSI^+) 231 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$) requires 231.0928; found 231.0930 (+0.8 ppm).

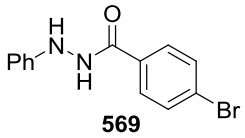
2-fluoro-*N*'-phenylbenzohydrazide



568

Following general procedure H, phenylhydrazine (0.91 mL, 9.25 mmol), Et_3N (1.29 mL, 9.25 mmol) and 2-fluorobenzoyl chloride (1.01 mL, 8.41 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **568** as a white solid (1.07 g, 55%); mp 107-109 °C; ν_{max} (KBr)/cm^{-1} 3272 (N-H), 3024 (C-H), 1639 (C=O), 1546, 1499; δ_H (400 MHz, CD_3OD) 6.80-6.84 (1H, m, NAr(4)*H*), 6.91 (2H, m, NAr(2,6)*H*), 7.18-7.31 (4H, m, Ar*H*), 7.53-7.58 (1H, m, Ar*H*), 7.72-7.76 (1H, m, Ar*H*); δ_C (75 MHz, CD_3OD) 114.3 (N*ArC*(2,6)), 117.3 (d, *J* 29.9, C(O)*ArC*(3)), 121.3 (N*ArC*(4)), 123.1 (d, *J* 19.7, C(O)*ArC*(1)), 125.8 (d, *J* 4.6, C(O)*ArC*(6)), 130.1 (N*ArC*(3,5)), 131.5 (d, *J* 3.3, C(O)*ArC*(5)), 134.5 (d, *J* 11.4, C(O)*ArC*(4)), 149.9 (N*ArC*(1)), 161.4 (d, *J* 331, C(O)*ArC*(2)), 167.2 (*C*=O); *m*/*z* (NSI^+) 231 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$) requires 231.0928; found 231.0930 (+0.8 ppm).

4-bromo-*N*'-phenylbenzohydrazide

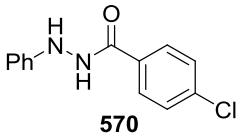


569

Following general procedure H, phenylhydrazine (0.91 mL, 9.25 mmol), Et_3N (1.29 mL, 9.25 mmol) and 4-bromobenzoyl chloride (1.85 g, 8.41 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **569** as a white solid (0.83 mg, 34%); mp 196-198 °C; {lit.[190] mp 198-199 °C}; ν_{max} (ATR)/cm^{-1} 3229 (N-H), 3048 (C-H), 1647 (C=O), 1589, 1530; δ_H (500 MHz, CD_3)S=O) 6.72 (1H, t, *J* 7.3, NAr(4)*H*), 6.79 (2H, d, *J* 8.0, NAr(2,6)*H*), 7.15 (2H, t, *J* 7.8, NAr(3,5)*H*), 7.23 (2H, d, *J* 8.4, C(O)Ar*H*), 7.87 (2H, d, *J* 8.4, C(O)Ar*H*), 7.96 (1H, s, ArN*H*), 10.5 (1H, s, C(O)N*H*); δ_C (125 MHz, (CD_3)S=O) 112.3 (N*ArC*(2,6)), 118.7 (N*ArC*(4)), 125.5 (C(O)*ArC*(4)), 128.8 (N*ArC*(3,5)), 129.4 (C(O)*ArC*), 131.6 (C(O)*ArC*), 132.1 (C(O)*ArC*(1)), 149.4 (N*ArC*(1)), 165.5 (*C*=O); *m*/*z*

(NSI$^+$) 291 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{13}H_{12}{}^{79}BrN_2O^+$ ([M+H]$^+$) requires 291.0128; found 291.0128 (+0.2 ppm).

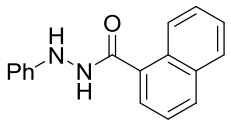
4-chloro-*N*'-phenylbenzohydrazide



570

Following general procedure H, phenylhydrazine (0.91 mL, 9.25 mmol), Et_3N (1.29 mL, 9.25 mmol) and 4-chlorobenzoyl chloride (1.08 mL, 8.41 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **570** as a white solid (1.17 g, 56%); mp 166-168 °C; {lit.[190] mp 193-195 °C}; δ_H (400 MHz, $CDCl_3$) 6.35 (1H, d, *J* 3.5, ArN*H*), 6.94-6.99 (3H, m, Ar*H*), 7.27-7.31 (2H, m, Ar*H*), 7.49 (2H, d, *J* 8.5 C(O)Ar(3,5)*H*), 7.82 (2H, d, *J* 8.5, C(O)Ar(2,6)*H*), 7.93 (1H, br s, C=ON*H*). Spectroscopic data are in accordance with the literature.[191]

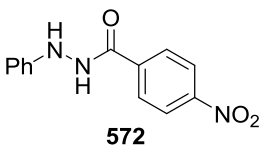
***N*'-phenyl-1-naphthohydrazide**



571

Following general procedure H, phenylhydrazine (0.91 mL, 9.25 mmol), Et_3N (1.29 mL, 9.25 mmol) and 1-naphthoyl chloride (1.27 mL, 8.41 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **571** as a white solid (740 mg, 34%); mp 194-196 °C; {lit.[192] mp 240 °C}; δ_H (300 MHz, $CDCl_3$) 6.52 (1H, d, *J* 4.3, ArN*H*), 6.99-7.05 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.32-7.37 (2H, m, NAr(3,5)*H*), 7.52-7.64 (3H, m, Ar*H*), 7.77-7.79 (2H, m, Ar*H*), 7.92-7.96 (1H, m, Ar*H*), 8.03 (1H, d, *J* 8.3, Ar*H*), 8.36-8.39 (1H, m, N*H*). Spectroscopic data are in accordance with the literature.[191]

4-nitro-*N*'-phenylbenzohydrazide

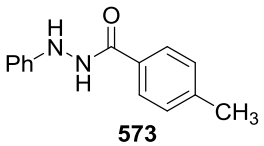


572

Following general procedure H, phenylhydrazine (1.82 mL, 18.5 mmol), Et_3N (2.58 mL, 16.8 mmol) and 4-nitrobenzoyl chloride (3.12 g, 16.8 mmol) in Et_2O (35 mL) gave, after

recrystallisation (EtOH), hydazide **572** as an orange solid (2.06 g, 48%); mp 198-200 °C; {lit.[193] mp 206 °C}; δ_H (400 MHz, $CDCl_3$) 6.37 (1H, d, *J* 3.0, ArN*H*), 6.96-7.00 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.31-7.33 (2H, m, NAr(3,5)*H*), 8.01-8.06 (3H, m, C(O)Ar(2,6)*H* and C=ON*H*), 8.38 (2H, d, *J* 8.8, C(O)Ar(3,5)*H*). Spectroscopic data are in accordance with the literature.[191]

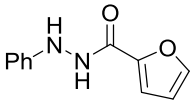
4-methyl-*N*'-phenylbenzohydrazide



573

Following general procedure H, phenylhydrazine (0.91 mL, 9.25 mmol), Et_3N (1.29 mL, 9.25 mmol) and *p*-toluoyl chloride (1.11 mL, 8.41 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **573** as a white solid (0.83 g, 44%); mp 166-167 °C; {lit.[193] mp 172 °C}; δ_H (300 MHz, $CDCl_3$) 2.36 (3H, s, CH_3), 6.26 (1H, d, *J* 3.5, ArN*H*), 6.87 (2H, d, *J* 8.2, C(O)Ar(3,5)*H*), 7.15-7.22 (5H, m, Ar*H*), 7.68 (2H, d, *J* 8.2, C(O)Ar(2,6)*H*), 7.76 (1H, br s, C=ON*H*). Spectroscopic data are in accordance with the literature.[191]

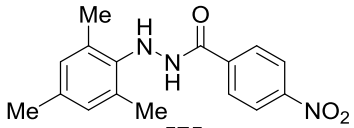
***N*'-phenylfuran-2-carbohydrazide**



574

Following general procedure H, phenylhydrazine (0.91 mL, 9.25 mmol), Et_3N (1.29 mL, 9.25 mmol) and 2-furoyl chloride (0.83 mL, 8.41 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **574** as a white solid (0.80 g, 47%); mp 141-142 °C; {lit.[194] mp 144-145 °C}; δ_H (300 MHz, $CDCl_3$) 6.24 (1H, br s, ArN*H*), 6.60 (1H, dd, *J* 3.5, 1.7, C(O)Ar(4)*H*), 6.94-6.98 (3H, m, Ar*H*), 7.24-7.35 (3H, m, Ar*H*), 7.56 (1H, d, *J* 1.0, C(O)Ar(5)*H*), 8.10 (1H, br s, C=ON*H*). Spectroscopic data are in accordance with the literature.[194]

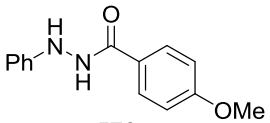
***N*'-mesityl-4-nitrobenzohydrazide**



575

Following general procedure H, mesitylhydrazine hydrochloride (1.00 g, 5.73 mmol), Et_3N (1.60 mL, 11.5 mmol) and 4-nitrobenzoyl chloride (0.97 g, 5.21 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **575** as a yellow solid (0.32 g, 21%); mp 214-216 °C; ν_{max} (KBr)/cm^{-1} 3235 (N-H), 3072 (C-H), 1675 (C=O), 1602, 1521 (N=O), 1349 (N=O); δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, CH_3), 2.49 (6H, s, 2 CH_3), 6.35 (1H, br s, ArN*H*), 6.89 (2H, s, NAr(3,5)*H*), 7.82 (1H, br s, C=ON*H*), 7.91-7.94 (2H, m, C(O)Ar(2,6)*H*), 8.31-8.34 (2H, m, C(O)Ar(3,5)*H*); δ_C (75 MHz, CD_3OD) 18.6 (2 *C*H_3), 20.1 (*C*H_3), 123.6 (C(O)*ArC*(3,5)), 128.0 (C(O)*ArC*(1)), 128.8 (*ArC*), 129.1 (*ArC*), 130.5 (N*ArC*(2,6)), 138.8 (N*ArC*(4)), 141.9 (N*ArC*(1)), 149.1 (C(O)*ArC*(4)), 164.5 (*C*=O); *m*/*z* ($APCI^+$) 300 ($[M+H]^+$, 100%); HRMS ($APCI^+$) $C_{16}H_{18}N_3O_3^+$ ($[M+H]^+$) requires 300.1343; found 300.1342 (-0.2 ppm).

4-methoxy-*N*'-phenylbenzohydrazide



576

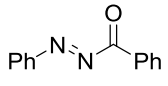
Following general procedure H, phenylhydrazine (0.91 mL, 9.25 mmol), Et_3N (1.29 mL, 9.25 mmol) and 4-methoxybenzoyl chloride (1.44 g, 8.41 mmol) in Et_2O (20 mL) gave, after recrystallisation (EtOH), hydazide **576** as a white solid (0.78 g, 38%); mp 171-173 °C; {lit.[193] mp 170 °C}; δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, OCH_3), 6.34 (1H, br s, ArN*H*), 6.39-7.01 (5H, m, Ar*H*), 7.26-7.30 (2H, m, Ar*H*), 7.81 (1H, br s, C=ON*H*), 7.83-7.87 (2H, m, C(O)Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[191]

General procedure I: *Diazene formation.*

To a solution of requisite hydrazide (1 eq) and pyridine (1.1 eq) in CH_2Cl_2 at −78 °C was added *N*-bromosuccinimide (1 eq) portion wise. The reaction mixture was warmed to rt and stirred for 30 minutes before being filtered. The filtrate was concentrated *in vacuo* and the resulting solid was triturated with Et_2O. The mixture was filtered and the filtrate was washed with HCl (1 M in H_2O) followed by sat. aq. $NaHCO_3$. The organic layer

was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture.

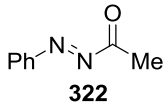
(*E*)-phenyl(phenyldiazenyl)methanone



313

Following general procedure I, hydrazide **319** (1.50 g, 7.08 mmol), pyridine (0.63 mL, 7.79 mmol) and *N*-bromosuccinimide (1.26 g, 7.08 mmol) in CH_2Cl_2 (7 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **313** as a red oil (1.17 g, 79%); δ_H (400 MHz, $CDCl_3$) 7.43-7.63 (6H, m, Ar*H*), 7.91-8.02 (4H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[107]

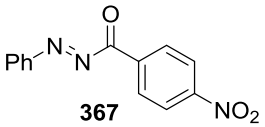
(*E*)-1-(phenyldiazenyl)ethanone



322

Following general procedure I, 1-acetyl-2-phenylhydrazine (0.22 g, 1.47 mmol), pyridine (0.13 mL, 1.61 mmol) and *N*-bromosuccinimide (0.26 g, 1.47 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 10:90), diazene **322** as a red oil (37.2 mg, 17%); δ_H (300 MHz, $CDCl_3$) 2.36 (3H, s, C*H*$_3$), 7.42-7.50 (3H, m, Ar*H*), 7.80-7.83 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[198]

(*E*)-(4-nitrophenyl)(phenyldiazenyl)methanone

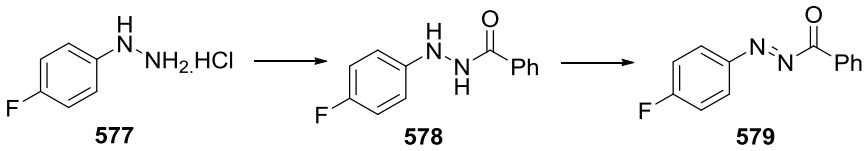


367

Following general procedure I, hydrazide **572** (2.00 g, 7.78 mmol), pyridine (0.69 mL, 8.56 mmol) and *N*-bromosuccinimide (1.39 g, 7.78 mmol) in CH_2Cl_2 (10 mL) gave, after chromatographic purification (eluent Et_2O:petrol 50:50), diazene **367** as a red solid (0.91 g, 46%); mp 127-129 °C; ν_{max} (KBr)/cm^{-1} 3080 (C-H), 1711 (C=O), 1605, 1529 (N=O), 1499, 1352 (N=O); δ_H (300 MHz, $CDCl_3$) 7.50-7.62 (3H, m, NAr(3,5)*H* and NAr(4)*H*), 7.94-7.97 (2H, m, NAr(2,6)*H*), 8.19-8.23 (2H, m, C(O)Ar(2,6)*H*), 8.29-8.33 (2H, m, C(O)Ar(3,5)*H*); δ_C (100 MHz, $CDCl_3$) 124.0 (*ArC*), 124.0 (*ArC*), 129.6 (*ArC*), 131.7

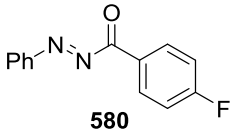
(*ArC*), 134.3 (N*ArC*(4)), 136.1 (C(O)*ArC*(1)), 151.1 (*ArC*), 152.1 (*ArC*), 179.7 (*C*=O); *m*/*z* (APCI$^+$) 256 ([M+H]$^+$, 100%); HRMS (APCI$^+$) $C_{13}H_{10}N_3O^+$ ([M+H]$^+$) requires 256.0717; found 256.0714 (-1.0 ppm).

(*E*)-((4-fluorophenyl)diazenyl)(phenyl)methanone



To a solution of 4-fluorophenylhydrazine hydrochloride **577** (2.00 g, 12.3 mmol) and Et_3N (3.43 mL, 24.6 mmol) in Et_2O (30 mL) at 0 °C was slowly added benzoyl chloride (1.29 mL, 11.2 mmol). After stirring at rt for 30 minutes the reaction mixture was concentration *in vacuo*. The solid was dissolved in CH_2Cl_2 and washed with HCl (1 M in H_2O). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude hydrazide **578** which was used without purification. Following general procedure I, hydrazide **578** (2.57 g, 11.2 mmol assuming 100% conversion), pyridine (1.07 mL, 12.3 mmol) and *N*-bromosuccinimide (1.98 g, 11.2 mmol) in CH_2Cl_2 (15 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **579** as a red solid (0.55 mg, 21% over 2 steps); mp 48-50 °C; ν_{max} (KBr)/cm^{-1} 3067 (C-H), 1702 (C=O), 1591, 1503; δ_H (300 MHz, $CDCl_3$) 7.26-7.32 (2H, m, NAr(3,5)*H*), 7.54-7.60 (2H, m, C(O)Ar(3,5)*H*), 7.68-7.74 (1H, m, C(O)Ar(4)*H*), 8.06-8.12 (4H, m, NAr(2,6)*H* and C(O)Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 116.5 (d, *J* 23.0, N*ArC*(3,5)), 126.0 (d, *J* 9.5, N*ArC*(2,6)), 128.9 (*ArC*), 130.6 (*ArC*), 130.9 (C(O)*ArC*(1)), 134.6 (C(O)*ArC*(4)), 148.7 (d, 2.9, N*ArC*(1)), 165.9 (d, *J* 254, N*ArC*(4)), 181.7 (*C*=O); *m*/*z* (ES$^+$) 251 ([M+Na]$^+$, 100%); HRMS (ES$^+$) $C_{13}H_9FN_2NaO^+$ ([M+Na]$^+$) requires 251.0597; found 251.0590 (-2.5 ppm).

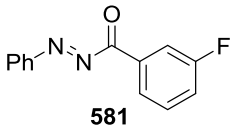
(*E*)-(4-fluorophenyl)(phenyldiazenyl)methanone



Following general procedure I, hydrazide **566** (0.37 g, 1.61 mmol), pyridine (0.14 mL, 1.77 mmol) and *N*-bromosuccinimide (0.29 g, 1.61 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **580** as a red oil (0.28 g,

76%); ν_{max} (thin film)/cm^{-1} 3068 (C-H), 1707 (C=O), 1597, 1507; δ_H (400 MHz, $CDCl_3$) 7.20-7.26 (2H, m, C(O)Ar(3,5)*H*), 7.58-7.67 (3H, m, Ar*H*), 8.02-8.05 (2H, m, Ar*H*), 8.12-8.17 (2H, m, C(O)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 116.3 (d, *J* 21.9, C(O)*ArC*(3,5)), 123.7 (N*ArC*(2,6)), 127.4 (d, *J* 2.7, C(O)*ArC*(1)), 129.4 (N*ArC*(3,5)), 133.4 (d, *J* 9.7, C(O)*ArC*(2,6)), 133.7 (N*ArC*(4)), 152.1 (N*ArC*(1)), 166.6 (d, *J* 256, C(O)*ArC*(4)), 180.5 (*C*=O); *m*/*z* (ES$^+$) 251 ([M+Na]$^+$, 100%); HRMS (ES$^+$) $C_{13}H_9FN_2NaO^+$ ([M+Na]$^+$) requires 251.0597; found 251.0602 (+2.1 ppm).

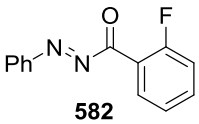
(*E*)-(3-fluorophenyl)(phenyldiazenyl)methanone



581

Following general procedure I, hydrazide **567** (488 mg, 2.13 mmol), pyridine (0.19 mL, 2.34 mmol) and *N*-bromosuccinimide (0.38 g, 2.13 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **581** as a red oil (0.36 g, 75%); ν_{max} (thin film)/cm^{-1} 3073 (C-H), 1716 (C=O), 1589, 1499; δ_H (400 MHz, $CDCl_3$) 7.37-7.42 (1H, m, Ar*H*), 7.54 (1H, td, *J* 8.0, 5.4, Ar*H*), 7.58-7.68 (3H, m, NAr(3,5)*H* and NAr(4)*H*), 7.81 (1H, ddd, *J* 9.0, 2.6, 1.5, Ar*H*), 7.88-7.90 (1H, m, Ar*H*), 8.02-8.05 (2H, m, NAr(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 117.2 (d, *J* 22.8, *ArC*), 121.7 (d, *J* 21.3, *ArC*), 123.8 (N*ArC*(2,6)), 126.4 (d, *J* 3.0, C(O)*ArC*(6)), 129.5 (N*ArC*(3,5)), 130.7 (d, *J* 7.4, C(O)*ArC*(5)), 133.0 (d, *J* 6.7, C(O)*ArC*(1)), 133.8 (N*ArC*(4)), 152.1 (N*ArC*(1)), 162.7 (d, *J* 247, C(O)*ArC*(3)), 180.6 (*C*=O); *m*/*z* (ES$^+$) 251 ([M+Na]$^+$, 100%); HRMS (ES$^+$) $C_{13}H_9FN_2NaO^+$ ([M+Na]$^+$) requires 251.0597; found 251.0602 (+2.1 ppm).

(*E*)-(2-fluorophenyl)(phenyldiazenyl)methanone

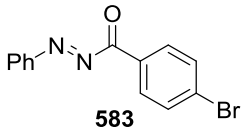


582

Following general procedure I, hydrazide **568** (0.80 g, 3.49 mmol), pyridine (0.31 mL, 3.84 mmol) and *N*-bromosuccinimide (0.62 g, 3.49 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **582** as a red oil (0.54 g, 68%); ν_{max} (thin film)/cm^{-1} 3066 (C-H), 1695 (C=O), 1609, 1586, 1505; δ_H (300 MHz, $CDCl_3$) 7.20 (1H, ddd, *J* 10.6, 8.4, 1.0, Ar*H*), 7.36 (1H, td, *J* 7.6, 0.9, Ar*H*), 7.56-7.71 (4H, m, Ar*H*), 7.98-8.02 (2H, m, Ar*H*), 8.13 (1H, ddd, *J* 7.8, 7.1, 1.8, Ar*H*); δ_C (75 MHz,

$CDCl_3$) 117.2 (d, *J* 29.3, C(O)*ArC*(3)), 119.3 (d, *J* 15.0, C(O)*ArC*(1)), 123.6 (N*ArC*(2,6)), 124.6 (d, *J* 4.8, C(O)*ArC*(5)), 129.4 (N*ArC*(3,5)), 132.5 (*ArC*), 133.4 (*ArC*), 136.4 (d, *J* 12.0, C(O)*ArC*(4)), 152.1 (N*ArC*(1)), 162.5 (d, *J* 346, C(O)*ArC*(2)), 180.9 (d, *J* 7.8, *C*=O); *m*/*z* (ES^+) 251 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{13}H_9FN_2NaO^+$ ($[M+Na]^+$) requires 251.0597; found 251.0593 (-1.4 ppm).

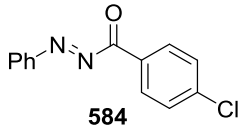
(*E*)-(4-bromophenyl)(phenyldiazenyl)methanone



583

Following general procedure I, hydrazide **569** (0.82 g, 2.82 mmol), pyridine (0.26 mL, 3.10 mmol) and *N*-bromosuccinimide (0.50 g, 2.82 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **583** as a red solid (0.67 g, 82%); mp 39-40 °C; {lit.[195] mp 38-39.5 °C}; δ_H (300 MHz, $CDCl_3$) 7.57-7.66 (3H, m, NAr(3,5)*H* and NAr(4)*H*), 7.68-7.72 (2H, m, Ar*H*), 7.95-7.99 (2H, m, Ar*H*), 8.01-8.04 (2H, m, NAr(2,6)*H*). Spectroscopic data are in accordance with the literature.[195]

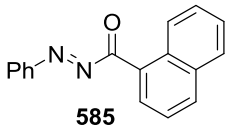
(*E*)-(4-chlorophenyl)(phenyldiazenyl)methanone



584

Following general procedure I, hydrazide **570** (1.16 g, 4.71 mmol), pyridine (0.42 mL, 5.18 mmol) and *N*-bromosuccinimide (0.84 g, 4.71 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **584** as a red oil (0.91 g, 76%); ν_{max} (thin film)/cm^{-1} 3064 (C-H), 1701 (C=O), 1591, 1500; δ_H (300 MHz, $CDCl_3$) 7.50-7.55 (2H, m, Ar*H*), 7.57-7.67 (3H, m, Ar*H*), 8.01-8.07 (4H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 123.8 (N*ArC*(2,6)), 129.4 (*ArC*), 129.5 (*ArC*), 131.9 (N*ArC*(4)), 131.9 (C(O)*ArC*(1)), 133.7 (*ArC*), 141.2 (C(O)*ArC*(4)), 152.1 (N*ArC*(1)), 180.8 (*C*=O); *m*/*z* (ES^+) 267 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_9H_{13}{}^{35}ClN_2NaO_3^+$ ($[M+Na]^+$) requires 267.0303; found 267.0302 (-0.3 ppm).

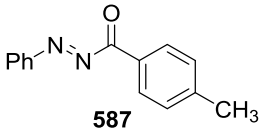
(*E*)-naphthalen-1-yl(phenyldiazenyl)methanone



585

Following general procedure I, hydrazide **571** (0.74 g, 2.81 mmol), pyridine (0.26 mL, 3.10 mmol) and *N*-bromosuccinimide (0.50 g, 2.81 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **585** as a red solid (0.58 g, 79%); mp 76-78 °C; ν_{max} (KBr)/cm^{-1} 3061 (C-H), 1697 (C=O), 1591, 1500; δ_H (400 MHz, $CDCl_3$) 7.54-7.66 (5H, m, Ar*H*), 7.76 (1H, ddd, *J* 8.6, 7.0, 1.4, Ar*H*), 7.96 (1H, dd, *J* 8.2, 0.4, Ar*H*), 8.05-8.07 (2H, m, Ar*H*), 8.15 (1H, d, *J* 8.2, Ar*H*), 8.31 (1H, dd, *J* 7.3, 1.2, Ar*H*), 9.25 (1H, d, *J* 8.7, C(O)Ar(8)*H*); δ_C (100 MHz, $CDCl_3$) 123.7 (N*ArC*(2,6)), 124.4 (*ArC*), 126.2 (*ArC*), 126.9 (*ArC*), 127.1 (*ArC*), 128.8 (*ArC*), 129.0 (*ArC*), 129.4 (*ArC*), 131.6 (*ArC*), 133.3 (*ArC*), 133.4 (*ArC*), 134.1 (C(O)*ArC*(1)), 135.6 (*ArC*), 152.1 (N*ArC*(1)), 183.1 (*C*=O); *m*/*z* (ES^+) 283 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{17}H_{12}N_2NaO^+$ ($[M+Na]^+$) requires 283.0847; found 283.0848 (+0.2 ppm).

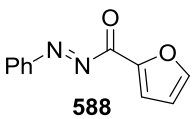
(*E*)-(phenyldiazenyl)(*p*-tolyl)methanone



587

Following general procedure I, hydrazide **573** (0.82 g, 3.63 mmol), pyridine (0.32 mL, 4.00 mmol) and *N*-bromosuccinimide (0.65 g, 3.63 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 15:85), diazene **587** as a red oil (0.63 g, 77%); δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 7.25 (2H, d, *J* 8.0, C(O)Ar(3,5)*H*), 7.47-7.55 (3H, m, Ar*H*), 7.87-7.89 (2H, d, *J* 8.0, C(O)Ar(2,6)*H*), 7.91-7.93 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[196]

(*E*)-furan-2-yl(phenyldiazenyl)methanone

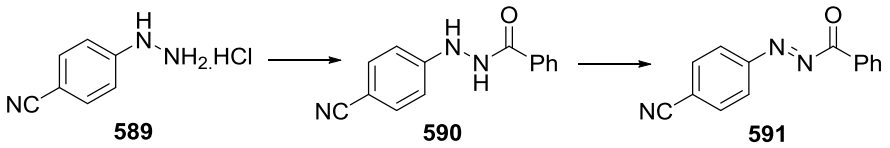


588

Following general procedure I, hydrazide **574** (0.79 g, 3.91 mmol), pyridine (0.35 mL, 4.30 mmol) and *N*-bromosuccinimide (0.69 g, 3.91 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **588** as a red oil (0.41 g, 52%); δ_H (300 MHz, $CDCl_3$) 6.70 (1H, dd, *J* 3.6, 1.7, C(O)Ar(4)*H*), 7.45 (1H, dd, *J* 3.6,

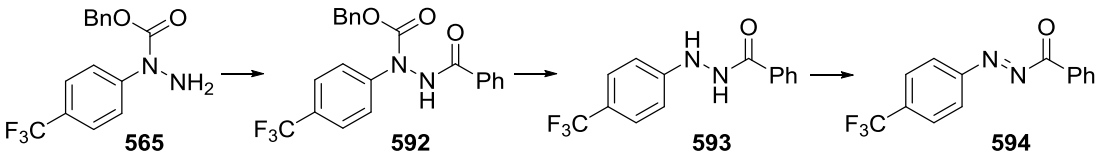
0.7, C(O)Ar(3)*H*), 7.58-7.69 (3H, m, NAr(3,5)*H* and NAr(4)*H*), 7.84 (1H, dd, *J* 1.7, 0.7, C(O)Ar(5)*H*), 8.03-8.07 (2H, m, NAr(2,6)*H*). Spectroscopic data are in accordance with the literature.[197]

(*E*)-4-(benzoyldiazenyl)benzonitrile



To a solution of 4-cyanophenylhydrazine hydrochloride **589** (2.00 g, 11.8 mmol) and Et_3N (3.29 mL, 23.6 mmol) in Et_2O (30 mL) at 0 °C was slowly added benzoyl chloride (1.24 mL, 10.7 mmol). After stirring at rt for 30 minutes the reaction mixture was concentration *in vacuo*. The solid was dissolved in CH_2Cl_2 and washed with HCl (1M in H_2O). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude hydrazide **590** which was used without purification. Following general procedure I, hydrazide **590** (2.54 g, 10.7 mmol assuming 100% conversion), pyridine (0.97 mL, 11.8 mmol) and *N*-bromosuccinimide (1.90 g, 10.7 mmol) in CH_2Cl_2 (15 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **591** as a purple solid (0.26 g, 10% over 2 steps); mp 110-112 °C; ν_{max} (KBr)/cm^{-1} 3043 (C-H), 2229 (C≡N), 1706 (C=O), 1598, 1506; δ_H (400 MHz, $CDCl_3$) 7.57 (2H, t, *J* 7.7, C(O)Ar(3,5)*H*), 7.73 (1H, t, *J* 7.4, C(O)Ar(4)*H*), 7.91 (2H, d, *J* 8.4, Ar*H*), 8.05 (2H, d, *J* 7.3, C(O)Ar(2,6)*H*), 8.09 (2H, d, *J* 8.4, Ar*H*); δ_C (75 MHz, $CDCl_3$) 116.5 (*C*≡N), 117.9 (N*ArC*(4)), 123.9 (*ArC*), 129.1 (*ArC*), 130.2 (C(O)*ArC*(1)), 130.6 (*ArC*), 133.5 (*ArC*), 135.0 (C(O)*ArC*(4)), 153.5 (N*ArC*(1)), 181.5 (*C*=O); *m*/*z* (ES^+) 236 ($[M+H]^+$, 100%); HRMS (ES^+) $C_{14}H_{10}N_3O^+$ ($[M+H]^+$) requires 236.0824; found 236.0824 (+0.2 ppm).

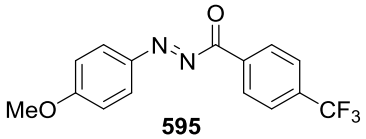
(*E*)-phenyl((4-(trifluoromethyl)phenyl)diazenyl)methanone



To a solution of **565** (1.00 g, 3.23 mmol) and Et_3N (0.49 mL, 3.55 mmol) in EtOAc (10 mL) at 0 °C was added benzoyl chloride (0.37 mL, 3.23 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was washed with HCl (1 M in H_2O) and sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and concentrated *in*

vacuo to give the crude acylated product **592** which was used without purification. To a solution of crude acylated product **592** (1.34 g, 3.23 mmol assuming 100% conversion) and 10% palladium on charcoal (0.34 g, 0.32 mmol, 10 mol%) in EtOAc (10 mL) was appended a balloon of hydrogen gas. The hydrogen gas was allowed to bubble through the reaction mixture at rt for 4 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to give the hydrazide **593** which was used without purification. Following general procedure I, hydrazide **593** (903 mg, 3.23 mmol assuming 100% conversion), pyridine (0.29 mL, 3.55 mmol) and *N*-bromosuccinimide (0.57 g, 3.23 mmol) in CH_2Cl_2 (10 mL) gave, after chromatographic purification (eluent Et_2O:petrol 10:90), diazene **594** as a red oil (0.60 g, 66% over 3 steps); ν_{max} (thin film)/cm^{-1} 3070 (C-H), 1716 (C=O), 1599; δ_H (500 MHz, $CDCl_3$) 7.46 (2H, t, *J* 7.8, C(O)Ar(3,5)*H*), 7.61 (1H, t, *J* 7.5, C(O)Ar(4)*H*), 7.76 (2H, d, *J* 8.3, C(O)Ar(2,6)*H*), 7.94-7.96 (2H, m, Ar*H*), 8.00 (2H, d, *J* 8.2, Ar*H*); δ_C (125 MHz, $CDCl_3$) 123.6 (q, *J* 271, *C*F_3), 123.7 (*ArC*), 126.7 (q, *J* 3.5, N*ArC*(3,5)), 129.0 (*ArC*), 130.3 (C(O)*ArC*(1)), 130.6 (*ArC*), 134.4 (q, *J* 32.5, N*ArC*(4)), 134.9 (C(O)*ArC*(4)), 153.6 (N*ArC*(1)), 181.7 (*C*=O); *m*/*z* (ES^+) 301 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{14}H_9F_3N_2NaO^+$ ($[M+Na]^+$) requires 301.0565; found 301.0566 (+0.4 ppm).

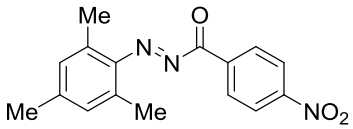
(*E*)-((4-methoxyphenyl)diazenyl)(4-(trifluoromethyl)phenyl)methanone



595

Following general procedure I, hydrazide **330** (3.50 g, 11.3 mmol), pyridine (1.02 mL, 12.4 mmol) and *N*-bromosuccinimide (2.00 g, 11.3 mmol) in CH_2Cl_2 (50 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **595** as a red solid (2.57 g, 74%) mp 56-58 °C; ν_{max} (KBr)/cm^{-1} 2936 (C-H), 1696 (C=O), 1597, 1504; δ_H (300 MHz, $CDCl_3$) 3.97 (3H, s, O*C*H_3), 7.07-7.11 (2H, m, NAr(3,5)*H*), 7.82 (2H, d, *J* 8.2, Ar*H*), 8.04-8.10 (2H, m, NAr(2,6)*H*), 8.29 (2H, d, *J* 8.1, Ar*H*); δ_C (100 MHz, $CDCl_3$) 55.8 (O*C*H_3), 114.7 (N*ArC*(3,5)), 123.5 (q, *J* 271, *C*F_3), 125.8 (q, *J* 3.6, C(O)*ArC*(3,5)), 126.6 (C(O)*ArC*(2,6)), 131.0 (N*ArC*(2,6)), 134.9 (N*ArC*(1)), 135.3 (q, *J* 32.7, C(O)*ArC*(4)), 146.8 (C(O)*ArC*(1)), 164.8 (N*ArC*(4)), 179.9 (*C*=O); *m*/*z* (ES^+) 331 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{15}H_{11}N_2NaO_2F_3^+$ ($[M+Na]^+$) requires 331.0670; found 331.0675 (+1.4 ppm).

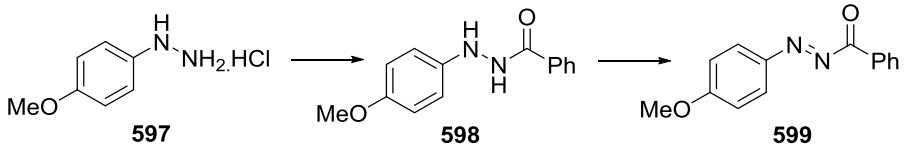
(*E*)-(mesityldiazenyl)(4-nitrophenyl)methanone



596

Following general procedure I, hydrazide **575** (0.28 g, 0.94 mmol), pyridine (0.09 mL, 1.03 mmol) and *N*-bromosuccinimide (0.17 g, 0.94 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent CH_2Cl_2:petrol 80:20), diazene **596** as a red solid (0.15 g, 53%); mp 104-106 °C; ν_{max} (KBr)/cm^{-1} 3109 (C-H), 2921, 1694 (C=O), 1606, 1535 (N=O), 1353 (N=O); δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 2.46 (6H, s, 2 CH_3), 6.95 (2H, s, NAr(3,5)*H*), 8.21 (2H, d, *J* 8.8, Ar*H*), 8.29 (2H, d, *J* 8.8, Ar*H*); δ_C (75 MHz, $CDCl_3$) 20.6 (2 *C*H_3), 21.5 (*C*H_3), 124.0 (*ArC*), 130.9 (*ArC*), 131.7 (*ArC*), 135.7 (N*ArC*(2,6)), 136.9 (N*ArC*(1)), 143.8 (N*ArC*(4)), 147.3 (C(O)*ArC*(1)), 150.9 (C(O)*ArC*(4)), 179.2 (*C*=O); *m/z* (ES^+) 298 ($[M+H]^+$, 100%); HRMS (ES^+) $C_{16}H_{16}N_3O_3^+$ ($[M+H]^+$) requires 298.1192; found 298.1186 (-1.8 ppm).

(*E*)-((4-methoxyphenyl)diazenyl)(phenyl)methanone

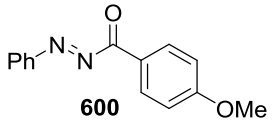


597 **598** **599**

To a solution of 4-methoxyphenylhydrazine hydrochloride **597** (0.38 g, 2.18 mmol) and Et_3N (0.61 mL, 4.36 mmol) in Et_2O (10 mL) at 0 °C was slowly added benzoyl chloride (0.23 mL, 1.98 mmol). After stirring at rt for 30 minutes the reaction mixture was concentration *in vacuo*. The solid was dissolved in CH_2Cl_2 and washed with HCl (1 M H_2O). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude hydrazide **598** which was used without purification. Following general procedure I, crude hydrazide **598** (0.37 g, 1.53 mmol), pyridine (0.14 mL, 1.68 mmol) and *N*-bromosuccinimide (0.27 g, 1.53 mmol) in CH_2Cl_2 (10 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **599** as a red solid (0.10 g, 21% over 2 steps); mp 50-52 °C; ν_{max} (KBr)/cm^{-1} 3098 (C-H), 1700 (C=O), 1599, 1503; δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 6.95-6.99 (2H, m, NAr(3,5)*H*), 7.43-7.47 (2H, m, C(O)Ar(3,5)*H*), 7.56-7.60 (1H, m, C(O)Ar(4)*H*), 7.93-7.97 (2H, m, NAr(2,6)*H*), 8.05 (2H, d, *J* 8.3, C(O)Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 55.8 (O*C*H_3), 114.5 (N*ArC*(3,5)), 126.2 (*ArC*), 128.8 (*ArC*), 130.7 (*ArC*), 131.7 (C(O)*ArC*(1)), 134.3 (C(O)*ArC*(4)), 146.8

(N*ArC*(1)), 164.2 (N*ArC*(4)), 181.6 (*C*=O); *m*/*z* (ES^+) 263 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{14}H_{12}N_2NaO^+$ ($[M+Na]^+$) requires 263.0796; found 263.0796 (+0.1 ppm).

(*E*)-(4-methoxyphenyl)(phenyldiazenyl)methanone



600

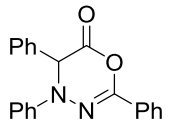
Following general procedure I, hydrazide **576** (0.78 g, 3.21 mmol), pyridine (0.29 mL, 3.53 mmol) and *N*-bromosuccinimide (0.57 g, 3.21 mmol) in CH_2Cl_2 (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80), diazene **600** as a red oil (0.59 g, 77%); ν_{max} (ATR)/cm^{-1} 2933 (C-H), 1694 (C=O), 1595, 1501; δ_H (300 MHz, $CDCl_3$) 3.91 (3H, s, OC*H*$_3$), 6.99-7.04 (2H, m, C(O)Ar(3,5)*H*), 7.55-7.62 (3H, m, Ar*H*), 8.00-8.09 (4H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 55.7 (O*C*H$_3$), 114.3 (C(O)*ArC*(3,5)), 123.6 (C(O)*ArC*(1)), 123.6 (N*ArC*(2,6)), 129.4 (N*ArC*(3,5)), 133.1 (C(O)*ArC*(2,6)), 133.4 (N*ArC*(4)), 152.2 (N*ArC*(1)), 164.7 (C(O)*ArC*(4)), 181.1 (*C*=O); *m*/*z* (ESI^+) 241 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{13}N_2O_2^+$ ($[M+H]^+$) requires 241.0977; found 241.0967 (-0.5 ppm).

General procedure J: *Intermolecular Michael addition-lactonisation.*

To a solution of acid (1.5 eq) in CH_2Cl_2 (~1 mL per 0.2 mmol of acid) were added *i*-Pr_2NEt (1.5 eq based on acid) and *p*-methoxybenzoyl chloride (1.5 eq based on acid) at rt. The reaction mixture was allowed to stir at rt for 10 minutes. The requisite Lewis base (0.1-20 mol%), Michael acceptor (1 eq) and *i*-Pr_2NEt (1.5 eq) were then added at the required temperature in that order. The reaction mixture was stirred at the required temperature until complete by TLC and was subsequently quenched by addition of HCl (1 M in H_2O). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture. Note: All racemic samples were obtained *via* this general procedure using DHPB **108** as catalyst.

Optimisation studies on compound 320

triphenyl-4H-1,3,4-oxadiazin-6(5*H*)-one



(±)-**302**

Following general procedure J, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), diazene **313** (42.0 mg, 0.20 mmol), DHPB **108** (7.60 mg, 0.04 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 2:98) (±)-**302** as a colourless oil (41.0 mg, 63%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 9.0 min, t_R(5*R*): 14.9 min; ν_{max} (thin film)/cm^{-1} 3063, 2977 (C-H), 1791 (C=O), 1596, 1495; δ_H (400 MHz, $CDCl_3$) 5.96 (1H, s, C(5)*H*), 6.89-6.92 (1H, m, N(4)Ar(4)*H*), 7.15-7.28 (9H, m, Ar*H*), 7.31-7.34 (3H, m, C(2)Ar(3,5)*H* and C(2)Ar(4)*H*), 7.86-7.89 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 59.5 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 121.9 (N(4)*ArC*(4)), 125.6 (*ArC*), 126.7 (*ArC*), 128.6 (*ArC*), 128.9 (C(2)*ArC*(1)), 129.1 (*ArC*), 129.4 (*ArC*), 129.4 (*ArC*), 130.3 (*ArC*), 131.2 (C(5)*ArC*(1)), 141.0 (N(4)*ArC*(1)), 144.3 (*C*(2)), 160.4 (*C*(6)); *m*/*z* ($APCI^+$) 328 ($[M]^+$, 12%); HRMS ($APCI^+$) $C_{21}H_{16}N_2O_2^+$ ($[M]^+$) requires 328.1206; found 328.1201 (-1.6 ppm).

Asymmetric Catalyst Screen:

Tetramisole hydrochloride (2*S*)-**106** (4.82 mg, 0.02 mmol, 10 mol%) gave approximately 65% conversion to the desired product after 16 h at rt.

Benzotetramisole (2*R*)-**107** (5.04 mg, 0.02 mmol, 10 mol%) gave approximately 20% conversion to the desired product after 16 h at rt.

HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%) gave full conversion to the desired product after 1 h at rt. Chromatographic purification (eluent Et_2O:petrol 2:98) gave (5*R*)-**320** as a colourless oil (43.0 mg, 66%); 95% *ee*.

Temperature Screen:

All reactions with HBTM-2.1 (2*S*,3*R*)-**112** (6.17 mg, 0.02 mmol, 10 mol%)

Reaction for 2 h at 0 °C gave, after chromatographic purification (eluent Et_2O:petrol 2:98) (5*R*)-**320** as a colourless oil (42.3 mg, 65%); 98% *ee*.

Reaction for 16 h at –30 °C gave, after chromatographic purification (eluent Et_2O:petrol 2:98) (5*R*)-**320** as a colourless oil (39.7 mg, 61%); 99% *ee*.

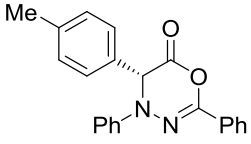
Reaction for 16 h at –78 °C gave, after chromatographic purification (eluent Et_2O:petrol 2:98) (5*R*)-**320** as a colourless oil (53.2 mg, 81%); 99% *ee*.

Catalyst Loading Screen:
All reactions at –78 °C for 16 h.

HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%) gave, after chromatographic purification (eluent Et_2O:petrol 2:98) (5*R*)-**320** as a colourless oil (54.3 mg, 83%); >99% *ee*.

HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%) gave, after chromatographic purification (eluent Et_2O:petrol 2:98) (5*R*)-**320** as a colourless oil (58.6 mg, 89%); $[\alpha]_D^{20}$-621.7 (*c* 1.075, CH_2Cl_2); >99% *ee*.

(5*R*)-2,4-diphenyl-5-(*p*-tolyl)-4*H*-1,3,4-oxadiazin-6(5*H*)-one

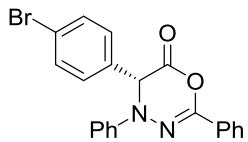


(5*R*)-**331**

Following general procedure J, *p*-tolylacetic acid (45.1 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**331** as a white solid (53.3 mg, 78%); mp 120-122 °C; $[\alpha]_D^{20}$-603.3 (*c* 0.75, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 8.7 min, t_R(5*R*): 20.2 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3059, 2931 (C-H), 1789 (C=O), 1597, 1494; δ_H (400

MHz, $CDCl_3$) 2.18 (3H, s, C*H*$_3$), 5.92 (1H, s, C(5)*H*), 6.89-6.93 (1H, m, N(4)Ar(4)*H*), 7.01 (2H, d, *J* 8.1, Ar*H*), 7.13-7.18 (4H, m, Ar*H*), 7.21-7.25 (2H, m, Ar*H*), 7.31-7.35 (3H, m, C(2)Ar(3,5)*H*, C(2)Ar(4)*H*), 7.85-7.90 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 21.1 (*C*H$_3$), 59.3 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 121.8 (N(4)*ArC*(4)), 125.6 (*ArC*), 126.6 (*ArC*), 128.1 (*ArC*), 128.6 (*ArC*), 128.9 (*ArC*), 129.4 (*ArC*), 130.0 (*ArC*), 130.2 (C(2)*ArC*(4)), 139.0 (C(5)*ArC*(4)), 140.9 (N(4)*ArC*(1)), 144.4 (*C*(2)), 160.6 (*C*(6)); *m*/*z* (APCI$^+$) 343 ([M+H]$^+$, 23%); HRMS (APCI$^+$) $C_{22}H_{19}N_2O_2^+$ ([M+H]$^+$) requires 343.1441; found 343.1438 (-0.9 ppm).

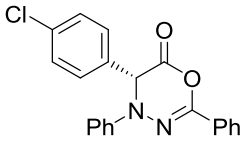
(5*R*)-5-(4-bromophenyl)-2,4-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one



(5*R*)-**332**

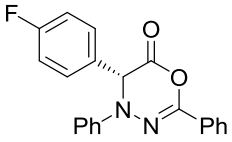
Following general procedure J, *p*-bromophenylacetic acid (64.5 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**332** as a white solid (64.9 mg, 80%); mp 38-40 °C; $[\alpha]_D^{20}$-572.0 (*c* 0.50, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 10.1 min, t_R(5*R*): 19.0 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3060, 2934 (C-H), 1789 (C=O), 1597, 1486; δ_H (300 MHz, $CDCl_3$) 5.92 (1H, s, C(5)*H*), 6.92-6.97 (1H, m, N(4)Ar(4)*H*), 7.13-7.18 (4H, m, Ar*H*), 7.22-7.28 (2H, m, Ar*H*), 7.33-7.37 (5H, m, Ar*H*), 7.86-7.89 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 59.1 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 122.1 (N(4)*ArC*(4)), 123.4 (C(5)*ArC*(4)), 125.6 (*ArC*), 128.4 (*ArC*), 128.6 (C(2)*ArC*(1)), 128.6 (*ArC*), 129.5 (*ArC*), 130.2 (C(5)*ArC*(1)), 130.5 (C(2)*ArC*(4)), 132.5 (*ArC*), 141.2 (N(4)*ArC*(1)), 144.0 (*C*(2)), 160.0 (*C*(6)); *m*/*z* (NSI$^+$) 439 ([M+CH_5O]$^+$, 95%); HRMS (NSI$^+$) $C_{22}H_{20}{}^{79}BrN_2O_3^+$ ([M+CH_5O]$^+$) requires 439.0652; found 439.0655 (+0.7 ppm).

(5*R*)-5-(4-chlorophenyl)-2,4-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one


(5*R*)-**333**

Following general procedure J, *p*-chlorophenylacetic acid (51.2 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**333** as a white solid (47.8 mg, 66%); mp 40-42 °C; $[\alpha]_D^{20}$-613.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 9.2 min, t_R(5*R*): 16.9 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 2933 (C-H), 1790 (C=O), 1598, 1490; δ_H (300 MHz, $CDCl_3$) 5.93 (1H, s, C(5)*H*), 6.93 (1H, t, *J* 7.2, N(4)Ar(4)*H*), 7.13-7.28 (8H, m, Ar*H*), 7.30-7.38 (3H, m, C(2)Ar(3,5)*H* and C(2)Ar(4)*H*), 7.84-7.90 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 59.0 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 122.1 (N(4)*ArC*(4)), 125.6 (*ArC*), 128.1 (*ArC*), 128.6 (*ArC*), 128.6 (*ArC*), 129.5 (*ArC*), 129.6 (*ArC*), 129.6 (*ArC*), 130.5 (C(2)*ArC*(4)), 135.2 (*ArC*), 141.2 (N(4)*ArC*(1)), 144.1 (*C*(2)), 160.1 (*C*(6)); *m*/*z* (NSI^+) 395 ($[M+CH_5O]^+$, 100%); HRMS (NSI^+) $C_{22}H_{20}{}^{35}ClN_2O_3^+$ ($[M+ CH_5O]^+$) requires 395.1157; found 395.1157 (+0.0 ppm).

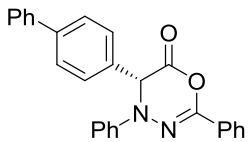
(5*R*)-5-(4-fluorophenyl)-2,4-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one


(5*R*)-**334**

Following general procedure J, *p*-fluorophenylacetic acid (46.2 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1.5:98.5) (5*R*)-**334** as a colourless oil (53.6 mg, 77%); $[\alpha]_D^{20}$-634.2 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 8.5 min, t_R(5*R*): 12.7 min, >99% *ee*; ν_{max} (thin film)/cm^{-1} 3063, 2928 (C-H), 1791 (C=O), 1597, 1506; δ_H (400 MHz,

$CDCl_3$) 5.94 (1H, s, C(5)*H*), 6.89-6.96 (3H, m, Ar*H*), 7.15-7.28 (2H, m, Ar*H*), 7.23-7.27 (4H, m, Ar*H*), 7.33-7.37 (3H, m, C(2)Ar(3,5)*H* and C(2)Ar(4)*H*), 7.87-7.90 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 58.9 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 116.4 (d, *J* 21.8, C(5)*ArC*(3,5)), 122.0 (N(4)*ArC*(4)), 125.6 (*ArC*), 126.9 (d, *J* 3.0, C(5)*ArC*(1)), 128.5 (*ArC*), 128.6 (*ArC*), 128.7 (C(2)*ArC*(1)), 129.4 (*ArC*), 130.4 (C(2)*ArC*(4)), 141.1 (N(4)*ArC*(1)), 144.1 (*C*(2)), 160.3 (*C*(6)), 163.1 (d, *J* 247, C(5)*ArC*(4)); *m*/*z* (NSI^+) 379 ($[M+CH_5O]^+$, 100%); HRMS (NSI^+) $C_{22}H_{20}FN_2O_3^+$ ($[M+ CH_5O]^+$) requires 379.1452; found 379.1454 (+0.4 ppm).

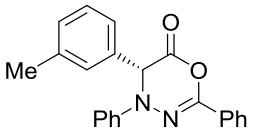
(5*R*)-5-([1,1'-biphenyl]-4-yl)-2,4-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one



(5*R*)-**335**

Following general procedure J, biphenylacetic acid (63.6 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**335** as a white solid (70.8 mg, 88%); mp 39-41 °C; $[\alpha]_D^{20}$-532.2 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 13.5 min, t_R(5*R*): 16.7 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3059, 2925 (C-H), 1790 (C=O), 1597, 1494; δ_H (400 MHz, $CDCl_3$) 6.01 (1H, s, C(5)*H*), 6.92-6.96 (1H, m, N(4)Ar(4)*H*), 7.20-7.37 (12H, m, Ar*H*), 7.40-7.44 (4H, m, Ar*H*), 7.90-7.92 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 59.3 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 121.9 (N(4)*ArC*(4)), 125.6 (*ArC*), 127.1 (*ArC*), 127.1 (*ArC*), 127.7 (*ArC*), 128.1 (*ArC*), 128.6 (*ArC*), 128.6 (C(2)*ArC*(1)), 128.8 (*ArC*), 129.4 (*ArC*), 130.1 (*ArC*), 130.3 (*ArC*), 140.1 (*ArC*), 141.1 (*C*(2)), 142.0 (*ArC*), 144.3 (*ArC*), 160.4 (*C*(6)); *m*/*z* ($APCI^+$) 405 ($[M+H]^+$, 100%); HRMS ($APCI^+$) $C_{27}H_{21}N_2O_2^+$ ($[M+H]^+$) requires 405.1598; found 405.1591 (-1.6 ppm).

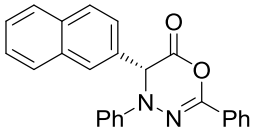
(5*R*)-2,4-diphenyl-5-(*m*-tolyl)-4*H*-1,3,4-oxadiazin-6(5*H*)-one



(5*R*)-**336**

Following general procedure J, *m*-tolylacetic acid (45.1 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**336** as a white solid (53.8 mg, 79%); mp 130-132 °C; $[\alpha]_D^{20}$-651.6 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 7.7 min, t_R(5*R*): 8.9 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3030, 2926 (C-H), 1789 (C=O), 1597, 1494; δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, CH_3), 5.91 (1H, s, C(5)*H*), 6.91 (1H, tt, *J* 7.2, 1.1, N(4)Ar(4)*H*), 7.00-7.03 (2H, m, Ar*H*), 7.06-7.11 (2H, m, Ar*H*), 7.14-7.17 (2H, m, Ar*H*), 7.21-7.26 (2H, m, Ar*H*), 7.31-7.35 (3H, m, C(2)Ar(3,5)*H* and C(2)Ar(4)*H*), 7.86-7.90 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 21.5 (*C*H_3), 59.5 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 121.8 (N(4)*ArC*(4)), 123.6 (*ArC*), 125.6 (*ArC*), 127.2 (*ArC*), 128.6 (*ArC*), 128.9 (C(2)*ArC*(1)), 129.2 (*ArC*), 129.4 (*ArC*), 129.9 (*ArC*), 130.2 (*ArC*), 131.2 (C(5)*ArC*(3)), 139.3 (C(5)*ArC*(1)), 140.9 (N(4)*ArC*(1)), 144.3 (*C*(2)), 160.5 (*C*(6)); *m*/*z* ($APCI^+$) 343 ($[M+H]^+$, 92%); HRMS ($APCI^+$) $C_{22}H_{19}N_2O_2^+$ ($[M+H]^+$) requires 343.1441; found 343.1438 (-0.9 ppm).

(5*R*)-5-(naphthalen-2-yl)-2,4-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one

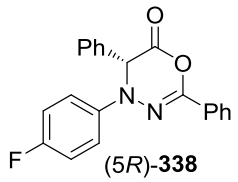


(5*R*)-**337**

Following general procedure J, 2-naphthylacetic acid (55.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**337** as a white solid (57.6 mg, 76%); mp 40-42 °C; $[\alpha]_D^{20}$-540.4 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 13.0 min, t_R(5*R*): 22.5

min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3058, 2935 (C-H), 1788 (C=O), 1596, 1494; δ_H (400 MHz, $CDCl_3$) 6.12 (1H, s, C(5)*H*), 6.90-6.94 (1H, m, N(4)Ar(4)*H*), 7.20-7.27 (4H, m, Ar*H*), 7.32-7.42 (6H, m, Ar*H*), 7.64-7.74 (4H, m, Ar*H*), 7.88-7.91 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 59.8 (*C*(5)), 114.6 (N(4)*ArC*(2,6)), 121.9 (N(4)*ArC*(4)), 123.7 (*ArC*), 125.6 (*ArC*), 126.2 (*ArC*), 126.7 (*ArC*), 126.8 (*ArC*), 127.7 (*ArC*), 128.2 (*ArC*), 128.6 (*ArC*), 128.6 (*ArC*), 128.8 (*ArC*), 129.4 (*ArC*), 129.5 (*ArC*), 130.3 (*ArC*), 133.2 (*ArC*), 133.4 (*ArC*), 141.1 (N(4)*ArC*(1)), 144.3 (*C*(2)), 160.4 (*C*(6)); *m*/*z* (APCI$^+$) 379 ([M+H]$^+$, 100%); HRMS (APCI$^+$) $C_{25}H_{19}N_2O_2^+$ ([M+H]$^+$) requires 379.1441; found 379.1433 (-2.1 ppm).

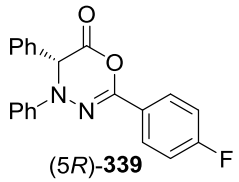
(5*R*)-4-(4-fluorophenyl)-2,5-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one



(5*R*)-**338**

Following general procedure J, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **579** (45.4 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**338** as a white solid (56.7 mg, 82%); mp 48-50 °C; $[\alpha]_D^{20}$-604.2 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 11.9 min, t_R(5*R*): 16.5 min, >99% *ee*; ν_{max} (thin film)/cm^{-1} 3062, 2924 (C-H), 1791 (C=O), 1600, 1506; δ_H (400 MHz, $CDCl_3$) 5.88 (1H, s, C(5)*H*), 6.90-6.95 (2H, m, N(4)Ar(2,6)*H*), 7.08-7.12 (2H, m, Ar*H*), 7.20-7.26 (5H, m, Ar*H*), 7.31-7.35 (3H, m, C(2)Ar(3,5)*H* and C(2)Ar(4)*H*), 7.85-7.87 (2H, m, C(2)Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 59.9 (*C*(5)), 116.0 (d, *J* 22.6, N(4)*ArC*(3,5)), 116.0 (d, *J* 7.7, N(4)*ArC*(2,6)), 125.6 (*ArC*), 126.7 (*ArC*), 128.6 (*ArC*), 128.7 (C(2)*ArC*(1)), 129.2 (*ArC*), 129.4 (*ArC*), 130.4 (*ArC*), 131.0 (C(5)*ArC*(1)), 140.7 (d, *J* 2.1, N(4)*ArC*(1)), 141.1 (*C*(2)), 158.4 (d, *J* 240, N(4)*ArC*(4)), 160.3 (*C*(6)); *m*/*z* (NSI$^+$) 379 ([M+CH_5O]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{20}FN_2O_3^+$ ([M+CH_5O]$^+$) requires 379.1452; found 379.1450 (-0.7 ppm).

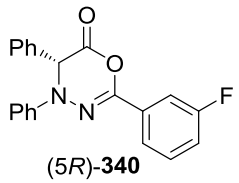
(5*R*)-2-(4-fluorophenyl)-4,5-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one



(5*R*)-**339**

Following general procedure J, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **580** (45.4 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**339** as a colourless oil (60.9 mg, 88%); $[\alpha]_D^{20}$-609.2 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 9.9 min, t_R(5*R*): 18.6 min, 99% *ee*; ν_{max} (thin film)/cm^{-1} 3064, 2920 (C-H), 1790 (C=O), 1597, 1496; δ_H (300 MHz, $CDCl_3$) 5.96 (1H, s, C(5)*H*), 6.89-6.94 (1H, m, N(4)Ar(4)*H*), 6.98-7.04 (2H, m, C(2)Ar(3,5)*H*), 7.13-7.17 (2H, m, Ar*H*), 7.20-7.28 (7H, m, Ar*H*), 7.83-7.89 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 59.5 (*C*(5)), 114.4 (N(4)*ArC*(2,6)), 115.8 (d, *J* 21.9, C(2)*ArC*(3,5)), 121.9 (N(4)*ArC*(4)), 125.0 (d, *J* 3.2, C(2)*ArC*(1)), 126.6 (*ArC*), 127.7 (d, *J* 8.4, C(2)*ArC*(2,6)), 129.1 (C(5)*ArC*(4)), 129.4 (*ArC*), 129.4 (*ArC*), 131.1 (C(5)*ArC*(1)), 140.4 (N(4)*ArC*(1)), 144.2 (*C*(2)), 160.2 (*C*(6)), 164.0 (d, *J* 250, C(2)*ArC*(4)); *m*/*z* (NSI^+) 379 ($[M+CH_5O]^+$, 100%); HRMS (NSI^+) $C_{22}H_{20}FN_2O_3^+$ ($[M+CH_5O]^+$) requires 379.1452; found 379.1456 (+0.9 ppm).

(5*R*)-2-(3-fluorophenyl)-4,5-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one

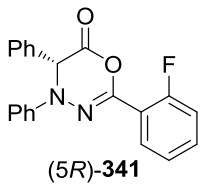


(5*R*)-**340**

Following general procedure J, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **581** (45.4 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**340** as a colourless oil (52.5 mg, 76%); $[\alpha]_D^{20}$-608.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 8.1 min, t_R(5*R*): 10.5 min, 99% *ee*; ν_{max}

(thin film)/cm^{-1} 3062 (C-H), 1792 (C=O), 1597, 1498; δ_H (400 MHz, $CDCl_3$) 5.96 (1H, s, C(5)*H*), 6.91-6.95 (1H, m, N(4)Ar(4)*H*), 7.02 (1H, tdd, *J* 8.3, 2.6, 0.9, C(2)Ar(4)*H*), 7.14-7.17 (2H, m, Ar*H*), 7.20-7.31 (8H, m, Ar*H*), 7.56-7.59 (1H, m, Ar*H*), 7.63-7.65 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 59.5 (*C*(5)), 112.6 (d, *J* 24.4, C(2)*ArC*(2)), 114.6 (N(4)*ArC*(2,6)), 117.2 (d, *J* 21.4, C(2)*ArC*(4)), 121.2 (d, *J* 2.7, C(2)*ArC*(6)), 122.2 (*ArC*), 126.6 (*ArC*), 129.2 (*ArC*), 129.4 (*ArC*), 129.4 (*ArC*), 130.2 (d, *J* 8.1, C(2)*ArC*(5)), 131.0 (d, *J* 5.6, C(2)*ArC*(1)), 131.0 (C(5)*ArC*(1)), 139.9 (N(4)*ArC*(1)), 144.1 (*C*(2)), 160.0 (*C*(6)), 162.9 (d, *J* 245, C(2)*ArC*(3)); *m*/*z* (NSI$^+$) 379 ([M+CH_5O]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{20}FN_2O_3^+$ ([M+CH_5O]$^+$) requires 379.1452; found 379.1456 (+0.9 ppm).

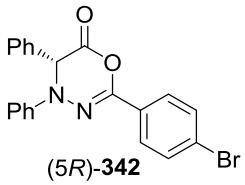
(5*R*)-2-(2-fluorophenyl)-4,5-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one



(5*R*)-**341**

Following general procedure J, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **582** (45.4 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**341** as a colourless oil (48.5 mg, 70%); $[\alpha]_D^{20}$-599.4 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 10.4 min, t_R(5*R*): 13.0 min, 99% *ee*; ν_{max} (thin film)/cm^{-1} 3064 (C-H), 2925, 1791 (C=O), 1597, 1495; δ_H (300 MHz, $CDCl_3$) 5.99 (1H, s, C(5)*H*), 6.92 (1H, tt, *J* 6.9, 1.4, N(4)Ar(4)*H*), 7.04-7.12 (2H, m, Ar*H*), 7.16-7.34 (10H, m, Ar*H*), 7.69 (1H, td, *J* 7.7, 1.7, C(2)Ar(6)*H*); δ_C (75 MHz, $CDCl_3$) 59.6 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 117.0 (d, *J* 28.8, C(2)*ArC*(3)), 117.3 (d, *J* 12.8, C(2)*ArC*(1)), 122.1 (N(4)*ArC*(4)), 124.1 (d, *J* 5.1, C(2)*ArC*(5)), 126.7 (N(4)*ArC*(3,5)), 128.7 (*ArC*), 129.1 (*ArC*), 129.4 (*ArC*), 129.4 (*ArC*), 131.1 (C(5)*ArC*(1)), 131.7 (d, *J* 11.2, C(2)*ArC*(4)), 137.7 (d, *J* 9.1, *C*(2)), 144.2 (N(4)*ArC*(1)), 160.2 (*C*(6)), 160.3 (d, *J* 342, C(2)*ArC*(2)); *m*/*z* (NSI$^+$) 379 ([M+CH_5O]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{20}FN_2O_3^+$ ([M+CH_5O]$^+$) requires 379.1452; found 379.1456 (+0.9 ppm).

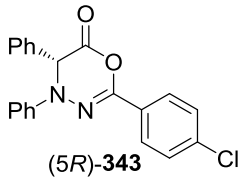
(5*R*)-2-(4-bromophenyl)-4,5-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one



(5*R*)-**342**

Following general procedure J, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **583** (57.8 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**342** as an off-white solid (63.3 mg, 78%); mp 44-46 °C; $[\alpha]_D^{20}$-609.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 12.8 min, t_R(5*R*): 24.1 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3062 (C-H), 1789 (C=O), 1597, 1497; δ_H (300 MHz, $CDCl_3$) 5.95 (1H, s, C(5)*H*), 6.89-6.95 (1H, m, N(4)Ar(4)*H*), 7.13-7.27 (9H, m, Ar*H*), 7.42-7.47 (2H, m, C(2)Ar(3,5)*H*), 7.70-7.75 (2H, m, C(2)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 59.5 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 122.1 (N(4)*ArC*(4)), 124.7 (*ArC*), 126.6 (*ArC*), 127.0 (*ArC*), 127.8 (*ArC*), 129.2 (C(5)*ArC*(4)), 129.4 (*ArC*), 129.4 (*ArC*), 131.0 (C(5)*ArC*(1)), 131.8 (*ArC*), 140.3 (N(4)*ArC*(1)), 144.1 (*C*(2)), 160.1 (*C*(6)); *m*/*z* (NSI^+) 439 ($[M+CH_5O]^+$, 100%); HRMS (NSI^+) $C_{22}H_{20}{}^{79}BrN_2O_3^+$ ($[M+CH_5O]^+$) requires 439.0652; found 439.0655 (+0.7 ppm).

(5*R*)-2-(4-chlorophenyl)-4,5-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one

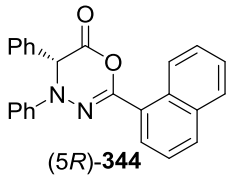


(5*R*)-**343**

Following general procedure J, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **584** (48.9 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**343** as an off-white solid (56.3 mg, 78%); mp 80-82 °C; $[\alpha]_D^{20}$-614.4 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 11.5 min, t_R(5*R*): 22.8 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 2966 (C-H), 1777 (C=O), 1595, 1497; δ_H (300 MHz,

$CDCl_3$) 5.95 (1H, s, C(5)*H*), 6.89-6.95 (1H, m, N(4)Ar(4)*H*), 7.13-7.32 (11H, m, Ar*H*), 7.77-7.82 (2H, m, C(2)Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 59.5 (*C*(5)), 114.5 (N(4)*ArC*(2,6)), 122.1 (N(4)*ArC*(4)), 126.6 (*ArC*), 126.8 (*ArC*), 127.3 (C(2)*ArC*(1)), 128.9 (*ArC*), 129.2 (C(5)*ArC*(4)), 129.4 (*ArC*), 129.4 (*ArC*), 131.1 (C(5)*ArC*(1)), 136.4 (C(2)*ArC*(4)), 140.2 (N(4)*ArC*(1)), 144.1 (*C*(2)), 160.1 (*C*(6)); *m*/*z* (NSI^+) 395 ($[M+CH_5O]^+$, 100%); HRMS (NSI^+) $C_{22}H_{20}ClN_2O_3^+$ ($[M+CH_5O]^+$) requires 395.1157; found 395.1158 (+0.3 ppm).

(5*R*)-2-(naphthalen-1-yl)-4,5-diphenyl-4*H*-1,3,4-oxadiazin-6(5*H*)-one



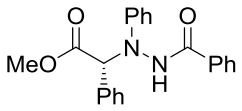
(5*R*)-**344**

Following general procedure J, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and *p*-methoxybenzoyl chloride (77.0 mg, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **585** (52.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 1:99) (5*R*)-**344** as an off-white solid (53.5 mg, 71%); mp 138-140 °C; $[\alpha]_D^{20}$-611.5 (*c* 1.0, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(5*S*): 15.7 min, t_R(5*R*): 16.9 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3063 (C-H), 1791 (C=O), 1599, 1506; δ_H (400 MHz, $CDCl_3$) 6.05 (1H, s, C(5)*H*), 6.93 (1H, tt, *J* 6.9, 1.4, N(4)Ar(4)*H*), 7.20-7.28 (7H, m, Ar*H*), 7.33-7.40 (3H, m, Ar*H*), 7.44 (1H, ddd, *J* 8.0, 6.9, 1.2, Ar*H*), 7.51 (1H, ddd, *J* 8.5, 6.9, 1.6, Ar*H*), 7.78-7.83 (2H, m, Ar*H*), 7.86 (1H, dd, *J* 7.4, 1.2, Ar*H*), 8.80-8.82 (1H, m, C(2)Ar(2)*H*); δ_C (75 MHz, $CDCl_3$) 59.5 (*C*(5)), 114.6 (N(4)*ArC*(2,6)), 122.1 (N(4)*ArC*(4)), 124.9 (*ArC*), 125.4 (*ArC*), 125.8 (*ArC*), 126.3 (*ArC*), 126.8 (*ArC*), 127.4 (*ArC*), 127.5 (*ArC*), 128.9 (*ArC*), 129.2 (*ArC*), 129.4 (*ArC*), 129.5 (*ArC*), 130.3 (*ArC*), 131.2 (*ArC*), 131.4 (*ArC*), 134.1 (*ArC*), 141.5 (N(4)*ArC*(1)), 144.5 (*C*(2)), 160.6 (*C*(6)); *m*/*z* (NSI^+) 397 ($[M+H_3O]^+$, 100%); HRMS (NSI^+) $C_{25}H_{21}N_2O_3^+$ ($[M+H_3O]^+$) requires 397.1547; found 397.1548 (+0.3 ppm).

General procedure K: *One-pot intermolecular Michael addition-lactonisation ring opening.*

To a solution of acid (1.5 eq) in CH_2Cl_2 (~1 mL per 0.2 mmol of acid) were added *i*-Pr_2NEt (1.5 eq based on acid) and benzoyl chloride (1.5 eq based on acid) at rt. The reaction mixture was allowed to stir at rt for 10 minutes. The requisite Lewis base (0.1-20 mol%), Michael acceptor (1 eq) and *i*-Pr_2NEt (1.5 eq) were then added at the required temperature in that order. The reaction mixture was stirred at the required temperature until complete by TLC. The required nucleophile was added and the reaction mixture was stirred at rt until ring-opening was complete by TLC. The reaction mixture was subsequently quenched by addition of HCl (1 M in H_2O). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture. Note: All racemic samples were obtained *via* this general procedure using DHPB **108** as catalyst.

(2*R*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-2-phenylacetate



(2*R*)-**321**

Following general procedure K, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent EtOAc:petrol 25:75) a rotameric mixture (ratio 91:9) of (2*R*)-**321** as a white solid (67.8 mg, 94%); mp 148-150 °C; $[\alpha]_D^{20}$-37.6 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 12.7 min, t_R(2*R*): 15.0 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3355 (N-H), 3075, 2950 (C-H), 1729 (C=O), 1687 (C=O), 1599; Data for major rotamer δ_H (300 MHz, $CDCl_3$) 3.74 (3H, s, CH_3), 5.82 (1H, s, C(2)*H*), 6.90-6.96 (3H, m, Ar*H*), 7.18-7.31 (7H, m, Ar*H*), 7.36-7.42 (3H, m, Ar*H*), 7.44-7.48 (2H, m, C(O)Ar(2,6)*H*), 8.43 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 52.5 (*C*H_3), 66.7 (*C*(2)), 114.8 (N*ArC*(2,6)), 121.7 (N*ArC*(4)), 127.0 (*ArC*), 128.6 (*ArC*), 128.6 (*ArC*), 128.9 (*ArC*), 129.1 (*ArC*), 129.5 (*ArC*), 131.8 (*ArC*), 133.0 (*ArC*), 133.3 (*ArC*), 148.4 (N*ArC*(1)), 166.6 (NH*C*=O), 173.1 (MeO*C*=O); Selected data for minor rotamer: δ_H (300 MHz, $CDCl_3$) 3.62 (3H, s, CH_3), 5.50 (1H, s, C(2)*H*), 7.90 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$)

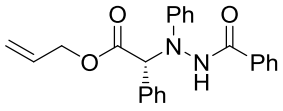
52.4 (*C*H_3), 68.0 (*C*(2)), 115.4 (N*ArC*(2,6)), 122.3 (N*ArC*(4)), 127.8 (*ArC*), 129.9 (*ArC*), 130.2 (*ArC*), 130.4 (*ArC*); *m*/*z* (NSI^+) 361 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{22}H_{21}N_2O_3^+$ ($[M+H]^+$) requires 361.1547; found 361.1546 (-0.2 ppm).

The same procedure using HBTM-2.1 (2*S*,3*R*)-**112** (0.31 mg, 0.001 mmol, 0.5 mol%) for 16 h at −78 °C gave (2*R*)-**321** as a white solid (61.0 mg, 85%), >99% ee.

The same procedure using HBTM-2.1 (2*S*,3*R*)-**112** (0.16 mg, 0.0005 mmol, 0.25 mol%) for 40 h at −78 °C gave (2*R*)-**321** as a white solid (60.0 mg, 83%), >99% ee.

The same procedure using HBTM-2.1 (2*S*,3*R*)-**112** (0.062 mg, 0.0002 mmol, 0.1 mol%) for 40 h at −78 °C gave (2*R*)-**321** as a white solid (43.0 mg, 60%), 99% ee. The conversion was determined to be 65% by analysis of the crude ^{1}H NMR.

(2*R*)-allyl 2-(2-benzoyl-1-phenylhydrazinyl)-2-phenylacetate

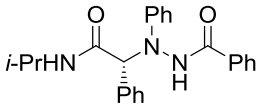


(2*R*)-**349**

Following general procedure K, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of allyl alcohol (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 40:60) a rotameric mixture (ratio 91:9) of (2*R*)-**349** as a colourless oil (63.8 mg, 83%); $[\alpha]_D^{20}$-30.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*): 18.1 min, t_R(2*S*): 21.8 min, 98% *ee*; ν_{max} (thin film)/cm^{-1} 3287 (N-H), 3064, 2948 (C-H), 1733 (C=O ester), 1683 (C=O amide), 1599; Data for major rotamer δ_H (500 MHz, $CDCl_3$) 4.75 (2H, d, *J* 5.1, C*H*$_2$), 5.26-5.32 (2H, m, C*H*$_2$=CH), 5.87-5.93 (2H, m, C(2)*H* and CH_2=C*H*), 6.98-7.06 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.31-7.43 (7H, m, Ar*H*), 7.48-7.59 (5H, m, Ar*H*), 8.51 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 66.2 (*C*H_2), 66.8 (*C*(2)), 114.9 (N*ArC*(2,6)), 119.6

(CH_2=CH), 121.7 (N*ArC*(4)), 127.0 (*ArC*), 128.6 (*ArC*), 128.6 (*ArC*), 128.9 (*ArC*), 129.1 (*ArC*), 129.4 (*ArC*), 131.2 (CH_2=*C*H), 131.7 (*ArC*), 133.0 (*ArC*), 133.2 (*ArC*), 148.3 (N*ArC*(1)), 166.5 (NH*C*=O), 172.3 (CH_2=CHCH$_2$*C*=O); Selected data for minor rotamer: δ_H (500 MHz, $CDCl_3$) 5.61 (1H, s, C(2)*H*), 7.98 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 65.8 (*C*H$_2$), 68.1 (*C*(2)), 115.4 (N*ArC*(2,6)), 122.3 (N*ArC*(4)), 127.8 (*ArC*), 129.8 (*ArC*), 130.2 (*ArC*); *m*/*z* (NSI$^+$) 387 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{24}H_{23}N_2O_3^+$ ([M+H]$^+$) requires 387.1703; found 387.1711 (+2.0 ppm).

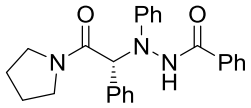
(2*R*)-2-(2-benzoyl-1-phenylhydrazinyl)-*N*-isopropyl-2-phenylacetamide



(2*R*)-**350**

Following general procedure K, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr$_2$NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr$_2$NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C followed by addition of isopropylamine (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et$_2$O:petrol 75:25) a rotameric mixture (ratio 93:7) of (2*R*)-**350** as a white solid (71.0 mg, 92%); mp 64-66 °C; $[\alpha]_D^{20}$-132 (*c* 0.125, CH_2Cl_2); Chiral HPLC Chiralpak IB (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 6.6 min, t_R(2*R*): 7.6 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3235 (N-H), 3064, 2971 (C-H), 1730 (C=O ester), 1653 (C=O amide), 1598; Data for major rotamer δ_H (500 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.6, C*H*$_3$), 1.21-1.26 (3H, m, C*H*$_3$), 4.13 (1H, s, *J* 6.5, C*H*), 5.29 (1H, s, C(2)*H*), 6.85 (2H, d, *J* 6.8, NAr(2,6)*H*), 7.00 (1H, t, *J* 7.3, NAr(4)*H*), 7.20-7.35 (11H, m, Ar*H*), 7.50 (1H, t, *J* 7.3, Ar*H*), 7.59 (1H, s, N*H*), 9.38 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 22.4 (*C*H$_3$), 22.5 (*C*H$_3$), 41.6 (*C*H), 72.0 (*C*(2)), 112.5 (N*ArC*(2,6)), 120.7 (N*ArC*(4)), 127.0 (*ArC*), 128.7 (*ArC*), 128.9 (*ArC*), 129.0 (*ArC*), 129.5 (*ArC*), 129.7 (*ArC*), 132.0 (*ArC*), 132.3 (*ArC*), 134.2 (*ArC*), 147.3 (N*ArC*(1)), 168.9 (*C*=O), 169.5 (*C*=O); Selected data for minor rotamer: δ_H (500 MHz, $CDCl_3$) 1.04 (6H, d, *J* 6.6, C*H*$_3$), 3.96-4.03 (1H, m, C*H*); δ_C (100 MHz, $CDCl_3$) 22.6 (*C*H$_3$), 41.5 (*C*H); *m*/*z* (NSI$^+$) 388 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{24}H_{26}N_3O_2^+$ ([M+H]$^+$) requires 388.2020; found 388.2027 (+1.9 ppm).

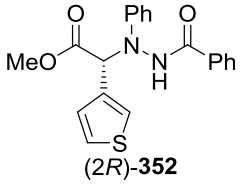
(2*R*)-*N*'-(2-oxo-1-phenyl-2-(pyrrolidin-1-yl)ethyl)-*N*'-phenylbenzohydrazide



(2*R*)-**351**

Following general procedure K, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of pyrrolidine (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O) a rotameric mixture (ratio 96:4) of (2*R*)-**351** as a colourless oil (69.7 mg, 87%); $[\alpha]_D^{20}$-96.6 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 6.3 min, t_R(2*R*): 11.1 min, 99% *ee*; ν_{max} (thin film)/cm^{-1} 3344 (N-H), 3063 (C-H), 1687 (C=O), 1582; Data for major rotamer δ_H (500 MHz, $CDCl_3$) 1.74-1.92 (4H, m, 2 C*H*$_2$), 3.07-3.10 (1H, m, C*H*H), 3.42-3.54 (3H, m, CH_2 and CH*H*), 5.77 (1H, s, C(2)*H*), 6.85-6.93 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.19-7.27 (7H, m, Ar*H*), 7.36 (1H, t, *J* 7.1, Ar*H*), 7.45 (2H, d, *J* 7.1, Ar*H*), 7.50 (2H, d, *J* 7.4, Ar*H*), 9.41 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 24.1 (*C*H_2), 26.1 (*C*H_2), 45.8 (N*C*H_2), 46.3 (N*C*H_2), 65.7 (*C*(2)), 114.9 (N*ArC*(2,6)), 121.4 (N*ArC*(4)), 127.1 (*ArC*), 128.4 (*ArC*), 128.7 (*ArC*), 128.8 (*ArC*), 129.4 (*ArC*), 129.5 (*ArC*), 131.5 (*ArC*), 133.2 (*ArC*), 133.4 (*ArC*), 149.2 (N*ArC*(1)), 166.4 (NH*C*=O), 170.7 (N*C*=O); Selected data for minor rotamer: δ_H (500 MHz, $CDCl_3$) 5.44 (1H, s, C(2)*H*), 8.65 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 23.9 (*C*H_2), 26.0 (*C*H_2), 67.7 (*C*(2)), 115.7 (N*ArC*(2,6)), 121.8 (N*ArC*(4)), 126.9 (*ArC*), 127.8 (*ArC*), 129.7 (*ArC*), 130.5 (*ArC*); *m*/*z* (NSI^+) 400 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{25}H_{26}N_3O_2^+$ ($[M+H]^+$) requires 400.2020; found 400.2026 (+1.6 ppm).

(2*R*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-2-(thiophen-3-yl)acetate

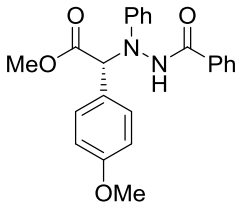


(2*R*)-**352**

Following general procedure K, thiophene-3-acetic acid (42.7 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of

MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent EtOAc:petrol 25:75) a rotameric mixture (ratio 91:9) of (2*R*)-**352** as a light yellow solid (63.1 mg, 86%); mp 128-130 °C; $[\alpha]_D^{20}$-26.2 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 28.0 min, t_R(2*R*): 31.5 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3355 (N-H), 3078, 2952 (C-H), 1727 (C=O ester), 1685 (C=O amide), 1600, 1514; Data for major rotamer δ_H (400 MHz, $CDCl_3$) 3.72 (3H, s, CH_3), 5.83 (1H, s, C(2)*H*), 6.87-6.95 (3H, m, Ar*H*), 7.16-7.23 (4H, m, Ar*H*), 7.28-7.33 (3H, m, Ar*H*), 7.38-7.42 (1H, m, Ar*H*), 7.49-7.51 (2H, m, C(O)Ar(2,6)*H*), 8.47 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.6 (*C*H_3), 62.7 (*C*(2)), 114.8 (N*ArC*(2,6)), 121.8 (N*ArC*(4)), 125.0 (*ArC*), 126.3 (*ArC*), 127.1 (*ArC*), 128.2 (*ArC*), 128.7 (*ArC*), 129.5 (*ArC*), 131.9 (*ArC*), 133.0 (*ArC*), 133.8 (*ArC*), 148.1 (N*ArC*(1)), 166.8 (NH*C*=O), 173.0 (MeO*C*=O); Selected data for minor rotamer: δ_H (400 MHz, $CDCl_3$) 3.59 (3H, s, CH_3), 5.56 (1H, s, C(2)*H*), 6.57 (1H, dd, *J* 5.0, 1.3, Ar*H*), 7.89 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 52.5 (*C*H_3), 62.8 (*C*(2)), 115.4 (N*ArC*(2,6)), 122.3 (N*ArC*(4)), 126.1 (*ArC*), 127.8 (*ArC*), 129.9 (*ArC*), 130.6 (*ArC*); *m*/*z* (NSI^+) 367 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{20}H_{19}N_2O_3S^+$ ($[M+H]^+$) requires 367.1111; found 367.1114 (+0.8 ppm).

(2*R*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-2-(4-methoxyphenyl)acetate

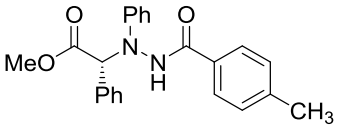


(2*R*)-**353**

Following general procedure K, 4-methoxyphenylacetic acid (49.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent EtOAc:petrol 30:70) a rotameric mixture (ratio 89:11) of (2*R*)-**353** as a light yellow solid (59.3 mg, 76%); mp 36-38 °C; $[\alpha]_D^{20}$-30.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 19.3 min, t_R(2*R*): 26.2 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3368 (N-H), 3060, 2952 (C-H), 1734 (C=O ester), 1675 (C=O amide), 1612, 1514; Data for major rotamer δ_H (300 MHz, $CDCl_3$)

3.66 (3H, s, CH_3), 3.71 (3H, s, CH_3), 5.75 (1H, s, C(2)*H*), 6.75-6.79 (2H, m, C(2)Ar(3,5)*H*), 6.85-6.95 (3H, m, Ar*H*), 7.18-7.24 (2H, m, Ar*H*), 7.26-7.34 (4H, m, Ar*H*), 7.36-7.42 (1H, m, Ar*H*), 7.48-7.52 (2H, m, C(O)Ar(2,6)*H*), 8.43 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.5 (*C*H_3), 55.2 (*C*H_3), 66.1 (*C*(2)), 114.0 (*ArC*), 114.8 (*ArC*), 121.6 (N*ArC*(4)), 125.2 (C(2)*ArC*(1)), 127.1 (*ArC*), 128.6 (*ArC*), 129.5 (*ArC*), 130.4 (*ArC*), 131.8 (C(O)*ArC*(4)), 133.0 (C(O)*ArC*(1)), 148.4 (N*ArC*(1)), 159.9 (C(2)*ArC*(4)), 166.6 (NH*C*=O), 173.3 (MeO*C*=O); Selected data for minor rotamer: δ_H (300 MHz, $CDCl_3$) 3.60 (3H, s, CH_3), 3.71 (3H, s, CH_3), 5.45 (1H, s, C(2)*H*), 6.56-6.59 (2H, m, C(2)Ar(3,5)*H*), 7.85 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.4 (*C*H_3), 55.4 (*C*H_3), 67.2 (*C*(2)), 115.3 (*ArC*), 122.2 (N*ArC*(4)), 127.8 (*ArC*), 129.9 (*ArC*), 131.4 (C(O)*ArC*(4)); *m*/*z* (NSI^+) 391 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{23}H_{23}N_2O_4^+$ ($[M+H]^+$) requires 391.1652; found 391.1655 (+0.7 ppm).

(2*R*)-methyl 2-(2-(4-methylbenzoyl)-1-phenylhydrazinyl)-2-phenylacetate

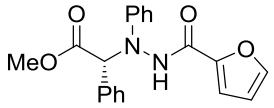


(2*R*)-**354**

Following general procedure K, phenylacetic acid (81.7 mg, 0.60 mmol), *i*-Pr_2NEt (156 μL, 0.90 mmol) and benzoyl chloride (104 μL, 0.90 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **587** (44.8 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 40:60) a rotameric mixture (ratio 92:8) of (2*R*)-**354** as a white solid (49.2 mg, 66%); mp 36-38 °C; $[\alpha]_D^{20}$-24.3 (*c* 1.0, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 11.9 min, t_R(2*R*): 14.3 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3374 (N-H), 3030, 2924 (C-H), 1750 (C=O ester), 1708 (C=O amide), 1599; Data for major rotamer δ_H (400 MHz, $CDCl_3$) 2.28 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 5.80 (1H, s, C(2)*H*), 6.86-6.95 (3H, m, Ar*H*), 7.08 (2H, d, *J* 7.9, Ar*H*), 7.19-7.27 (5H, m, Ar*H*), 7.34-7.39 (4H, m, Ar*H*), 8.40 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 21.5 (*C*H_3), 52.5 (O*C*H_3), 66.7 (*C*(2)), 114.8 (N*ArC*(2,6)), 121.6 (N*ArC*(4)), 127.1 (*ArC*), 128.6 (*ArC*), 128.9 (C(2)*ArC*(4)), 129.1 (*ArC*), 129.2 (*ArC*), 129.5 (*ArC*), 130.0 (C(O)*ArC*(1)), 133.3 (C(2)*ArC*(1)), 142.3 (C(O)*ArC*(4)), 148.5 (N*ArC*(1)), 166.5 (NH*C*=O), 173.1 (MeO*C*=O); Selected data for minor rotamer: δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s, CH_3),

3.61 (3H, s, OCH_3), 5.51 (1H, s, C(2)*H*), 6.70-6.80 (2H, m, Ar*H*), 7.84 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 22.7 (*C*H_3), 52.4 (O*C*H_3), 68.0 (*C*(2)), 115.4 (N*ArC*(2,6)), 122.2 (N*ArC*(4)), 127.8 (*ArC*), 128.0 (*ArC*), 129.8 (*ArC*), 130.2 (*ArC*); *m*/*z* (NSI^+) 375 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{23}H_{23}N_2O_3^+$ ($[M+H]^+$) requires 375.1703; found 375.1706 (+0.7 ppm).

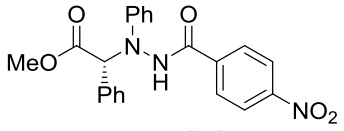
(2*R*)-methyl 2-(2-(furan-2-carbonyl)-1-phenylhydrazinyl)-2-phenylacetate



(2*R*)-**355**

Following general procedure K, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **588** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 93:7) of (2*R*)-**355** as a white solid (59.5 mg, 85%); mp 148-150 °C; $[\alpha]_D^{20}$-38.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 16.2 min, t_R(2*R*): 21.5 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3345 (N-H), 3097, 2950 (C-H), 1729 (C=O ester), 1695 (C=O amide), 1598; Data for major rotamer δ_H (300 MHz, $CDCl_3$) 3.72 (3H, s, OCH_3), 5.77 (1H, s, C(2)*H*), 6.36 (1H, dd, *J* 3.5, 1.8, C(O)Ar(4)*H*), 6.86-6.96 (4H, m, Ar*H*), 7.18-7.24 (5H, m, Ar*H*), 7.34-7.38 (3H, m, Ar*H*), 8.67 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.5 (O*C*H_3), 66.7 (*C*(2)), 112.0 (C(O)*ArC*(4)), 115.0 (N*ArC*(2,6)), 115.5 (C(O)*ArC*(3)), 121.8 (N*ArC*(4)), 128.6 (*ArC*), 128.9 (*ArC*), 129.2 (*ArC*), 129.4 (*ArC*), 133.1 (C(2)*ArC*(1)), 144.4 (C(O)*ArC*(5)), 146.6 (*ArC*), 148.4 (*ArC*), 157.2 (NH*C*=O), 172.7 (MeO*C*=O); Selected data for minor rotamer: δ_H (300 MHz, $CDCl_3$) 3.65 (3H, s, OCH_3), 5.65 (1H, s, C(2)*H*), 6.14 (1H, dd, *J* 3.5, 1.7, C(O)Ar(4)*H*), 7.82 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.5 (*C*H_3), 67.6 (*C*(2)), 112.0 (*ArC*), 115.2 (*ArC*), 117.2 (*ArC*), 122.4 (*ArC*), 128.5 (*ArC*), 129.8 (*ArC*), 130.0 (*ArC*), 144.9 (*ArC*); *m*/*z* (NSI^+) 351 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{20}H_{19}N_2O_4^+$ ($[M+H]^+$) requires 351.1339; found 351.1339 (-0.1 ppm).

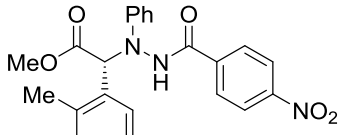
(2*R*)-methyl 2-(2-(4-nitrobenzoyl)-1-phenylhydrazinyl)-2-phenylacetate



(2*R*)-**356**

Following general procedure K, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **367** (51.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 69:31) of (2*R*)-**356** as a light yellow solid (67.8 mg, 84%); mp 58-56 °C; $[\alpha]_D^{20}$-47.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 20.9 min, t_R(2*R*): 30.6 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3412 (N-H), 3075, 2953 (C-H), 1735 (C=O ester), 1678 (C=O amide), 1599, 1525 (N=O), 1346 (N=O); Data for major rotamer δ_H (300 MHz, $CDCl_3$) 3.74 (3H, s, OC*H*$_3$), 5.81 (1H, s, C(2)*H*), 6.91-6.95 (3H, m, Ar*H*), 7.21-7.28 (5H, m, Ar*H*), 7.35-7.39 (2H, m, Ar*H*), 7.55-7.58 (2H, m, C(O)Ar(2,6)*H*), 8.10-8.13 (2H, m, C(O)Ar(3,5)*H*), 8.62 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.6 (O*C*H$_3$), 66.8 (*C*(2)), 114.9 (N*ArC*(2,6)), 122.1 (N*ArC*(4)), 123.8 (*ArC*), 128.3 (*ArC*), 128.7 (*ArC*), 129.1 (*ArC*), 129.1 (*ArC*), 129.6 (*ArC*), 133.1 (*ArC*), 138.5 (*ArC*), 148.0 (*ArC*), 148.6 (*ArC*), 164.8 (NH*C*=O), 173.1 (MeO*C*=O); Selected data for minor rotamer: δ_H (300 MHz, $CDCl_3$) 3.61 (3H, s, OC*H*$_3$), 5.46 (1H, s, C(2)*H*), 7.77-7.80 (2H, m, C(O)Ar(3,5)*H*), 8.12 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.6 (O*C*H$_3$), 68.4 (*C*(2)), 115.8 (N*ArC*(2,6)), 122.3 (N*ArC*(4)), 123.0 (*ArC*), 128.6 (*ArC*), 128.9 (*ArC*), 130.1 (*ArC*), 130.3 (*ArC*), 132.4 (*ArC*), 138.6 (*ArC*), 149.7 (*ArC*), 171.4 (NH*C*=O), 171.5 (MeO*C*=O); *m*/*z* (NSI^+) 406 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{22}H_{20}N_3O_5^+$ ($[M+H]^+$) requires 406.1397; found 406.1399 (+0.4 ppm).

(2*R*)-methyl 2-(2-(4-nitrobenzoyl)-1-phenylhydrazinyl)-2-(*o*-tolyl)acetate

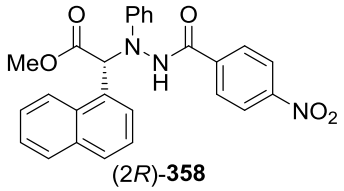


(2*R*)-**357**

Following general procedure K, *o*-tolylacetic acid (45.1 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-

2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **367** (51.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 55:45) of (2*R*)-**357** as a light yellow solid (67.7 mg, 81%); mp 56-58 °C; $[\alpha]_D^{20}$-30.0 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak IA (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 11.7 min, t_R(2*R*): 16.1 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3333 (N-H), 3085, 2962 (C-H), 1721 (C=O ester), 1679 (C=O amide), 1598, 1529 (N=O), 1348 (N=O); Data for both rotamers δ_H (400 MHz, $CDCl_3$) 1.69 (3H, s, C*H*$_3$), 2.53 (3H, s, C*H*$_3$), 3.60 (3H, s, OC*H*$_3$), 3.73 (3H, s, OC*H*$_3$), 5.64 (1H, s, C(2)*H*), 5.91 (1H, s, C(2)*H*), 6.74-6.76 (1H, m, Ar*H*), 6.82-6.85 (2H, m, NAr(2,6)*H*), 6.90-7.07 (7H, m, Ar*H*), 7.12-7.21 (6H, m, Ar*H*), 7.23-7.27 (2H, m, Ar*H*), 7.36-7.40 (2H, m, Ar*H*), 7.55-7.58 (2H, m, C(O)Ar(2,6)*H*), 7.79-7.82 (2H, m, C(O)Ar(3,5)*H*), 8.10-8.13 (2H, m, C(O)Ar(3,5)*H*), 8.18 (1H, s, N*H*), 8.50 (1H, s, N*H*); Data for both rotamers δ_C (100 MHz, $CDCl_3$) 18.5 (*C*H_3), 19.2 (*C*H_3), 52.5 (O*C*H_3), 52.6 (O*C*H_3), 63.8 (*C*(2)), 65.2 (*C*(2)), 114.3 (N*ArC*(2,6)), 115.5 (N*ArC*(2,6)), 121.7 (*ArC*), 122.3 (*ArC*), 123.0 (*ArC*), 123.8 (*ArC*), 125.5 (*ArC*), 126.7 (*ArC*), 127.7 (*ArC*), 128.2 (*ArC*), 128.4 (*ArC*), 129.3 (*ArC*), 129.6 (*ArC*), 129.7 (*ArC*), 129.9 (*ArC*), 130.2 (*ArC*), 130.8 (*ArC*), 130.8 (*ArC*), 131.2 (*ArC*), 131.3 (*ArC*), 138.2 (*ArC*), 138.6 (*ArC*), 138.7 (*ArC*), 139.8 (*ArC*), 148.0 (*ArC*), 148.6 (*ArC*), 14.8.8 (*ArC*), 149.7 (*ArC*), 164.7 (*C*=O), 171.7 (C=O), 171.9 (C=O), 173.6 (*C*=O); *m*/*z* (NSI^+) 442 ($[M+Na]^+$, 42%); HRMS (NSI^+) $C_{23}H_{21}N_3NaO_5^+$ ($[M+Na]^+$) requires 442.1373; found 442.1375 (+0.4 ppm).

(2*R*)-methyl 2-(naphthalen-1-yl)-2-(2-(4-nitrobenzoyl)-1-phenylhydrazinyl)acetate

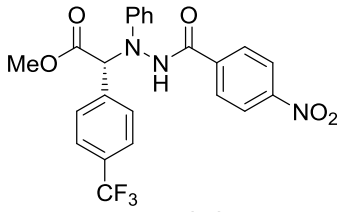


(2*R*)-**358**

Following general procedure K, 1-naphthylacetic acid (55.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **367** (51.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 78:22) of (2*R*)-**358** as a light yellow solid

(72.0 mg, 79%); mp 74-76 °C; $[\alpha]_D^{20}$+20.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 13.2 min, t_R(2*R*): 29.0 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3415 (N-H), 3062, 2953 (C-H), 1735 (C=O ester), 1670 (C=O amide), 1599, 1522 (N=O), 1344 (N=O); Data for major rotamer δ_H (400 MHz, $CDCl_3$) 3.66 (3H, s, OCH_3), 6.30 (1H, s, C(2)*H*), 6.53-6.56 (2H, m, Ar*H*), 6.96-7.00 (1H, m, Ar*H*), 7.10 (1H, t, *J* 7.3, Ar*H*), 7.16-7.19 (1H, m, Ar*H*), 7.23-7.32 (6H, m, Ar*H*), 7.41-7.47 (3H, m, Ar*H*), 7.59 (1H, d, *J* 8.1, Ar*H*), 7.75-7.79 (1H, m, Ar*H*), 8.16 (1H, s, N*H*); Data for both rotamers δ_C (100 MHz, $CDCl_3$) 52.7 (O*C*H_3), 52.7 (O*C*H_3), 63.5 (*C*(2)), 63.9 (*C*(2)), 114.5 (*ArC*), 115.0 (*ArC*), 122.0 (*ArC*), 122.1 (N*ArC*(2,6)), 122.1 (N*ArC*(2,6)), 122.9 (*ArC*), 123.7 (*ArC*), 123.7 (*ArC*), 124.3 (*ArC*), 125.3 (*ArC*), 125.8 (*ArC*), 126.2 (*ArC*), 126.6 (*ArC*), 126.8 (*ArC*), 127.3 (*ArC*), 127.4 (*ArC*), 127.4 (*ArC*), 128.2 (*ArC*), 128.5 (*ArC*), 128.7 (*ArC*), 128.7 (*ArC*), 129.3 (*ArC*), 129.8 (*ArC*), 130.4 (*ArC*), 130.4 (*ArC*), 130.5 (*ArC*), 131.7 (*ArC*), 132.3 (*ArC*), 133.6 (*ArC*), 133.8 (*ArC*), 137.5 (*ArC*), 138.5 (*ArC*), 148.0 (*ArC*), 148.0 (*ArC*), 148.5 (*ArC*), 149.6 (*ArC*), 164.3 (*C*=O), 171.6 (C=O), 172.0 (C=O), 173.5 (*C*=O); Selected data for minor rotamer δ_H(400 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 6,52 (1H, s, C(2)*H*), 7.03-7.05 (2H, m, Ar*H*), 8.04-8.07 (2H, m, Ar*H*), 8.18 (1H, d, *J* 8.7, Ar*H*), 8.57 (1H, s, N*H*); *m*/*z* (NSI^+) 478 ($[M+Na]^+$, 97%); HRMS (NSI^+) $C_{26}H_{21}N_3NaO_5^+$ ($[M+Na]^+$) requires 478.1373; found 478.1377 (+0.7 ppm).

(2*R*)-methyl 2-(2-(4-nitrobenzoyl)-1-phenylhydrazinyl)-2-(4-(trifluoromethyl)phenyl)acetate

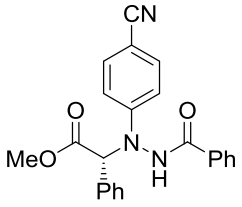


(2*R*)-**359**

Following general procedure K, 4-trifluoromethylphenylacetic acid (61.3 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **367** (51.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 74:26) of (2*R*)-**359** as a

light yellow solid (78.5 mg, 83%); mp 150-152 °C; $[\alpha]_D^{20}$-26.6 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (80% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 40 °C) t_R(2*S*): 7.5 min, t_R(2*R*): 17.8 min, 97% *ee*; ν_{max} (KBr)/cm^{-1} 3412 (N-H), 3085, 2956 (C-H), 1735 (C=O ester), 1680 (C=O amide), 1600, 1524 (N=O), 1323 (N=O); Data for major rotamer δ_H (400 MHz, $CDCl_3$) 3.77 (3H, s, OC*H*$_3$), 5.83 (1H, s, C(2)*H*), 6.93-6.97 (2H, m, Ar*H*), 7.23-7.28 (2H, m, Ar*H*), 7.34-7.41 (1H, m, Ar*H*), 7.52 (4H, s, Ar*H*), 7.58-7.61 (2H, m, C(O)Ar(2,6)*H*), 8.11-8.15 (2H, m, C(O)Ar(3,5)*H*), 8.71 (1H, s, N*H*); Data for both rotamers δ_C (100 MHz, $CDCl_3$) 52.8 (O*C*H$_3$), 52.9 (O*C*H$_3$), 66.4 (*C*(2)), 67.9 (*C*(2)), 115.1 (N*ArC*(2,6)), 115.8 (N*ArC*(2,6)), 122.4 (*ArC*), 122.6 (*ArC*), 123.4 (*ArC*), 123.9 (*ArC*), 125.1 (*ArC*), 125.6 (q, *J* 3.6, *ArC*), 125.7 (q, *J* 3.6, *ArC*), 128.2 (*ArC*), 128.6 (*ArC*), 129.4 (*ArC*), 129.7 (*ArC*), 130.2 (*ArC*), 130.6 (*ArC*), 131.0 (*ArC*), 131.3 (*ArC*), 136.4 (*ArC*), 137.3 (*ArC*), 138.1 (*ArC*), 147.7 (*ArC*), 148.2 (*ArC*), 148.8 (*ArC*), 149.9 (*ArC*), 164.6 (*C*=O), 170.7 (C=O), 171.1 (C=O), 172.5 (*C*=O); Selected data for minor rotamer: δ_H (400 MHz, $CDCl_3$) 3.65 (3H, s, OC*H*$_3$), 5.12 (1H, s, C(2)*H*), 6.90-6.92 (2H, m, Ar*H*), 7.03-7.10 (3H, m, Ar*H*), 7.15-7.18 (2H, m, Ar*H*), 7.78-7.81 (2H, m, C(O)Ar(3,5)*H*), 8.17 (1H, s, N*H*); *m*/*z* (NSI^+) 396 ($[M+Na]^+$, 65%); HRMS (NSI^+) $C_{23}H_{18}F_3N_3NaO_5^+$ ($[M+Na]^+$) requires 496.1091; found 496.1094 (+0.7 ppm). Note: Enantiomeric excess was 92% when methanolysis carried out at rt. When the product is re-subjected to the reaction conditions at rt the ee drops with time.

(2*R*)-methyl 2-(2-benzoyl-1-(4-(cyano)phenyl)hydrazinyl)-2-phenylacetate

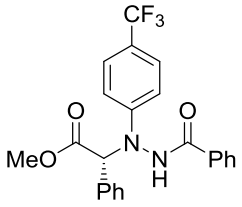


(2*R*)-**360**

Following general procedure K, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **591** (47.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 60:40) a rotameric mixture (ratio 94:6) of (2*R*)-**360** as a white solid (71.5 mg, 93%); mp 72-74 °C; $[\alpha]_D^{20}$-46.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (80%

IPA:hexane, flow rate 1 mL min^{-1}, 254 nm, 40 °C) t_R(2*R*): 5.8 min, t_R(2*S*): 12.9 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3412 (N-H), 2954 (C-H), 2220 (C≡N), 1748 (C=O amide), 1684 (C=O ester), 1604, 1508; Data for major rotamer δ_H (300 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 5.83 (1H, s, C(2)*H*), 6.89-6.94 (2H, m, NAr(2,6)*H*), 7.21-7.49 (12H, m, Ar*H*), 8.37 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.9 (O*C*H_3), 66.4 (*C*(2)), 103.7 (N*ArC*(4)), 114.1 (N*ArC*(2,6)), 119.4 (*C*≡N), 127.0 (*ArC*), 128.7 (*ArC*), 128.8 (*ArC*), 129.3 (*ArC*), 129.4 (*ArC*), 132.0 (*ArC*), 132.1 (*ArC*), 132.2 (*ArC*), 133.8 (*ArC*), 151.5 (N*ArC*(1)), 166.4 (NH*C*=O), 172.2 (MeO*C*=O); Selected data for minor rotamer: δ_H (300 MHz, $CDCl_3$) 3.65 (3H, s, OCH_3), 5.56 (1H, s, C(2)*H*), 6.78 (2H, dd, *J* 8.2, 1.0, NAr(2,6)*H*), 7.81 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.9 (*C*H_3), 67.5 (*C*(2)), 115.2 (*ArC*), 127.3 (*ArC*), 127.5 (*ArC*), 130.4 (*ArC*), 134.2 (*ArC*); *m*/*z* (NSI^+) 386 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{23}H_{20}N_3O_3^+$ ($[M+H]^+$) requires 386.1499; found 386.1502 (+0.7 ppm). Note: Enantiomeric excess was 91% when methanolysis carried out at rt. When the product is re-treated with *i*-Pr_2NEt at rt the ee drops with time.

(2*R*)-methyl 2-(2-benzoyl-1-(4-(trifluoromethyl)phenyl)hydrazinyl)-2-phenylacetate

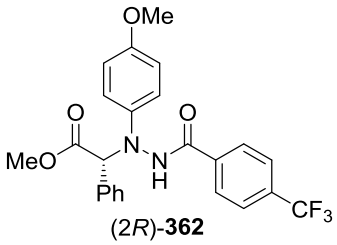


(2*R*)-**361**

Following general procedure K, phenylacetic acid (0.20 g, 1.50 mmol), *i*-Pr_2NEt (0.39 mL, 2.25 mmol) and benzoyl chloride (0.26 mL, 2.25 mmol) in CH_2Cl_2 (10 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.08 mg, 0.01 mmol, 1 mol%), diazene **594** (0.28 g, 1.00 mmol) and *i*-Pr_2NEt (0.26 mL, 1.50 mmol) for 16 h at −78 °C followed by addition of MeOH (10 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 30:70) a rotameric mixture (ratio 94:6) of (2*R*)-**361** as a white solid (0.34 g, 86%); mp 120-122 °C; $[\alpha]_D^{20}$-48.6 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (30% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*): 9.0 min, t_R(2*S*): 15.5 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3392 (N-H), 2952 (C-H), 1738 (C=O etser), 1682 (C=O amide), 1616; Data for major rotamer δ_H (300 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 5.97 (1H, s, C(2)*H*), 7.07 (2H, d, *J* 8.6, NAr(2,6)*H*), 7.32-7.38 (5H, m, Ar*H*), 7.47-7.58 (7H, m, Ar*H*), 8.67 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.7 (O*C*H_3), 66.8 (*C*(2)), 114.0

(N*ArC*(2,6)), 122.8 (q, *J* 32.9, N*ArC*(4)), 124.5 (q, *J* 269, *C*F_3), 126.8 (q, *J* 3.5, N*ArC*(3,5)), 127.1 (*ArC*), 128.7 (*ArC*), 128.7 (*ArC*), 129.2 (*ArC*), 129.3 (*ArC*), 132.1 (*ArC*), 132.4 (*ArC*), 132.7 (*ArC*), 151.0 (N*ArC*(1)), 166.6 (NH*C*=O), 172.4 (MeO*C*=O); Selected data for minor rotamer: δ_H (300 MHz, $CDCl_3$) 3.72 (3H, s, OCH_3), 5.70 (1H, s, C(2)*H*), 8.04 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 52.7 (O*C*H_3), 67.8 (*C*(2)), 114.9 (N*ArC*(2,6)), 127.3 (*ArC*), 127.7 (*ArC*), 130.3 (*ArC*), 130.8 (*ArC*); *m*/*z* (NSI^+) 429 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{23}H_{20}F_3N_2O_3^+$ ($[M+H]^+$) requires 429.1421; found 429.1422 (+0.3 ppm).

(2*R*)-methyl 2-(1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)benzoyl)hydrazinyl)-2-phenylacetate



(2*R*)-**362**

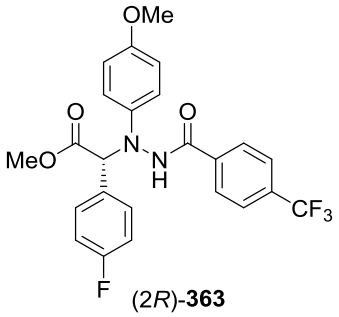
Following general procedure K, phenylacetic acid (40.9 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **595** (61.6 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 76:24) of (2*R*)-**362** as a light yellow oil (68.8 mg, 75%); $[\alpha]_D^{20}$-34.6 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (50% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*): 19.0 min, t_R(2*S*): 34.7 min, 99% *ee*; ν_{max} (thin film)/cm^{-1} 3283 (N-H), 2955 (C-H), 1737 (C=O ester), 1674 (C=O amide), 1511; Data for major rotamer δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 5.69 (1H, s, C(2)*H*), 6.77-6.79 (2H, m, NAr(2,6)*H*), 6.93-6.95 (2H, m, NAr(3,5)*H*), 7.07-7.11 (1H, m, Ar*H*), 7.21-7.28 (3H, m, Ar*H*), 7.37-7.39 (1H, m, Ar*H*), 7.54 (4H, m, Ar*H*), 8.63 (1H, s, N*H*); Data for both rotamers δ_C (100 MHz, $CDCl_3$) 52.4 (O*C*H_3), 52.5 (O*C*H_3) 55.6 (O*C*H_3), 55.6 (O*C*H_3), 67.7 (*C*(2)), 69.3 (*C*(2)), 114.7 (N*ArC*(2,6)), 115.1 (N*ArC*(2,6)), 117.3 (N*ArC*(3,5)), 117.7 (N*ArC*(3,5)), 124.0 (q, *J* 3.8, C(O)*ArC*(3,5)), 125.6 (q, *J* 3.5, C(O)*ArC*(3,5)), 127.5 (*ArC*), 128.1 (*ArC*), 128.7 (*ArC*), 128.8 (*ArC*), 128.9 (*ArC*), 129.0 (*ArC*), 129.0 (*ArC*), 130.0 (*ArC*), 131.7 (*ArC*), 132.6 (*ArC*), 133.2 (*ArC*), 133.5 (*ArC*), 136.2 (*ArC*), 136.4 (*ArC*), 142.0 (N*ArC*(1)), 142.4 (N*ArC*(1)), 155.2

(N*ArC*(4)), 158.9 (N*ArC*(4)), 165.3 (*C*=O), 171.6 (*C*=O), 172.3 (*C*=O), 173.3 (*C*=O); Selected data for minor rotamer: δ_H (400 MHz, $CDCl_3$) 3.60 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 5.32 (1H, s, C(2)*H*), 6.87-6.92 (2H, m, Ar*H*), 8.15 (1H, s, N*H*); *m*/*z* (NSI^+) 459 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{24}H_{22}F_3N_2O_4^+$ ($[M+H]^+$) requires 459.1526; found 459.1520 (-1.3 ppm).

Scale-up:

Following general procedure K, phenylacetic acid (1.33 g, 9.74 mmol), *i*-Pr_2NEt (2.53 mL, 14.6 mmol) and benzoyl chloride (1.70 mL, 14.6 mmol) in CH_2Cl_2 (40 mL), HBTM-2.1 (2*S*,3*R*)-**112** (20.0 mg, 0.065 mmol, 1 mol%), diazene **595** (2.00 g, 6.49 mmol) and *i*-Pr_2NEt (1.69 mL, 9.74 mmol) for 16 h at –78 °C rt followed by addition of MeOH (10 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 76:24) of (2*R*)-**362** as a light yellow oil (2.83 g, 95%); 99% *ee*.

(2*R*)-methyl 2-(4-fluorophenyl)-2-(1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)benzoyl)hydrazinyl)acetate

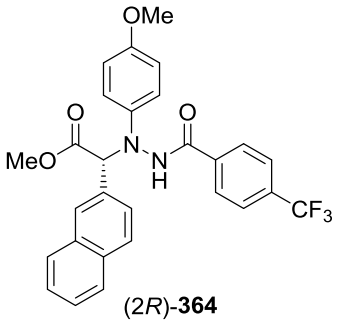


(2*R*)-**363**

Following general procedure K, 4-fluorophenylacetic acid (0.23 g, 1.50 mmol), *i*-Pr_2NEt (0.39 mL, 2.25 mmol) and benzoyl chloride (0.26 mL, 2.25 mmol) in CH_2Cl_2 (10 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.08 mg, 0.01 mmol, 1 mol%), diazene **595** (0.31 g, 1.00 mmol) and *i*-Pr_2NEt (0.26 mL, 1.50 mmol) for 16 h at –78 °C followed by addition of MeOH (10 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 40:60) a rotameric mixture (ratio 79:21) of (2*R*)-**363** as a white solid (0.38 g, 79%); mp 68-70 °C; $[\alpha]_D^{20}$-43.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (50% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 17.0 min, t_R(2*R*): 26.4 min, 99% *ee*; ν_{max} (KBr)/cm^{-1} 3363 (N-H), 2956 (C-H), 1741 (C=O ester), 1674 (C=O amide), 1513; Data for major rotamer δ_H (400 MHz, $CDCl_3$) 3.75 (3H, s, OCH_3), 3.78

(3H, s, OCH_3), 5.77 (1H, s, C(2)*H*), 6.86 (2H, d, *J* 9.0, Ar*H*), 6.98-7.05 (4H, m, Ar*H*), 7.47 (2H, dd, *J* 8.4, 5.3, Ar*H*), 7.59 (2H, d, *J* 8.2, Ar*H*), 7.66 (2H, d, *J* 8.2, Ar*H*), 8.96 (1H, s, N*H*); Data for both rotamers δ_C (75 MHz, $CDCl_3$) 52.4 (OCH_3), 52.5 (OCH_3), 55.4 (OCH_3), 55.5 (OCH_3), 67.1 (*C*(2)), 68.5 (*C*(2)), 114.7 (*ArC*), 115.1 (*ArC*), 115.7 (d, *J* 21.7, C(2)*ArC*(3,5)), 115.7 (d, *J* 21.7, C(2)*ArC*(3,5)), 117.6 (*ArC*), 117.7 (*ArC*), 123.6 (q, *J* 271, *C*F_3), 123.6 (q, *J* 271, *C*F_3), 124.0 (q, *J* 3.5, C(O)*ArC*(3,5)), 125.6 (q, *J* 3.6, C(O)*ArC*(3,5)), 127.6 (*ArC*), 128.2 (*ArC*), 128.7 (d, *J* 3.2, C(2)*ArC*(1)), 129.6 (d, *J* 3.2, C(2)*ArC*(1)), 130.8 (d, *J* 8.3, C(2)*ArC*(2,6)), 131.9 (d, *J* 8.5, C(2)*ArC*(2,6)), 133.4 (q, *J* 32.5, C(O)*ArC*(4)), 133.4 (q, *J* 32.5, C(O)*ArC*(4)), 136.2 (*ArC*), 136.2 (*ArC*), 141.9 (*ArC*), 142.1 (*ArC*), 155.3 (*ArC*), 155.7 (*ArC*), 162.8 (d, *J* 247, C(2)*ArC*(4)), 162.8 (d, *J* 248 C(2)*ArC*(4)), 165.4 (*C*=O), 171.7 (*C*=O), 172.0 (*C*=O), 172.9 (*C*=O); Selected data for minor rotamer: δ_H (400 MHz, $CDCl_3$) 3.68 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.43 (1H, s, C(2)*H*), 7.19 (2H, d, *J* 9.0 Ar*H*), 7.36 (2H, d, *J* 8.1, Ar*H*), 8.29 (1H, s, N*H*); *m*/*z* (NSI^+) 477 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{24}H_{21}F_4N_2O_4^+$ ($[M+H]^+$) requires 477.1432; found 477.1420 (-2.5 ppm).

(2*R*)-methyl 2-(1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)benzoyl)hydrazinyl)-2-(naphthalen-2-yl)acetate

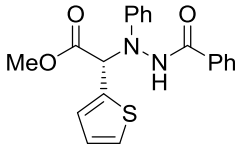


(2*R*)-**364**

Following general procedure K, 2-naphthylacetic acid (0.28 g, 1.50 mmol), *i*-Pr_2NEt (0.39 mL, 2.25 mmol) and benzoyl chloride (0.26 mL, 2.25 mmol) in CH_2Cl_2 (10 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.08 mg, 0.01 mmol, 1 mol%), diazene **595** (0.31 mg, 1.00 mmol) and *i*-Pr_2NEt (0.26 mL, 1.50 mmol) for 16 h at −78 °C followed by addition of MeOH (10 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 45:55) a rotameric mixture (ratio 70:30) of (2*R*)-**364** as a light yellow solid (0.41 g, 80%); mp 74-76 °C; $[\alpha]_D^{20}$-75.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*S*): 12.5 min, t_R(2*R*): 14.5 min, 98% *ee*; ν_{max} (KBr)/cm^{-1} 3414 (N-H), 2954 (C-H), 1735 (C=O ester), 1670 (C=O

amide), 1510; Data for major rotamer δ_H (300 MHz, $CDCl_3$) 3.79 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.03 (1H, s, C(2)*H*), 6.92 (2H, d, *J* 9.0, Ar*H*), 7.16 (2H, d, *J* 9.1, Ar*H*), 7.48-7.59 (6H, m, Ar*H*), 7.73-7.93 (5H, m, Ar*H*), 9.07 (1H, s, N*H*); Data for both rotamers δ_C (75 MHz, $CDCl_3$) 52.5 (O*C*H_3), 52.6 (O*C*H_3), 55.5 (O*C*H_3), 55.6 (O*C*H_3), 68.1 (*C*(2)), 69.2 (*C*(2)), 114.7 (*ArC*), 115.2 (*ArC*), 117.6 (*ArC*), 117.8 (*ArC*), 123.8 (q, *J* 3.5, C(O)*ArC*(3,5)), 125.5 (q, *J* 3.6, C(O)*ArC*(3,5)), 126.5 (*ArC*), 126.6 (*ArC*), 126.7 (*ArC*), 126.7 (*ArC*), 126.7 (*ArC*), 126.8 (*ArC*), 127.2 (*ArC*), 127.5 (*ArC*), 127.8 (*ArC*), 127.9 (*ArC*), 128.1 (*ArC*), 128.2 (*ArC*), 128.2 (*ArC*), 128.4 (*ArC*), 128.6 (*ArC*), 129.9 (*ArC*), 130.1 (*ArC*), 131.3 (*ArC*), 133.0 (*ArC*), 133.1 (*ArC*), 133.3 (*ArC*), 133.4 (*ArC*), 136.0 (*ArC*), 136.4 (*ArC*), 142.2 (*ArC*), 142.4 (*ArC*), 155.3 (*ArC*), 155.6 (*ArC*), 165.5 (*C*=O), 171.7 (*C*=O), 172.1 (*C*=O), 173.1 (*C*=O); Selected data for minor rotamer: δ_H (300 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.68 (1H, s, C(2)*H*), 6.77 (2H, d, *J* 8.1 Ar*H*), 7.04 (2H, d, *J* 9.0, Ar*H*), 7.29 (2H, d, *J* 9.0, Ar*H*), 7.66 (2H, d, *J* 8.3, Ar*H*), 8.42 (1H, s, N*H*); *m*/*z* (NSI^+) 509 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{28}H_{24}F_3N_2O_4^+$ ($[M+H]^+$) requires 509.1683; found 509.1680 (-0.5 ppm).

(2*S*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-2-(thiophen-2-yl)acetate

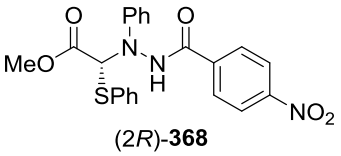


(2*S*)-**366**

Following general procedure K, thiophene-2-acetic acid (42.7 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at –78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent EtOAc:petrol 25:75) a rotameric mixture (ratio 92:8) of (2*S*)-**366** as a light yellow solid (59.8 mg, 82%); mp 116-118 °C; $[\alpha]_D^{20}$-12.0 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak IB (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(2*R*): 16.5 min, t_R(2*S*): 19.7 min, 54% *ee*; ν_{max} (KBr)/cm^{-1} 3346 (N-H), 3066, 2952 (C-H), 1729 (C=O ester), 1685 (C=O amide), 1599; Data for major rotamer δ_H (300 MHz, $CDCl_3$) 3.72 (3H, s, CH_3), 5.98 (1H, s, C(2)*H*), 6.85-6.96 (4H, m, Ar*H*), 7.09 (1H, d, *J* 3.5, Ar*H*), 7.18-7.24 (3H, m, Ar*H*), 7.31-7.36 (2H, m, Ar*H*), 7.40-7.45 (1H, m, Ar*H*), 7.60-7.63 (2H, m, C(O)Ar(2,6)*H*), 8.54 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 52.8 (*C*H_3), 62.3 (*C*(2)), 115.1

(N*ArC*(2,6)), 122.0 (N*ArC*(4)), 126.7 (*ArC*), 127.3 (*ArC*), 127.3 (*ArC*), 127.4 (*ArC*), 128.7 (*ArC*), 129.5 (*ArC*), 132.0 (*ArC*), 132.8 (C(O)*ArC*(1)), 135.0 (C(2)*ArC*(2)), 147.8 (N*ArC*(1)), 166.7 (NH*C*=O), 172.2 (MeO*C*=O); Selected data for minor rotamer δ_H (300 MHz, $CDCl_3$) 3.60 (3H, s, CH_3), 5.65 (1H, s, C(2)*H*), 7.94 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 52.7 (*C*H_3), 62.5 (*C*(2)), 115.6 (N*ArC*(2,6)), 122.5 (N*ArC*(4)), 127.1 (*ArC*), 127.8 (*ArC*), 128.0 (*ArC*), 129.9 (*ArC*), 130.1 (*ArC*), 130.6 (*ArC*); *m*/*z* (NSI^+) 367 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{20}H_{19}N_2O_3S^+$ ($[M+H]^+$) requires 367.1111; found 367.1115 (+1.1 ppm).

(2*R*)-methyl 2-(2-(4-nitrobenzoyl)-1-phenylhydrazinyl)-2-(phenylthio)acetate

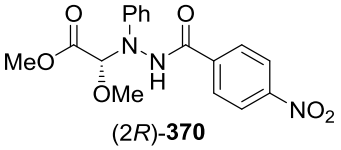


(2*R*)-**368**

Following general procedure K, (phenylthio)acetic acid (50.5 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (0.62 mg, 0.002 mmol, 1 mol%), diazene **367** (51.0 mg, 0.20 mmol) and *i*-Pr_2NEt (52.0 μL, 0.30 mmol) for 16 h at −78 °C followed by addition of MeOH (2 mL) and stirring for 1 h at −78 °C gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 87:13) of (2*R*)-**368** as an orange oil (72.7 mg, 83%); $[\alpha]_D^{20}$+5.0 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak IA (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*R*): 13.1 min, t_R(2*S*): 20.2 min, 98% *ee*; ν_{max} (ATR)/cm^{-1} 3269 (N-H), 3061, 2953 (C-H), 1736 (C=O ester), 1682 (C=O amide), 1597, 1523 (N=O), 1348 (N=O); Data for major rotamer δ_H (300 MHz, $CDCl_3$) 3.70 (3H, s, OCH_3), 5.69 (1H, s, C(2)*H*), 6.82-6.91 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.13-7.25 (5H, m, Ar*H*), 7.60-7.64 (2H, m, Ar*H*), 7.95-8.00 (2H, m, C(O)Ar(2,6)*H*), 8.22-8.25 (2H, m, C(O)Ar(3,5)*H*), 8.81 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 53.1 (O*C*H_3), 72.1 (*C*(2)), 115.7 (N*ArC*(2,6)), 122.7 (N*ArC*(4)), 124.0 (C(O)*ArC*(3,5)), 128.8 (*ArC*), 129.1 (*ArC*), 129.4 (*ArC*), 129.5 (*ArC*), 132.6 (C(2)*ArC*(1)), 133.7 (C(2)*ArC*(4)), 138.6 (C(O)*ArC*(1)), 146.8 (*ArC*), 150.0 (*ArC*), 165.2 (NH*C*=O), 169.7 (MeO*C*=O); Selected data for minor rotamer: δ_H (300 MHz, $CDCl_3$) 3.57 (3H, s, OCH_3), 5.60 (1H, s, C(2)*H*), 7.50 (2H, d, *J* 8.8, Ar*H*), 7.83 (2H, d, *J* 8.8, Ar*H*), 8.17 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 53.1 (O*C*H_3), 72.3 (*C*(2)), 116.4 (N*ArC*(2,6)), 122.8 (N*ArC*(4)), 123.8 (C(O)*ArC*(3,5)), 127.3 (*ArC*), 127.8 (*ArC*), 130.2 (*ArC*), 139.4 (C(O)*ArC*(1)), 147.5

(*ArC*), 168.6 (NH*C*=O), 172.4 (MeO*C*=O); *m*/*z* (ES^+) 460 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{22}H_{19}N_3NaO_5S^+$ ($[M+Na]^+$) requires 460.0943; found 460.0932 (-2.4 ppm).

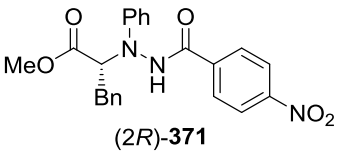
(2*R*)-methyl 2-methoxy-2-(2-(4-nitrobenzoyl)-1-phenylhydrazinyl)acetate



(2*R*)-**370**

Following general procedure K, methoxyacetic acid (23.0 μL, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.16 mg, 0.02 mmol, 10 mol%), diazene **367** (51.0 mg, 0.20 mmol) and PS-BEMP (~2.2 mmol/g, 0.23 g, 0.5 mmol) for 16 h at rt followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 70:30) a rotameric mixture (ratio 95:5) of (2*R*)-**370** as an orange solid (38.7 mg, 54%); mp 122-124 °C; $[\alpha]_D^{20}$+15.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 22.4 min, t_R(2*R*): 24.7 min, 83% *ee*; ν_{max} (ATR)/cm^{-1} 3278 (N-H), 3071, 2960 (C-H), 1748 (C=O ester), 1676 (C=O amide), 1597, 1525 (N=O), 1346 (N=O); Data for major rotamer δ_H (400 MHz, $CDCl_3$) 3.56 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 5.28 (1H, s, C(2)*H*), 6.93-7.00 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.22-7.26 (2H, m, NAr(3,5)*H*), 7.93-7.96 (2H, m, C(O)Ar(2,6)*H*), 8.21-8.24 (2H, m, C(O)Ar(3,5)*H*), 8.41 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 53.0 (OCH_3), 57.5 (OCH_3), 89.3 (*C*(2)), 115.8 (N*ArC*(2,6)), 122.8 (N*ArC*(3,5)), 124.0 (C(O)*ArC*(3,5)), 128.7 (*ArC*), 129.5 (*ArC*), 138.4 (C(O)*ArC*(1)), 146.2 (*ArC*), 150.0 (*ArC*), 165.2 (NH*C*=O), 168.3 (MeO*C*=O); Selected data for minor rotamer δ_H (400 MHz, $CDCl_3$) 3.45 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 4.93 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 53.4 (OCH_3), 90.7 (*C*(2)), 114.0 (*ArC*(2)), 121.9 (*ArC*(4)), 127.3 (*ArC*); *m*/*z* (ES^+) 382 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{17}H_{17}N_3NaO_6^+$ ($[M+Na]^+$) requires 382.1015; found 382.1023 (+2.0 ppm).

(2*R*)-methyl 2-(2-(4-benzoyl)-1-phenylhydrazinyl)-3-phenylpropanoate



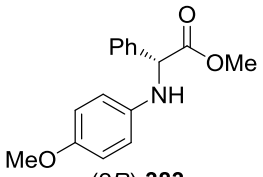
(2*R*)-**371**

Following general procedure K, 3-phenylpropionic acid (45.1 mg, 0.30 mmol), *i*-Pr_2NEt (78.0 μL, 0.45 mmol) and benzoyl chloride (52.2 μL, 0.45 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.16 mg, 0.02 mmol, 10 mol%), diazene **367** (51.0 mg, 0.20 mmol) and PS-BEMP (~2.2 mmol/g, 227 mg, 0.5 mmol) for 16 h at rt followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 40:60) a rotameric mixture (ratio 90:10) of (2*R*)-**371** as a light yellow solid (51.8 mg, 62%); mp 42-44 °C; $[\alpha]_D^{20}$-28.4 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (40% IPA:hexane, flow rate 1 $mLmin^{-1}$, 211 nm, 30 °C) t_R(2*R*): 9.8 min, t_R(2*S*): 18.1 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3279 (N-H), 3065, 2943 (C-H), 1728 (C=O ester), 1686 (C=O amide), 1597, 1522 (N=O), 1344 (N=O); Data for major rotamer δ_H (400 MHz, $CDCl_3$) 3.10 (1H, dd, *J* 13.6, 8.2, C*H*H), 3.39 (1H, dd, *J* 13.6, 6.1, CH*H*), 3.52 (3H, s, OCH_3), 4.71 (1H, dd, *J* 8.2, 6.1, C(2)*H*), 6.83-6.92 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.16-7.26 (7H, m, Ar*H*), 7.99-8.02 (2H, m, C(O)Ar(2,6)*H*), 8.26-8.29 (2H, m, C(O)Ar(3,5)*H*), 8.86 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 37.1 (CH_2), 52.1 (OCH_3), 65.2 (*C*(2)), 115.3 (N*ArC*(2,6)), 122.3 (N*ArC*(4)), 124.1 (C(O)*ArC*(3,5)), 127.2 (C(2)*ArC*(4)), 128.6 (*ArC*), 128.7 (*ArC*), 129.2 (*ArC*), 129.5 (*ArC*), 136.5 (*ArC*), 138.2 (*ArC*), 147.9 (*ArC*), 150.1 (*ArC*), 164.8 (NH*C*=O), 174.2 (MeO*C*=O); Selected data for minor rotamer: δ_H (400 MHz, $CDCl_3$) 3.47 (3H, s, OCH_3), 7.42 (2H, d, *J* 8.9, Ar*H*), 8.20 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 35.6 (CH_2), 52.1 (OCH_3), 66.3 (*C*(2)), 116.4 (N*ArC*(2,6)), 122.8 (N*ArC*(4)), 128.2 (*ArC*), 128.5 (*ArC*), 130.0 (*ArC*); *m*/*z* (ES^+) 442 ($[M+Na]^+$, 100%); HRMS (ES^+) $C_{23}H_{21}N_3NaO_5^+$ ($[M+Na]^+$) requires 442.1379; found 442.1363 (-3.6 ppm).

General procedure L: *Samarium iodide N-N bond cleavage.*

To a solution of hydrazide (1 eq) in MeOH was added SmI_2 (0.1 M in THF, 3 eq) and the reaction mixture was allowed to stir at −78 °C for 10 minutes. The reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with ethyl acetate (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture. Note: All racemic samples for HPLC analysis were obtained *via* the same general procedure using racemic hydrazide products.

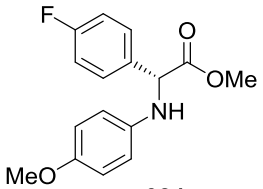
(2*R*)-methyl 2-((4-methoxyphenyl)amino)-2-phenylacetate



(2*R*)-**383**

Following general procedure L, ester (2*R*)-**362** (0.23 g, 0.50 mmol) and SmI_2 (0.1 M in THF, 15.0 mL, 1.50 mmol) in MeOH (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 20:80) (2*R*)-**383** as a white solid (112 mg, 83%); mp 104-106 °C; {lit.[199] mp 107-108 °C}; $[\alpha]_D^{20}$-99.2 (*c* 0.125, $CHCl_3$); {lit.[119] $[\alpha]_D^{20}$+97.6 (c 1.29 in $CHCl_3$) for a 98% ee sample (2*S*)-configuration}; Chiral HPLC Chiralcel OJ-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm, 30 °C) t_R(2*R*): 28.1 min, t_R(2*S*): 30.9 min, 99% *ee*; δ_H (300 MHz, $CDCl_3$) 3.73 (3H, s, OC*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 4.69 (1H, br s, N*H*), 5.05 (1H, s, C(2)*H*), 6.54-6.59 (2H, m, Ar*H*), 6.72-6.76 (2H, m, Ar*H*), 7.33-7.41 (3H, m, Ar*H*), 7.50-7.53 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[200] Note: Enantiomeric excess was 91% when reaction carried out at rt.

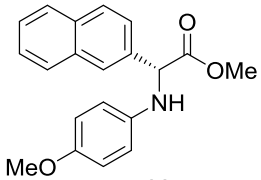
(2*R*)-methyl 2-(4-fluorophenyl)-2-((4-methoxyphenyl)amino)acetate



(2*R*)-**384**

Following general procedure L, ester (2*R*)-**363** (0.24 g, 0.50 mmol) and SmI_2 (0.1 M in THF, 15.0 mL, 1.50 mmol) in MeOH (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 25:75) (2*R*)-**384** as a light yellow solid (110 mg, 76%); mp 102-104 °C; {lit.[199] mp 99-100 °C}; $[\alpha]_D^{20}$-86.8 (*c* 0.25, CH_2Cl_2); {lit.[119] $[\alpha]_D^{20}$+70.4 (c 1.40 in $CHCl_3$) for a 93% ee sample (2*S*)-configuration}; Chiral HPLC Chiralpak AD-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 13.7 min, t_R(2*R*): 15.9 min, 98% *ee*; δ_H (300 MHz, $CDCl_3$) 3.64 (3H, s, OC*H*$_3$), 3.66 (3H, s, OC*H*$_3$), 4.60 (1H, br s, N*H*), 4.92 (1H, s, C(2)*H*), 6.42-6.45 (2H, m, Ar*H*), 6.64-6.67 (2H, m, Ar*H*), 6.94-7.00 (2H, m, C(2)Ar(3,5)*H*), 7.37-7.42 (2H, m, C(2)Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[119]

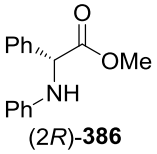
(2*R*)-methyl 2-((4-methoxyphenyl)amino)-2-(naphthalen-2-yl)acetate



(2*R*)-**385**

Following general procedure L, ester (2*R*)-**364** (0.25 g, 0.50 mmol) and SmI_2 (0.1 M in THF, 15.0 mL, 1.50 mmol) in MeOH (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 25:75) (2*R*)-**385** as a colourless oil (131 mg, 82%); $[\alpha]_D^{20}$-180.4 (*c* 0.25, CH_2Cl_2); {lit.[119] $[\alpha]_D^{20}$+130.6 (c 1.60 in $CHCl_3$) for a 97% ee sample (2*S*)-configuration}; Chiral HPLC Chiralcel OJ-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm, 30 °C) t_R(2*R*): 30.4 min, t_R(2*S*): 33.0 min, 98% *ee*; δ_H (300 MHz, $CDCl_3$) 3.59 (3H, s, OC*H*$_3$), 3.62 (3H, s, OC*H*$_3$), 4.73 (1H, br s, N*H*), 5.09 (1H, s, C(2)*H*), 6.47-6.51 (2H, m, Ar*H*), 6.59-6.65 (2H, m, Ar*H*), 7.36-7.41 (2H, m, Ar*H*), 7.51 (1H, dd, *J* 8.6, 1.8, Ar*H*), 7.71-7.76 (3H, m, Ar*H*), 7.87 (1H, s, C(2)Ar(1)*H*). Spectroscopic data are in accordance with the literature.[119]

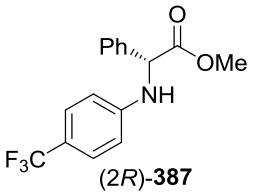
(2*R*)-methyl 2-phenyl-2-(phenylamino)acetate



(2*R*)-**386**

Following general procedure L, ester (2*R*)-**321** (0.18 g, 0.50 mmol) and SmI_2 (0.1 M in THF, 15.0 mL, 1.50 mmol) in MeOH (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 25:75) (2*R*)-**386** as a white solid (110 mg, 91%); mp 73-74 °C; {lit.[201] mp 79-80 °C}; $[\alpha]_D^{20}$-51.5 (*c* 0.2, CH_2Cl_2); {lit.[119] $[\alpha]_D^{20}$+49.9 (c 0.9 in $CHCl_3$) for a 97% ee sample (2*S*)-configuration}; Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 23.7 min, t_R(2*R*): 26.1 min, 99% *ee*; δ_H (300 MHz, $CDCl_3$) 3.63 (3H, s, OC*H*$_3$), 4.87 (1H, d, *J* 5.7, N*H*), 5.00 (1H, d, *J* 5.9, C(2)*H*), 6.47 (2H, dd, *J* 8.6, 0.9, NAr(2,6)*H*), 6.58-6.64 (1H, m, NAr(4)*H*), 7.00-7.06 (2H, m, NAr(3,5)*H*), 7.21-7.29 (3H, m, C(2)Ar(3,5)*H* and C(2)Ar(4), 7.39-7.43 (2H, m, C(2)Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[119]

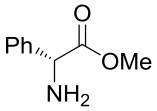
(2*R*)-methyl 2-phenyl-2-((4-(trifluoromethyl)phenyl)amino)acetate



(2*R*)-**387**

Following general procedure L, ester (2*R*)-**361** (0.21 g, 0.50 mmol) and SmI_2 (0.1 M in THF, 15.0 mL, 1.50 mmol) in MeOH (5 mL) gave, after chromatographic purification (eluent Et_2O:petrol 25:75) (2*R*)-**387** as a colourless oil (117 mg, 76%); $[\alpha]_D^{20}$-98.0 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*R*): 13.6 min, t_R(2*S*): 14.7 min, 98% *ee*; δ_H (300 MHz, $CDCl_3$) 3.66 (3H, s, OC*H*$_3$), 5.01 (1H, d, *J* 5.7, C(2)*H*), 5.28 (1H, d, *J* 5.5, N*H*), 6.47 (2H, d, *J* 8.5, NAr(2,6)*H*), 7.23-7.31 (5H, m, Ar*H*), 7.37-7.40 (2H, m, C(2)Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[202]

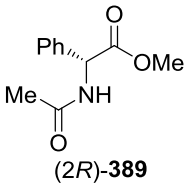
(2*R*)-methyl 2-amino-2-phenylacetate



(2*R*)-**388**

To a solution of PMP protected amine (2*R*)-**383** (34.5 mg, 0.13 mmol) in MeCN:H_2O (1:1, 10 mL) was added periodic acid (28.9 mg, 0.13 mmol) and H_2SO_4 (1 M in H_2O, 0.13 mL, 0.13 mmol) and the reaction mixture was allowed to stir for 16 h at rt. The reaction mixture was washed with CH_2Cl_2. The aqueous layer was retained, basified with sat. aq. $NaHCO_3$ and extracted with ethyl acetate (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give (2*R*)-**388** as a yellow oil (9.8 mg, 47%); $[\alpha]_D^{20}$-192 (*c* 0.025, CH_2Cl_2); {lit.[102(c)] $[\alpha]_D^{20}$+202.3 (c 0.49 in CH_2Cl_2) for a 91% ee sample (2*S*)-configuration}; δ_H (300 MHz, $CDCl_3$) 1.97 (2H, br s, N*H*$_2$), 3.63 (3H, s, OC*H*$_3$), 4.55 (1H, s, C(2)*H*), 7.23-7.30 (5H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[102(c)]

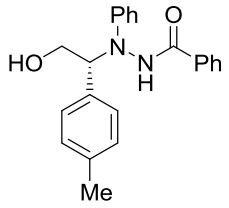
(2*R*)-methyl 2-acetamido-2-phenylacetate



(2*R*)-**389**

To a solution of amine (2*R*)-**388** (6.0 mg, 0.036 mmol) and Et_3N (5.58 μL, 0.04 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added acetic anhydride (3.78 μL, 0.04 mmol) and the reaction mixture was stirred at rt for 30 minutes. The reaction mixture was washed several times with H_2O and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give acylated amine (2*R*)-**389** as a yellow oil (6.8 mg, 90%); $[\alpha]_D^{20}$-188 (*c* 0.05, CH_2Cl_2); {lit.[203] $[\alpha]_D^{20}$-36 (c 1.00 in $CHCl_3$) for a 24% ee sample (2*R*)-configuration}; Chiral HPLC Chiralcel OJ-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 16.1 min, t_R(2*R*): 17.9 min, 90% *ee*; δ_H (300 MHz, $CDCl_3$) 1.97 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 5.52 (1H, d, *J* 7.3, C(2)*H*), 6.42 (1H, br s, N*H*), 7.27-7.29 (5H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[120(c)]

(1*R*)-*N*'-(2-hydroxy-1-(*p*-tolyl)ethyl)-*N*'-phenylbenzohydrazide



(1*R*)-**390**

To a solution of (2*R*)-**331** (33.9 mg, 0.10 mmol) in THF (1 mL) was added $LiAlH_4$ (2M in THF, 0.5 mL, 1.0 mmol) and the reaction mixture was allowed to stir at rt for 10 minutes. The reaction mixture was quenched by addition of sat. aq. NH_4Cl and extracted with Et_2O (x 3). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 60:40) gave (1*R*)-**390** as a white solid (33.6 mg, 97%); mp 148-150 °C; $[\alpha]_D^{20}$-73.2 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (30% IPA:hexane, flow rate 1 mL min^{-1}, 254 nm, 30 °C) t_R(1*R*): 7.4 min, t_R(1*S*): 10.7 min, >99% *ee*; ν_{max} (KBr)/cm^{-1} 3551 (O-H), 3412 (N-H), 2933 (C-H), 1662 (C=O), 1597, 1497; δ_H (500 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 3.78 (1H, td, *J* 11.7, 3.6, C(2)*H*H), 3.94 (1H, t, *J* 10.5, C(2)H*H*), 4.61 (1H, br s, O*H*), 5.18 (1H, d, *J* 7.2, C(1)*H*)), 6.82 (1H, t, *J* 7.3, NAr(4)*H*), 6.94 (2H, d, *J* 8.1, NAr(2,6)*H*), 7.02-7.05 (4H, m, Ar*H*), 7.17-7.20 (2H, m, Ar*H*), 7.41 (2H, t, *J* 7.6, C(O)Ar(3,5)*H*), 7.51 (1H, t, *J* 7.4, C(O)Ar(4)*H*), 7.74 (2H, d, *J* 7.6, C(O)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 21.1 (*C*H_3), 61.2 (*C*(2)), 65.2 (*C*(1)), 114.2 (N*ArC*(2,6)), 120.6 (N*ArC*(4)), 127.3 (*ArC*), 127.5 (*ArC*), 129.0 (*ArC*), 129.5 (*ArC*), 129.7 (*ArC*), 131.8 (*ArC*), 132.4 (*ArC*), 132.7 (C(O)*ArC*(4)),

138.3 (C(1)*ArC*(1)), 148.6 (N*ArC*(1)), 168.7 (*C*=O); *m*/*z* (NSI^+) 347 ($[M+H]^+$, 35%); HRMS (NSI^+) $C_{22}H_{23}N_2O_2^+$ ($[M+H]^+$) requires 347.1754; found 347.1760 (+1.7 ppm).

9.4.2 References and Notes

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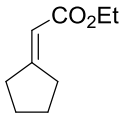
9.5 Experimental for Chapter 5

9.5.1 Experimental Procedures and Characterisation Data

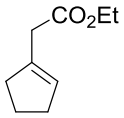
ethyl 2-cyclopentylideneacetate



419

To a suspension of 60% NaH in mineral oil (1.23 g, 51.4 mmol) in Et_2O (120 mL) at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (10.2 mL, 51.4 mmol) and the reaction mixture was stirred for 5 minutes at 0 °C. A solution of cyclopentanone (4.42 mL, 50.0 mmol) in Et_2O (10 mL) was added and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was diluted with water and extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 10:90) gave ester **419** as a colourless oil (7.00 g, 91%); δ_H (500 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, C*H*$_3$), 1.68 (2H, quintet, *J* 6.8, C*H*$_2$), 1.77 (2H, quintet, *J* 7.0, C*H*$_2$), 2.44-2.47 (2H, m, C*H*$_2$C=), 2.78-2.81 (2H, m, C*H*$_2$C=), 4.17 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 5.82 (1H, quintet, *J* 2.2, =C*H*). Spectroscopic data are in accordance with the literature.[204]

ethyl 2-(cyclopent-1-en-1-yl)acetate

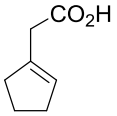


601

To a solution of *i*-Pr_2NH (5.82 mL, 41.2 mmol) in THF (80 mL) at 0 °C was added 2.5 M *n*-BuLi (16.5 mL, 41.2 mmol) and the reaction mixture was stirred at that temperature for 30 minutes. The reaction mixture was cooled to −78 °C and a solution of ester **419** (5.88 g, 38.2 mmol) in THF (25 mL) was added dropwise over 15 minutes before stirring for a further 20 minutes. The reaction mixture was quenched by addition of sat. aq. NH_4Cl and the reaction mixture was warmed to rt before being poured into water and extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give ester **601** as a light yellow oil (5.68 g, 97%); δ_H (500 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1, C*H*$_3$), 1.93 (2H, quintet, *J* 7.5, C*H*$_2$), 2.33-2.38 (4H, m,

C*H*$_2$ and C*H*$_2$), 3.14 (2H, s, C*H*$_2$CO$_2$Et), 4.17 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 5.55-5.57 (1H, m, =C*H*). Spectroscopic data are in accordance with the literature.[205]

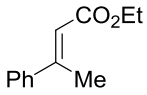
2-(cyclopent-1-en-1-yl)acetic acid



416

A solution of ester **601** (4.15 g, 27.0 mmol) in 0.5 M KOH (80.8 mL, 40.4 mmol) was heated at reflux for 16 h. Once cooled to rt the reaction mixture was extracted with Et$_2$O (x 3). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Recrystallisation from petrol gave acid **416** as a white solid (2.74 g, 59%); mp 44-46 °C; {lit[206] mp 50-51 °C}; δ_H (300 MHz, CDCl$_3$) 1.90-2.00 (2H, m, C*H*$_2$), 2.37-2.42 (4H, m, C*H*$_2$ and C*H*$_2$), 3.21 (2H, s, C*H*$_2$CO$_2$H), 5.63 (1H, m, =C*H*). Spectroscopic data are in accordance with the literature.[206]

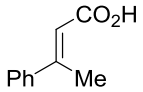
(*E*)-ethyl 3-phenylbut-2-enoate



602

To a suspension of 60% NaH in mineral oil (1.00 g, 41.6 mmol) in THF (35 mL) at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (8.26 mL, 41.6 mmol) dropwise over 30 minutes and the reaction mixture was stirred for 30 minutes at rt. A solution of acetophenone (4.85 mL, 41.6 mmol) in THF (15 mL) was added dropwise and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was diluted with water and extracted with Et$_2$O (x 3). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et$_2$O:petrol 5:95) gave ester **602** as a colourless oil (2.35 g, 30%); δ_H (500 MHz, CDCl$_3$) 1.35 (3H, t, *J* 7.1, CH$_2$C*H*$_3$), 2.61 (3H, d, *J* 1.3, C*H*$_3$), 4.25 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 6.16 (1H, q, *J* 1.2, =C*H*), 7.38-7.42 (3H, m, Ar*H*), 7.50-7.52 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[207]

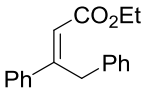
(*E*)-3-phenylbut-2-enoic acid



420

A solution of ester **602** (2.35 g, 12.4 mmol) in 0.5 M KOH (37.1 mL, 18.6 mmol) was heated at reflux for 16 h. Once cooled to rt the reaction mixture was extracted with Et_2O (x 3). The reaction mixture was treated with 1M H_2SO_4 until acidic and extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallisation from Et_2O gave acid **420** as a white solid (1.39 g, 70%); mp 94-96 °C; {lit.[207] mp 95-97 °C}; δ_H (500 MHz, $CDCl_3$) 2.64 (3H, d, *J* 1.2, C*H*$_3$), 6.21 (1H, q, *J* 1.2, =C*H*), 7.41-7.44 (3H, m, Ar*H*), 7.51-7.54 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[208]

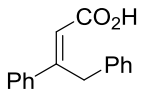
(*E*)-ethyl 3,4-diphenylbut-2-enoate



603

To a suspension of 60% NaH in mineral oil (2.04 g, 51.0 mmol) in THF (50 mL) at 0 °C was added ethyl 2-(diethoxyphosphoryl)acetate (10.1 mL, 51.0 mmol) dropwise over 30 minutes and the reaction mixture was stirred for 30 minutes at rt. A solution of 1,2-diphenylethanone (10 g, 51.0 mmol) in THF (20 mL) was added dropwise and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was diluted with water and extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 5:95) gave ester **603** as a colourless oil (2.35 g, 17%); δ_H (300 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1, CH_2CH_3), 4.27 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 4.55 (2H, s, C*H*$_2$Ph), 6.29 (1H, d, =C*H*), 7.14-7.27 (5H, m, Ar*H*), 7.33-7.36 (3H, m, Ar*H*), 7.42-7.48 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[209]

(*E*)-3,4-diphenylbut-2-enoic acid

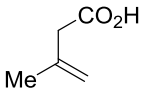


421

A solution of ester **603** (2.35 g, 8.84 mmol) in 0.5 M KOH (26.8 mL, 13.3 mmol) was heated at reflux for 16 h. Once cooled to rt the reaction mixture was extracted with Et_2O (x 3). The reaction mixture was treated with 1M H_2SO_4 until acidic and extracted with

Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 25:75) gave acid **421** as a white solid (210 mg, 10%); mp 122-124 °C; {lit.[210] mp 138-139 °C}; δ_H (300 MHz, $CDCl_3$) 4.59 (2H, s, C*H*$_2$Ph), 6.34 (1H, s, =C*H*), 7.18-7.29 (5H, m, Ar*H*), 7.34-7.39 (3H, m, Ar*H*), 7.46-7.49 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[210]

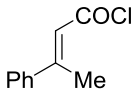
3-methylbut-3-enoic acid



422

To a solution of 3-methylbut-3-en-1-ol (2.00 mL, 19.8 mmol) in acetone (100 mL) at 0 °C was added 2.68 M Jones' reagent (10.4 mL, 27.7 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was washed with 2M NaOH and then the aqueous layer acidified with conc HCl and extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual oil was purified by distillation to give acid **422** as a colourless oil (1.50 g, 76%); bp 88-90 °C (20 mmHg); {lit.[211] bp 90-95 °C (53 mmHg)}; δ_H (500 MHz, $CDCl_3$) 1.87 (3H, s, C*H*$_3$), 3.11 (2H, s, C*H*$_2$), 4.92 (1H, s, =C*H*H), 4.99 (1H, s, =CH*H*). Spectroscopic data are in accordance with the literature.[211]

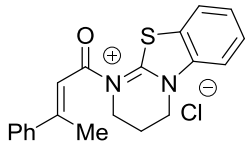
(*E*)-3-phenylbut-2-enoyl chloride



403

A solution of acid **420** (5.00 g, 30.9 mmol) in toluene (40 mL) at 0 °C was added oxalyl chloride (8.87 mL, 101 mmol) and DMF (1 drop) and the reaction mixture was stirred at rt for 5 h before being concentrated *in vacuo*. The residual oil was purified by distillation to give acid chloride **403** as a colourless oil (4.91 g, 88%); bp 140-142 °C (22 mmHg); {lit.[212] bp 78-80 °C (0.08 mmHg)}; δ_H (500 MHz, $CDCl_3$) 2.59 (3H, s, C*H*$_3$), 6.50 (1H, s, =C*H*), 7.44-7.48 (3H, m, Ar*H*), 7.54-7.56 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[124(b)]

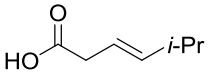
(*E*)-1-(3-phenylbut-2-enoyl)-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-1-ium chloride



427

To a solution of acid chloride **403** (250 mg, 1.39 mmol) in DCM (10 mL) was added DHPB **108** (263 mg, 1.39 mmol) and the reaction mixture was stirred at rt for 5 minutes before being filtered to give salt **427** as a white solid (270 mg, 73%); mp 164-166 °C (dec); ν_{max} (ATR)/cm^{-1} 3443, 3381, 3036 (C-H), 1666 (C=O), 1606, 1533; δ_H (300 MHz, DMSO) 2.46-2.50 (2H, m, $CH_2CH_2CH_2$), 2.56 (3H, d, *J* 1.0, CH_3), 4.44 (2H, t, *J* 5.6, CH_2), 4.53 (2H, t, *J* 5.7, CH_2), 6.93 (1H, q, *J* 1.2, =C*H*), 7.50-7.52 (3H, m, Ar*H*), 7.66-7.83 (4H, m, Ar*H*), 8.07 (1H, d, *J* 8.3, Ar*H*), 8.32 (1H, dd, *J* 7.9, 0.6, Ar*H*); δ_C (75 MHz, DMSO) 18.5 ($CH_2CH_2CH_2$), 18.7 (CH_3), 44.8 (CH_2), 45.8 (CH_2), 114.5 (=*C*H or *ArC*), 114.6 (=*C*H or *ArC*), 123.7 (*ArC*), 125.7 (4ry *ArC*), 126.8 (*ArC*), 126.9 (*ArC*), 128.6 (*ArC*), 128.7 (*ArC*), 130.1 (*ArC*), 136.7 (4ry *ArC*), 140.6 (4ry *ArC*), 158.6 (*C*=CH), 160.8 (*C*=N), 166.8 (*C*=O); *m/z* (NSI$^+$) 335 ([M-Cl]$^+$, 58%); HRMS (NSI$^+$) $C_{20}H_{19}N_2OS^+$ ([M-Cl]$^+$) requires 335.1213; found 335.1219 (+1.9 ppm).

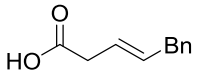
(*E*)-5-methylhex-3-enoic acid



436

A solution of piperidine (39.5 μL, 0.40 mmol) and acetic acid (22.9 μL, 0.40 mmol) in DMSO (1 mL) was stirred at rt for 5 minutes after which time a solution of malonic acid (4.16 g, 40.0 mmol) and isovaleraldehyde (4.29 mL, 40.0 mmol) in DMSO (20 mL) was added. The reaction mixture was stirred at rt for 20 minutes and then at 100 °C for 16 h. Once cooled to rt, the reaction mixture was diluted with H_2O and extracted with Et_2O (x 3). The combined organic fractions were washed with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 30:70) gave acid **436** as a colourless oil (2.93 g, 57%); δ_H (400 MHz, $CDCl_3$) 0.99 (6H, d, *J* 6.8, $CH(CH_3)_2$), 2.26-2.34 (1H, m, C(5)*H*), 3.07 (2H, dt, *J* 6.6, 0.9, C(2)H_2), 5.47 (1H, dtd, *J* 15.4, 6.7, 1.1, C(3)*H*), 5.54-5.60 (1H, m, C(4)*H*). Spectroscopic data are in accordance with the literature.[213]

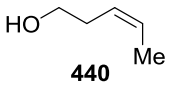
(*E*)-5-phenylpent-3-enoic acid



437

A solution of piperidine (39.5 μL, 0.40 mmol) and acetic acid (22.9 μL, 0.40 mmol) in DMSO (1 mL) was stirred at rt for 5 minutes after which time a solution of malonic acid (4.16 g, 40.0 mmol) and 3-phenylpropionaldehyde (5.28 mL, 40.0 mmol) in DMSO (20 mL) was added. The reaction mixture was stirred at rt for 20 minutes and then at 100 °C for 16 h. Once cooled to rt, the reaction mixture was diluted with H_2O and extracted with Et_2O (x 3). The combined organic fractions were washed with H_2O, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 25:75) gave acid **437** as a colourless oil (4.15 g, 59%); δ_H (400 MHz, $CDCl_3$) 3.13 (2H, dq, *J* 6.8, 1.1, C(5)H_2), 3.40 (2H, d, *J* 6.7, C(2)H_2), 5.63 (1H, dtt, *J* 15.3, 6.9, 1.4, C(3)*H*), 5.77 (1H, dtt, *J* 15.3, 6.7, 1.3, C(4)*H*), 7.18-7.23 (3H, m, Ar(2,6)*H* and Ar(4)*H*), 7.28-7.32 (2H, m, Ar(3,5)*H*). Spectroscopic data are in accordance with the literature.[214]

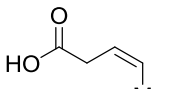
(*Z*)-pent-3-en-1-ol



440

Lindlar's catalyst (5% on $CaCO_3$, Pb poisoned, 900 mg (45 mg Pd), 0.43 mmol) was degassed in a RB flask. Quinoline (0.72 mL, 6.04 mmol), Et_2O (150 mL) and pent-3-yn-1-ol (2.74 mL, 29.7 mmol) were added and a balloon of H_2 gas was appended to the reaction flask. H_2 gas was bubbled through the reaction mixture at rt for 20 h. The reaction mixture was filtered through Celite concentrated *in vacuo* and the residual oil was purified by distillation to give alcohol **440** (94:6 (*Z*):(*E*)) as a colourless oil (1.64 g, 64%); bp 140-141 °C (760 mmHg); {lit.[135] bp 140 °C (760 mmHg)}; Data for (*Z*)-isomer: δ_H (500 MHz, $CDCl_3$) 1.65-1.68 (3H, m, CH_3), 2.32-2.37 (2H, m, C(2)H_2), 3.66 (2H, q, *J* 6.2, C(1)H_2), 5.37-5.43 (1H, m, C(4)*H*), 5.62-5.68 (1H, m, C(3)*H*); Selected data for (*E*)-isomer: δ_H (500 MHz, $CDCl_3$) 1.68-1.70 (3H, m, CH_3), 2.23-2.28 (2H, m, C(2)H_2). Spectroscopic data are in accordance with the literature.[135]

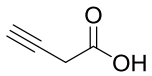
(*Z*)-pent-3-enoic acid



438

To $K_2Cr_2O_7$ (56.1 mg, 0.19 mmol), HNO_3 (343 mg, 3.81 mmol) and $NaIO_4$ (8.97 g, 42.0 mmol) in H_2O (25 mL) was added a solution of alcohol **440** (1.64 g, 19.1 mmol) in MeCN (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 8 h followed by rt for 16 h. The inorganic salts were filtered and washed with Et_2O. H_2O was added and the reaction mixture was extracted with Et_2O (x 3). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual oil was purified by distillation to give acid **438** (94:6 (*Z*):(*E*)) as a colourless oil (0.69 g, 36%); bp 100-102 °C (22 mmHg); {lit.[135] bp 100 °C (20 mmHg)}; Data for (*Z*)-isomer: δ_H (500 MHz, $CDCl_3$) 1.64 (3H, dt, *J* 6.8, 0.8, C*H*$_3$), 3.14 (2H, dd, *J* 7.2, 0.4, C(2)*H*$_2$), 3.66 (2H, q, *J* 6.2, C(1)*H*$_2$), 5.56 (1H, dtq, *J* 10.7, 7.1, 1.8, C(3)*H*), 5.66-5.73 (1H, m, C(4)*H*); Selected data for (*E*)-isomer: δ_H (500 MHz, $CDCl_3$) 1.70 (3H, dt, *J* 6.3, 1.3, C*H*$_3$), 3.06 (2H, dt, *J* 6.7, 1.2, C(2)*H*$_2$). Spectroscopic data are in accordance with the literature.[135]

But-3-ynoic acid



450

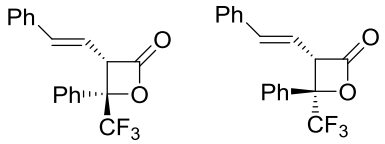
To a solution of CrO_3 (1.39 g, 13.9 mmol) in water (36 mL) at 0 °C was added 18.4 M H_2SO_4 (9.6 mL, 177 mmol). A solution of but-3-yn-1-ol (0.54 mL, 7.10 mmol) in acetone (7 mL) was added over 1 h before the reaction mixture was allowed to stir for a further 3.5 h at 0 °C. The reaction mixture was extracted with Et_2O (x 3) and the combined organic extracts were washed with water, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallisation (Et_2O/petrol) gave acid **450** as an off-white solid (124 mg, 21%); mp 80-82 °C; {lit.[215] mp 84 °C}; δ_H (400 MHz, $CDCl_3$) 2.28 (1H, t, *J* 2.6, C*H*), 3.42 (2H, d, *J* 2.6, C*H*$_2$), 8.91 (1H, s, CO$_2$*H*). Spectroscopic data are in accordance with the literature.[216]

General procedure M: *Intermolecular formal [2+2] and [4+2] cycloadditions.*

To a solution of acid (1-2 eq) in CH_2Cl_2 (~1 mL per 0.2 mmol of acid) were added *i*-Pr_2NEt (1.5 eq based on acid) and pivaloyl chloride (1.5 eq based on acid) at rt. The reaction mixture was allowed to stir at rt for 10 minutes. The requisite Lewis base (0.1-20 mol%), 2π or 4π electrophile (1 eq) and *i*-Pr_2NEt (2.5 eq) were then added at the required temperature in that order. The reaction mixture was stirred at the required temperature until complete by TLC and was subsequently quenched by addition of HCl

(1 M in H_2O). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture. Note: All racemic samples were obtained *via* this general procedure using HBTM-2.1 (±)-**112** as catalyst.

(3*S*,4*S*)-4-phenyl-3-[(*E*)-2-phenylethynyl]-4-(trifluoromethyl)oxetan-2-one and (3*S*,4*R*)-4-phenyl-3-[(*E*)-2-phenylethynyl]-4-(trifluoromethyl)oxetan-2-one



(3*S*,4*S*)-**424** (3*S*,4*R*)-**426**

Following general procedure M, (*E*)-4-phenylbut-3-enoic acid **423** (259 mg, 1.60 mmol), *i*Pr_2NEt (0.42 mL, 2.40 mmol) and pivaloyl chloride (296 μL, 2.40 mmol) in CH_2Cl_2 (10 mL), DHPB **108** (15.2 mg, 0.08 mmol, 10 mol%), 2,2,2-trifluoro-1-phenylethan-1-one **404** (109 μL, 0.80 mmol) and *i*Pr_2NEt (0.35 ml, 2.00 mmol) for 1.5 h at rt gave crude lactones **424** and **426** (60:40 dr). Chromatographic purification (eluent Et_2O:petrol 2.5:97.5) gave lactone **424** (>98:2 dr) as a white solid (110 mg, 43%) and lactone **426** (>98:2 dr) as a white solid (73.4 mg, 29%).

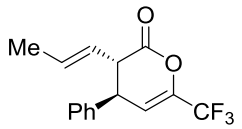
Following general procedure M, (*E*)-4-phenylbut-3-enoic acid **423** (259 mg, 1.60 mmol), *i*-Pr_2NEt (0.42 mL, 2.40 mmol) and pivaloyl chloride (296 μL, 2.40 mmol) in CH_2Cl_2 (10 mL), HBTM-2.1 (2*S*,3*R*)-**112** (24.6 mg, 0.08 mmol, 10 mol%), 2,2,2-trifluoro-1-phenylethan-1-one **404** (109 μL, 0.80 mmol) and *i*-Pr_2NEt (0.35 ml, 2.00 mmol) for 1.5 h at −78 °C gave crude lactones (3*S*,4*S*)-**424** and (3*S*,4*R*)-**426** (65:35 dr). Chromatographic purification (eluent Et_2O:petrol 2.5:97.5) gave lactone (3*S*,4*S*)-**424** (>98:2 dr) as a white solid (98.3 mg, 39%) and lactone (3*S*,4*R*)-**426** (>98:2 dr) as a white solid (52.6 mg, 21 %):

Data for lactone (3*S*,4*S*)-**424**: mp 66 °C; $[\alpha]_D^{20}$-14.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (0.5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*R*,4*R*): 9.6 min, t_R(3*S*,4*S*): 12.6 min, 79% *ee*; ν_{max} (ATR)/cm^{-1} 3080, 3030 (C-H), 1847 (C=O), 1698; δ_H (400 MHz, $CDCl_3$) 4.95-4.98 (1H, m, C(3)*H*), 5.64 (1H, dd, *J* 15.7, 9.4, PhCH=C*H*), 6.71 (1H, d, *J* 15.7, PhC*H*=CH), 7.20-7.23 (2H, m, Ar*H*), 7.27-7.31 (3H, m, Ar*H*), 7.46-7.49 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 60.9 (*C*(3)), 79.5 (q, *J* 32.8, *C*(4)), 116.1 (PhCH=*C*H), 123.6 (q, *J* 280, *C*F_3), 126.9 (*ArC*), 127.3 (*ArC*), 128.8 (*ArC*), 128.8

(*ArC*), 128.9 (4ry *ArC*), 129.0 (*ArC*), 130.1 (*ArC*), 135.3 (C(4)*ArC*(1), 138.4 (Ph*C*H=CH), 165.9 (*C*(2)=O); δ_F (376 MHz, $CDCl_3$) -78.7 (C*F*$_3$); *m*/*z* (APCI$^+$) 319 ([M+H]$^+$, 100%); HRMS (APCI$^+$) $C_{18}H_{14}F_3O_2^+$ ([M+H]$^+$) requires 319.0940; found 319.0940 (-0.1 ppm).

Data for lactone (3*S*,4*R*)-**426**: mp 110-112 °C; $[\alpha]_D^{20}$-93.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*S*,4*S*): 13.1 min, t_R(3*R*,4*R*): 14.9 min, 77% *ee*; ν_{max} (ATR)/cm^{-1} 3080, 2944 (C-H), 1834 (C=O), 1692; δ_H (400 MHz, $CDCl_3$) 4.77 (1H, d, *J* 8.7, C(3)*H*), 6.38-6.47 (1H, m, PhCH=C*H*), 6.83-6.88 (1H, m, PhC*H*=CH), 7.34-7.50 (9H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 64.9 (*C*(3)), 79.6 (q, *J* 30.1, *C*(4)), 115.1 (PhCH=*C*H), 123.3 (q, *J* 281, *C*F$_3$), 126.3 (*ArC*), 127.1 (*ArC*), 128.9 (*ArC*), 128.9 (*ArC*), 129.1 (*ArC*), 130.2 (*ArC*), 132.9 (4ry *ArC*), 135.4 (C(4)*ArC*(1)), 139.0 (Ph*C*H=CH), 165.9 (*C*(2)=O); δ_F (376 MHz, $CDCl_3$) -74.2 (C*F*$_3$); *m*/*z* (APCI$^+$) 319 ([M+H]$^+$, 100%); HRMS (APCI$^+$) $C_{18}H_{14}F_3O_2^+$ ([M+H]$^+$) requires 319.0940; found 319.0941 (+0.2 ppm).

(3*S*,4*R*)-4-phenyl-3-((*E*)-prop-1-en-1-yl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

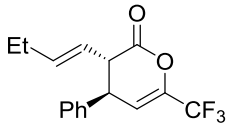


(3*S*,4*R*)-**431**

Following general procedure M, (*E*)-pent-3-enoic acid (40.6 μL, 0.40 mmol), *i*-Pr$_2$NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.16 mg, 0.02 mmol, 5 mol%), enone **220** (80.0 mg, 0.40 mmol) and *i*-Pr$_2$NEt (174 μL, 1.0 mmol) for 5 minutes at rt gave crude lactone (3*S*,4*R*)-**431** (88:12 dr). Chromatographic purification (eluent Et$_2$O:petrol 4:96) gave lactone (3*S*,4*R*)-**431** (88:12 dr) as a colourless oil (89.8 mg, 80%); $[\alpha]_D^{20}$-212.4 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) major diastereoisomer: t_R(3*S*,4*R*): 9.7 min, t_R(3*R*,4*S*): 13.2 min, 96% *ee*; minor diastereoisomer t_R: 10.7 min, t_R: 14.8 min, 15% *ee*; ν_{max} (ATR)/cm^{-1} 3060, 3027 (C-H), 1784 (C=O), 1699; Data for major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 1.68 (3H, t, *J*, 5.9, C*H*$_3$), 3.43 (1H, t, *J* 6.9, C(3)*H*), 3.70-3.75 (1H, m, C(4)*H*), 5.44-5.56 (2H, m, C(3)C*H*=CHCH$_3$ and C(3)CH=C*H*CH$_3$), 6.09 (1H, d, *J* 4.5, C(5)*H*), 7.11 (2H, d, *J* 7.8,

C(4)Ar(2,6)*H*), 7.31-7.40 (3H, m, C(4)Ar(3,5)*H* and C(4)Ar(4)*H*); δ_C (75 MHz, $CDCl_3$) 18.0 (*C*H_3), 43.2 (*C*(4)), 49.8 (*C*(3)), 109.7 (q, *J* 3.5, *C*(5)), 118.5 (q, *J* 270, *C*F_3), 123.8 (C(3)*C*H=CHCH$_3$), 127.4 (*ArC*), 128.1 (*ArC*), 129.2 (*ArC*), 132.1 (C(3)CH=*C*HCH$_3$), 138.7 (C(4)ArC(1)), 140.8 (q, *J* 37.9, *C*(6)), 166.0 (*C*(2)); *m*/*z* (NSI^+) 300 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{15}H_{17}F_3NO_2^+$ ($[M+NH_4]^+$) requires 300.1206; found 300.1206 (+0.0 ppm). Selected data for minor diastereoisomer: δ_H (500 MHz, $CDCl_3$) 3.63 (1H, t, *J* 7.8, C(3)*H*), 3.86-3.88 (1H, m, C(4)*H*), 5.13 (1H, dd, *J* 15.4, 8.6, C(3)C*H*=CHCH$_3$), 5.69 (1H, dq, *J* 14.7, 7.1, C(3)CH=C*H*CH$_3$), 6.23 (1H, d, *J* 5.7, C(5)*H*), 7.11 (2H, d, *J* 7.7, Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 18.0 (*C*H$_3$), 43.0 (*C*(4)), 47.7 (*C*(3)), 110.8 (q, *J* 3.5, *C*(5)), 122.6 (C(3)*C*H=CHCH$_3$), 128.2 (*ArC*), 128.3 (*ArC*), 129.1 (*ArC*), 132.2 (C(3)CH=*C*HCH$_3$), 166.6 (*C*(2)).

(3*S*,4*R*)-3-((*E*)-but-1-en-1-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

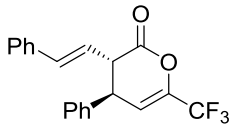


(3*S*,4*R*)-**432**

Following general procedure M, (*E*)-hex-3-enoic acid (47.4 μL, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.16 mg, 0.02 mmol, 5 mol%), enone **220** (80.0 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.0 mmol) for 5 minutes at rt gave crude lactone (3*S*,4*R*)-**432** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 3:97) gave lactone (3*S*,4*R*)-**432** (93:7 dr) as a colourless oil (98.7 mg, 83%); $[\alpha]_D^{20}$-191.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) major diastereoisomer: t_R(3*S*,4*R*): 8.9 min, t_R(3*R*,4*S*): 12.4 min, 96% *ee*; minor diastereoisomer t_R: 9.9 min, t_R: 14.4 min, 12% *ee*; ν_{max} (ATR)/cm^{-1} 3065, 2968 (C-H), 1786 (C=O), 1699; Data for major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.5, C*H*$_3$), 2.00-2.06 (2H, m, C*H*$_2$CH$_3$), 3.42 (1H, t, *J* 7.1, C(3)*H*), 3.71-3.74 (1H, m, C(4)*H*), 5.41-5.45 (1H, m, C(3)C*H*=CHCH$_2$CH$_3$ or C(3)CH=C*H*CH$_2$CH$_3$), 5.49-5.54 (1H, m, C(3)C*H*=CHCH$_2$CH$_3$ or C(3)CH=C*H*CH$_2$CH$_3$), 6.10 (1H, d, *J* 4.6, C(5)*H*), 7.14-7.16 (2H, m, C(4)Ar(2,6)*H*), 7.31-7.40 (3H, m, C(4)Ar(3,5)*H* and C(4)Ar(4)*H*); δ_C (125 MHz, $CDCl_3$) 13.1 (*C*H$_3$), 25.5 (*C*H$_2$CH$_3$), 43.2 (*C*(4)), 49.8 (*C*(3)), 109.7 (q, *J* 3.5, *C*(5)), 118.5 (q, *J* 270, *C*F_3), 121.6 (C(3)*C*H=CHCH$_2$CH$_3$), 127.5 (*ArC*), 128.1 (*ArC*), 129.2

(*ArC*), 138.7 (C(4)ArC(1)), 138.8 (C(3)CH=*C*HCH$_2$CH$_3$), 140.8 (q, *J* 37.9, *C*(6)), 166.1 (*C*(2)); *m*/*z* (NSI$^+$) 297 ([M+H]$^+$, 20%); HRMS (NSI$^+$) $C_{16}H_{16}F_3O_2^+$ ([M+H]$^+$) requires 297.1097; found 297.1101 (+1.4 ppm). Selected data for minor diastereoisomer: δ_H (500 MHz, $CDCl_3$) 3.63 (1H, t, *J* 7.7, C(3)*H*), 3.87-3.90 (1H, m, C(4)*H*), 5.10 (1H, ddt, *J* 15.5, 8.5, 1.6, C(3)C*H*=CHCH$_2$CH$_3$), 5.70 (1H, dt, *J* 15.4, 6.4, C(3)CH=C*H*CH$_2$CH$_3$), 6.23 (1H, d, *J* 5.7, C(5)*H*), 7.11 (2H, d, *J* 8.0, Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 43.0 (*C*(4)), 47.6 (*C*(3)), 110.7 (q, *J* 3.5, *C*(5)), 120.5 (C(3)*C*H=CHCH$_2$CH$_3$), 128.2 (*ArC*), 128.2 (*ArC*), 129.0 (*ArC*), 138.9 (C(3)CH=*C*HCH$_2$CH$_3$), 166.6 (*C*(2)).

(3*S*,4*R*)-4-phenyl-3-((*E*)-styryl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one

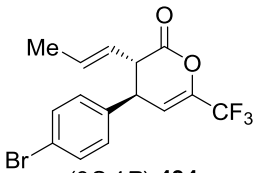


(3*S*,4*R*)-**433**

Following general procedure M, (*E*)-4-phenylbut-3-enoic acid (64.9 mg, 0.40 mmol), *i*-Pr$_2$NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.16 mg, 0.02 mmol, 5 mol%), enone **220** (80.0 mg, 0.40 mmol) and *i*-Pr$_2$NEt (174 μL, 1.0 mmol) for 5 minutes at −78 °C gave crude lactone (3*S*,4*R*)-**433** (95:5 dr). Chromatographic purification (eluent Et$_2$O:petrol 7.5:92.5) gave lactone (3*S*,4*R*)-**433** (95:5 dr) as a colourless oil (113 mg, 82%); $[\alpha]_D^{20}$-159.6 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) major diastereoisomer: t_R(3*R*,4*S*): 12.3 min, t_R(3*S*,4*R*): 13.9 min, 60% *ee*; minor diastereoisomer t_R: 8.00 min, t_R: 10.6 min, 52% *ee*; ν_{max} (ATR)/cm^{-1} 3063, 3030 (C-H), 1782 (C=O), 1699, 1601; Data for major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 3.65 (1H, t, *J* 7.6, C(3)*H*), 3.85-3.90 (1H, m, C(4)*H*), 6.15-6.20 (2H, m, C(5)*H* and C(3)C*H*=CHPh), 6.36 (1H, d, *J* 15.9, C(3)CH=C*H*Ph), 7.21 (2H, d, *J* 7.5, Ar*H*), 7.28-7.42 (8H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 43.3 (*C*(4)), 50.0 (*C*(3)), 109.9 (q, *J* 3.3, *C*(5)), 118.5 (q, *J* 270, *C*F$_3$), 122.0 (C(3)*C*H=CHPh), 126.6 (*ArC*), 127.5 (*ArC*), 128.3 (*ArC*), 128.4 (*ArC*), 128.7 (Ar*C*), 129.4 (Ar*C*), 135.7 (C(3)CH=*C*HPh), 135.8 (4ry *ArC*), 138.5 (4ry *ArC*), 141.0 (q, *J* 38.0, *C*(6)), 165.6 (*C*(2)); *m*/*z* (NSI$^+$) 345 ([M+H]$^+$, 15%); HRMS (NSI$^+$) $C_{20}H_{16}F_3O_2^+$ ([M+H]$^+$) requires 345.1097; found 345.1098 (+0.3 ppm). Selected data for minor diastereoisomer: δ_H (500 MHz, $CDCl_3$) 3.99 (1H, t, *J* 6.2, C(4)*H*), 5.84 (1H, dd, *J* 16.0, 8.6, C(3)C*H*=CHPh), 6.30 (1H, d, *J* 5.9, C(5)*H*), 6.59 (1H, d, *J* 16.0, C(3)CH=C*H*Ph), 7.16 (2H, d, *J* 7.6, Ar*H*); δ_C (125 MHz, $CDCl_3$) 47.9 (*C*(3)), 110.7 (q, *J*

3.4, *C*(5)), 121.4 (C(3)*C*H=CHPh), 128.2 (*ArC*), 128.5 (*ArC*), 129.3 (*ArC*), 135.4 (C(3)CH=*C*HPh), 166.2 (*C*(2)).

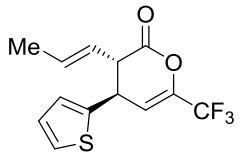
(3*S*,4*R*)-4-(4-bromophenyl)-3-((*E*)-prop-1-en-1-yl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*S*,4*R*)-**434**

Following general procedure M, (*E*)-pent-3-enoic acid (40.6 μL, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.16 mg, 0.02 mmol, 5 mol%), enone **552** (112 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.0 mmol) for 5 minutes at rt gave crude lactone (3*S*,4*R*)-**434** (80:20 dr). Chromatographic purification (eluent Et_2O:petrol 3:97) gave lactone (3*S*,4*R*)-**434** (95:5 dr) as a colourless oil (105 mg, 73%); $[\alpha]_D^{20}$-201.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralcel OD-H (1% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) major diastereoisomer: t_R(3*R*,4*S*): 10.1 min, t_R(3*S*,4*R*): 11.8 min, 92% *ee*; minor diastereoisomer t_R: 9.3 min, t_R: 12.8 min, 90% *ee*; ν_{max} (ATR)/cm^{-1} 2987 (C-H), 1786 (C=O), 1753, 1660; Data for major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 1.69 (3H, t, *J*, 6.4, C*H*$_3$), 3.37 (1H, t, *J* 7.4, C(3)*H*), 3.68-3.71 (1H, m, C(4)*H*), 5.43 (1H, ddd, *J* 15.3, 7.5, 1.3, C(3)C*H*=CHCH$_3$), 5.52 (1H, dq, *J* 15.4, 6.3, C(3)CH=C*H*CH$_3$), 6.03 (1H, d, *J* 4.4, C(5)*H*), 7.02-7.04 (2H, m, C(4)Ar(3,5)*H*), 7.50-7.52 (2H, m, C(4)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 18.0 (*C*H$_3$), 42.6 (*C*(4)), 49.6 (*C*(3)), 109.1 (q, *J* 3.5, *C*(5)), 118.4 (q, *J* 270, *C*F$_3$), 122.1 (C(4)*ArC*(4)), 123.4 (C(3)*C*H=CHCH$_3$), 129.1 (C(4)*ArC*(3,5)), 132.3 (C(4)*ArC*(2,6)), 132.6 (C(3)CH=*C*HCH$_3$), 137.7 (C(4)ArC(1)), 141.1 (q, *J* 38, *C*(6)), 165.7 (*C*(2)); *m*/*z* (NSI^+) 378 ($[M+NH_4]^+$, 56%); HRMS (NSI^+) $C_{15}H_{16}{}^{78}BrF_3NO_2{}^+$ ($[M+NH_4]^+$) requires 378.0311; found 378.0311 (+0.0 ppm). Selected data for minor diastereoisomer: δ_H (500 MHz, $CDCl_3$) 3.62 (1H, t, *J* 7.8, C(3)*H*), 3.82-3.85 (1H, m, C(4)*H*), 5.09-5.14 (1H, m, C(3)C*H*=CHCH$_3$), 5.65-5.72 (1H, m, C(3)CH=C*H*CH$_3$), 6.18 (1H, d, *J* 5.7, C(5)*H*); δ_C (75 MHz, $CDCl_3$) 18.0 (*C*H$_3$), 44.4 (*C*(4)), 47.4 (*C*(3)).

(3*S*,4*R*)-3-((*E*)-prop-1-en-1-yl)-4-(thiophen-2-yl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*S*,4*R*)-**435**

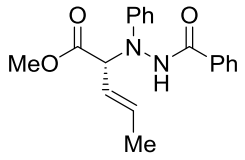
Following general procedure M, (*E*)-pent-3-enoic acid (40.6 μL, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (6.16 mg, 0.02 mmol, 5 mol%), enone **561** (82.4 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.0 mmol) for 5 minutes at rt gave crude lactone (3*S*,4*R*)-**435** (84:16 dr). Chromatographic purification (eluent Et_2O:petrol 4:96) gave lactone (3*S*,4*R*)-**435** (84:16 dr) as a colourless oil (95.8 mg, 83%); $[\alpha]_D^{20}$-187.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AS-H (0.5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) major diastereoisomer: t_R(3*S*,4*R*): 14.1 min, t_R(3*R*,4*S*): 16.1 min, 93% *ee*; ν_{max} (ATR)/cm^{-1} 2998 (C-H), 1784 (C=O), 1699, 1674; Data for major diastereoisomer: δ_H (300 MHz, $CDCl_3$) 1.72-1.74 (3H, m, CH_3), 3.55 (1H, td, *J* 6.7, 0.7, C(3)*H*), 4.00-4.04 (1H, m, C(4)*H*), 5.47 (1H, ddq, *J* 15.4, 8.4, 1.7, C(3)C*H*=CHCH$_3$), 5.63-5.75 (1H, m, C(3)CH=C*H*CH$_3$), 6.16 (1H, d, *J* 5.0, C(5)*H*), 6.89-6.90 (1H, m, Ar*H*), 6.98-7.03 (1H, m, Ar*H*), 7.27-7.30 (1H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 18.0 (*C*H$_3$), 38.1 (*C*(4)), 50.5 (*C*(3)), 109.1 (q, *J* 3.5, *C*(5)), 118.4 (q, *J* 270, *C*F_3), 123.2 (C(3)*C*H=CHCH$_3$), 125.4 (*ArC*), 125.4 (*ArC*), 127.4 (*ArC*), 132.4 (C(3)CH=*C*HCH$_3$), 140.7 (q, *J* 37.9, *C*(6)), 141.2 (C(4)ArC(1)), 165.4 (*C*(2)); *m*/*z* ($APCI^+$) 289 ($[M+H]^+$, 100%); HRMS ($APCI^+$) $C_{13}H_{12}F_3O_2S^+$ ($[M+H]^+$) requires 289.0505; found 289.0507 (+0.8 ppm). Selected data for minor diastereoisomer: δ_H (500 MHz, $CDCl_3$) 3.64 (1H, t, *J* 7.5, C(3)*H*), 4.13-4.18 (1H, m, C(4)*H*), 5.35 (1H, ddq, *J* 15.4, 8.4, 1.7, C(3)C*H*=CHCH$_3$), 6.28 (1H, d, *J* 5.8, C(5)*H*); δ_C (75 MHz, $CDCl_3$) 18.1 (*C*H$_3$), 38.0 (*C*(4)), 48.0 (*C*(3)), 110.7 (q, *J* 3.5, *C*(5)), 122.5 (C(3)*C*H=CHCH$_3$), 125.7 (*ArC*), 126.3 (*ArC*), 127.4 (*ArC*), 132.7 (C(3)CH=*C*HCH$_3$), 166.2 (*C*(2)).

General procedure N: *One-pot intermolecular Michael addition-lactonisation ring opening.*

To a solution of acid (1 eq) in CH_2Cl_2 (~1 mL per 0.2 mmol of acid) were added *i*-Pr_2NEt (1.5 eq based on acid) and pivaloyl chloride (1.5 eq based on acid) at rt. The reaction mixture was allowed to stir at rt for 10 minutes. The requisite Lewis base (0.1-20 mol%), Michael acceptor (1 eq) and *i*-Pr_2NEt (2.5 eq) were then added at the required

temperature in that order. The reaction mixture was stirred at the required temperature until complete by TLC. Methanol was added and the reaction mixture was stirred at rt until ring-opening was complete by TLC. The reaction mixture was subsequently quenched by addition of HCl (1 M in H_2O). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture. Note: All racemic samples were obtained *via* this general procedure using DHPB **108** as catalyst.

(2*R*,*E*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)pent-3-enoate

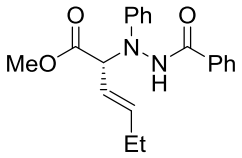


(2*R*)-**441**

Following general procedure N, (*E*)-pent-3-enoic acid (40.6 μL, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%), diazene **313** (84.0 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 40:60) a rotameric mixture (ratio 95:5) of (2*R*)-**441** as a white solid (105 mg, 80%); mp 108-110 °C; $[\alpha]_D^{20}$-67.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 13.2 min, t_R(2*R*): 17.3 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3350 (N-H), 2949 (C-H), 1721 (C=O ester), 1698 (C=O amide), 1597; Data for major rotamer δ_H (500 MHz, $CDCl_3$) 1.72 (3H, d, *J* 4.7, CH_3CH=), 3.78 (3H, s, OCH_3), 5.25-5.26 (1H, m, C(2)*H*), 5.79-5.89 (2H, m, C*H*=CHCH$_3$ and CH=C*H*CH$_3$), 6.94-6.97 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.27-7.30 (2H, m, NAr(3,5)*H*), 7.50 (2H, t, *J* 7.6, C(O)Ar(3,5)*H*), 7.58 (1H, t, *J* 7.4, C(O)Ar(4)*H*), 7.86-7.88 (2H, m, C(O)Ar(2,6)*H*), 8.64 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 18.1 (*C*H_3CH=), 52.3 (O*C*H_3), 64.5 (*C*(2)), 114.7 (N*ArC*(2,6)), 121.5 (N*ArC*(4)), 123.6 (*C*H=CHCH$_3$), 127.2 (*ArC*), 128.8 (*ArC*), 129.4 (*ArC*), 132.0 (*ArC* or CH=*C*HCH$_3$), 132.3 (*ArC* or CH=*C*HCH$_3$), 133.0 (C(O)*ArC*(1)), 148.1 (N*ArC*(1)), 167.4 (NH*C*=O), 173.3 (MeO*C*=O); Selected data for minor rotamer δ_H (500 MHz, $CDCl_3$) 1.65 (3H, d, *J* 5.9, CH_3CH=), 3.67 (3H, s, OCH_3), 4.97 (1H, d, *J* 7.1, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 18.1 (*C*H_3CH=), 52.3 (O*C*H_3), 65.8 (*C*(2)), 115.0 (N*ArC*(2,6)); *m*/*z* (NSI^+) 325 ($[M+H]^+$,

100%); HRMS (NSI$^+$) $C_{19}H_{21}N_2O_3^+$ ([M+H]$^+$) requires 325.1547; found 325.1548 (+0.4 ppm).

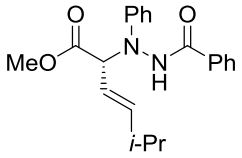
(2*R*,*E*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)hex-3-enoate



(2*R*)-**442**

Following general procedure N, (*E*)-hex-3-enoic acid (47.4 μL, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%), diazene **313** (84.0 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 40:60) a rotameric mixture (ratio 95:5) of (2*R*)-**442** as a white solid (115 mg, 85%); mp 98-100 °C; $[\alpha]_D^{20}$-54.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 11.3 min, t_R(2*R*): 15.6 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3352 (N-H), 2990 (C-H), 1721 (C=O ester), 1688 (C=O amide), 1597, 1508; Data for major rotamer δ_H (500 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.5, C*H*$_3$CH$_2$), 2.03-2.13 (2H, m, CH$_3$C*H*$_2$) 3.68 (3H, s, OC*H*$_3$), 5.29 (1H, d, *J* 4.5, C(2)*H*), 5.77-5.90 (2H, m, C*H*=CHCH$_2$CH$_3$ and CH=C*H*CH$_2$CH$_3$), 6.97-6.99 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.27-7.32 (2H, m, NAr(3,5)*H*), 7.47-7.56 (2H, m, C(O)Ar(3,5)*H*), 7.56-7.62 (1H, m, C(O)Ar(4)*H*), 7.86-7.90 (2H, m, C(O)Ar(2,6)*H*), 8.65 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 13.0 (*C*H$_3$CH$_2$), 25.5 (CH$_3$*C*H$_2$), 52.3 (O*C*H$_3$), 64.5 (*C*(2)), 114.6 (N*ArC*(2,6)), 121.5 (N*ArC*(4) or *C*H=CHCH$_2$CH$_3$), 121.7 (N*ArC*(4) or *C*H=CHCH$_2$CH$_3$), 127.2 (*ArC*), 128.8 (*ArC*), 129.4 (*ArC*), 129.7 (*ArC*), 132.1 (CH=*C*HCH$_2$CH$_3$), 133.0 (C(O)*ArC*(1)), 148.1 (N*ArC*(1)), 167.4 (NH*C*=O), 173.4 (MeO*C*=O); Selected data for minor rotamer: δ_H (500 MHz, $CDCl_3$) 3.68 (3H, s, OC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 52.2 (O*C*H$_3$), 66.1 (*C*(2)), 115.0 (N*ArC*(2,6)); *m*/*z* (NSI$^+$) 325 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{19}H_{21}N_2O_3^+$ ([M+H]$^+$) requires 325.1547; found 325.1548 (+0.4 ppm).

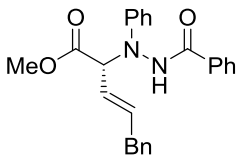
(2*R*,*E*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-5-methylhex-3-enoate



(2*R*)-**443**

Following general procedure N, acid **436** (51.2 mg, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%), diazene **313** (84.0 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 40:60) a rotameric mixture (ratio 95:5) of (2*R*)-**443** as a white solid (104 mg, 74%); mp 128-130 °C; $[\alpha]_D^{20}$-66.6 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 14.5 min, t_R(2*R*): 19.0 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3326 (N-H), 2988 (C-H), 1719 (C=O Ester), 1678 (C=O Amide), 1597, 1506; Data for major rotamer: δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, CH(CH_3)CH_3), 0.92 (3H, t, *J* 6.8, CH(CH_3)CH_3), 2.27-2.34 (1H, m, C*H*(CH_3)CH_3), 3.78 (3H, s, OCH_3), 5.27-5.28 (1H, m, C(2)*H*), 5.72-5.80 (2H, m, C*H*=CHCH(CH_3)CH_3 and CH=C*H*CH(CH_3)CH_3), 6.93-6.97 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.26-7.30 (2H, m, NAr(3,5)*H*), 7.46-7.49 (2H, m, C(O)Ar(3,5)*H*), 7.54-7.58 (1H, m, C(O)Ar(4)*H*), 7.85-7.88 (2H, m, C(O)Ar(2,6)*H*), 8.64 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (CH(CH_3)CH_3), 22.0 (CH(CH_3)CH_3), 31.1 (C*H*(CH_3)CH_3), 52.3 (O*C*H_3), 64.4 (*C*(2)), 114.8 (N*ArC*(2,6)), 120.0 (*C*H=CHCH(CH_3)CH_3), 121.5 (N*ArC*(4)), 127.3 (C(O)*ArC*(2,6)), 128.8 (C(O)*ArC*(3,5)), 129.4 (N*ArC*(3,5)), 132.1 (C(O)*ArC*(4)), 133.0 (C(O)*ArC*(1)), 143.9 (CH=*C*HCH(CH_3)CH_3), 148.2 (N*ArC*(1)), 167.3 (NH*C*=O), 173.4 (MeO*C*=O); Selected data for minor rotamer: δ_H (500 MHz, $CDCl_3$) 3.66 (3H, s, OCH_3), 5.01 (1H, d, *J* 7.0, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (CH(CH_3)CH_3), 21.5 (CH(CH_3)CH_3), 31.1 (C*H*(CH_3)CH_3), 52.2 (O*C*H_3), 66.3 (*C*(2)), 115.2 (N*ArC*(2,6)), 146.1 (CH=*C*HCH_2CH_3), 148.8 (N*ArC*(1)), 172.0 (MeO*C*=O); *m*/*z* (NSI^+) 353 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{21}H_{25}N_2O_3^+$ ($[M+H]^+$) requires 353.1860; found 353.1862 (+0.7 ppm).

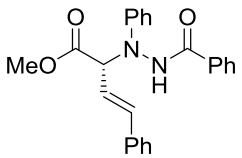
(2*R*,*E*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-5-phenylpent-3-enoate



(2*R*)-**444**

Following general procedure N, acid **437** (70.4 mg, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%), diazene **313** (84.0 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 96:4) of (2*R*)-**444** as a white solid (123 mg, 77%); mp 136-138 °C; $[\alpha]_D^{20}$-70.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm, 30 °C) t_R(2*S*): 28.5 min, t_R(2*R*): 41.2 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3323 (N-H), 2890 (C-H), 1730 (C=O Ester), 1686 (C=O Amide), 1599, 1514; Data for major rotamer: δ_H (500 MHz, $CDCl_3$) 3.41 (2H, d, *J* 6.1, C*H*HPh and CH*H*Ph), 3.78 (3H, s, OCH_3), 5.34-5.35 (1H, m, C(2)*H*), 5.89-6.00 (2H, m, C*H*=CHBn and CH=C*H*Bn), 6.96-6.99 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.05-7.03 (CH_2Ar(2,6)*H*), 7.12-7.15 (CH_2Ar(3,5)*H* and CH_2Ar(4)*H*), 7.28-7.32 (2H, m, NAr(3,5)*H*), 7.48-7.51 (2H, m, C(O)Ar(3,5)*H*), 7.58-7.62 (1H, m, C(O)Ar(4)*H*), 7.85-7.86 (2H, m, C(O)Ar(2,6)*H*), 8.68 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 38.9 (*C*H_2Ph), 52.4 (O*C*H_3), 64.5 (*C*(2)), 114.7 (N*ArC*(2,6)), 121.6 (N*ArC*(4)), 124.1 (*C*H=CHBn), 126.2 (CH_2*ArC*(4)), 127.3 (C(O)*ArC*(2,6)), 128.4 (*ArC*), 128.6 (*ArC*), 128.8 (C(O)*ArC*(3,5)), 129.4 (N*ArC*(3,5)), 132.1 (C(O)*ArC*(4)), 132.8 (C(O)*ArC*(1)), 135.7 (CH=*C*HBn), 138.9 (CH_2*ArC*(1)), 148.1 (N*ArC*(1)), 167.1 (NH*C*=O), 173.1 (MeO*C*=O); Selected data for minor rotamer δ_H (500 MHz, $CDCl_3$) 3.67 (3H, s, OCH_3), 5.06-5.08 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 38.8 (*C*H_2Ph), 52.3 (O*C*H_3), 66.2 (*C*(2)), 115.2 (N*ArC*(2,6)), 148.7 (N*ArC*(1)); *m*/*z* (NSI^+) 401 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{25}H_{25}N_2O_3^+$ ($[M+H]^+$) requires 401.1860; found 401.1859 (-0.2 ppm).

(2*R*,*E*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-4-phenylbut-3-enoate

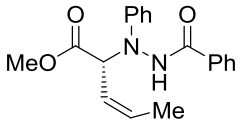


(2*R*)-**445**

Following general procedure N, (*E*)-4-phenylbut-3-enoic acid (64.9 mg, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%), diazene **313** (84.0 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of

MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 40:60) a rotameric mixture (ratio 95:5) of (2*R*)-**445** as an off-white solid (109 mg, 71%); mp 116-118 °C; $[\alpha]_D^{20}$-19.6 (*c* 0.25, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 22.0 min, t_R(2*R*): 27.9 min, 91% *ee*; ν_{max} (ATR)/cm^{-1} 3325 (N-H), 3057, 2959 (C-H), 1728 (C=O ester), 1693 (C=O amide), 1599; Data for major rotamer δ_H (500 MHz, $CDCl_3$) 3.84 (3H, s, CH_3), 5.50 (1H, d, *J* 5.1, C(2)*H*), 6.54 (1H, dd, *J* 16.3, 5.7, C*H*=CHPh), 6.76 (1H, d, *J* 16.3, CH=C*H*Ph), 6.99-7.04 (3H, m, Ar*H*), 7.24-7.41 (7H, m, Ar*H*), 7.44 (2H, t, *J* 8.7, C(O)Ar(3,5)*H*), 7.54 (1H, t, *J* 7.4, C(O)Ar(4)*H*), 7.83 (2H, d, *J* 7.4, C(O)Ar(2,6)*H*), 8.72 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 52.6 (*C*H_3), 64.9 (*C*(2)), 114.8 (N*ArC*(2,6)), 121.7 (N*ArC*(4) or *C*H=CHPh), 122.1 (N*ArC*(4) or *C*H=CHPh), 126.8 (*ArC*), 127.2 (*ArC*), 128.3 (*ArC*), 128.7 (*ArC*), 128.8 (*ArC*), 129.5 (*ArC*), 132.1 (*ArC*), 133.0 (4ry *ArC*), 135.0 (CH=*C*HPh), 135.9 (4ry *ArC*), 148.0 (N*ArC*(1)), 167.6 (NH*C*=O), 172.8 (MeO*C*=O); Selected data for minor rotamer: δ_H (500 MHz, $CDCl_3$) 3.73 (3H, s, CH_3), 5.21 (1H, d, *J* 7.2, C(2)*H*), 6.02 (1H, dd, *J* 16.1, 7.2, C*H*=CHPh), 7.98 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 52.5 (*C*H_3), 66.1 (*C*(2)), 115.1 (N*ArC*(2,6)), 137.5 (CH=*C*HPh); *m*/*z* (NSI^+) 387 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{24}H_{23}N_2O_3^+$ ($[M+H]^+$) requires 387.1703; found 387.1704 (-0.2 ppm).

(2*R*,*Z*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)pent-3-enoate

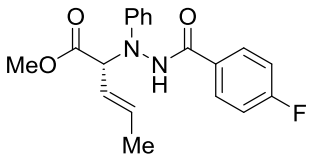


(2*R*)-**446**

Following general procedure A, acid **438** (40.0 mg, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%), diazene **313** (84.0 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 95:5) of (2*R*)-**446** (94:6 (*Z*):(*E*)) as a colourless oil (93.7 mg, 72%); $[\alpha]_D^{20}$-76.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm, 30 °C) t_R(2*S*): 19.1 min, t_R(2*R*): 23.6 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3291 (N-H), 2953 (C-H), 1732 (C=O Ester), 1674 (C=O Amide), 1599; Data for major isomer (*Z*) and major rotamer: δ_H (400 MHz, $CDCl_3$) 1.88 (3H, dd, *J* 7.0,

1.8, C*H*$_3$CH=), 3.75 (3H, s, OC*H*$_3$), 5.48 (1H, d, *J* 8.2, C(2)*H*), 5.61-5.67 (1H, m, C*H*=CHCH$_3$), 5.91 (1H, dqd, *J* 10.7, 7.0, 1.0, CH=C*H*CH$_3$), 6.93-6.99 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.26-7.30 (2H, m, NAr(3,5)*H*), 7.46-7.51 (2H, m, C(O)Ar(3,5)*H*), 7.54-7.59 (1H, m, C(O)Ar(4)*H*), 7.88-7.91 (2H, m, C(O)Ar(2,6)*H*), 8.67 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*H$_3$CH=), 52.6 (O*C*H$_3$), 59.8 (*C*(2)), 114.7 (N*ArC*(2,6)), 121.6 (N*ArC*(4)), 121.7 (*C*H=CHCH$_3$), 127.4 (C(O)*ArC*(2,6)), 128.9 (C(O)*ArC*(3,5)), 129.5 (N*ArC*(3,5)), 132.2 (C(O)*ArC*(4), 132.7 (CH=*C*HCH$_3$), 132.8 (C(O)*ArC*(1)), 148.3 (N*ArC*(1)), 167.0 (NH*C*=O), 173.6 (MeO*C*=O); *m*/*z* (NSI$^+$) 325 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{19}H_{21}N_2O_3^+$ ([M+H]$^+$) requires 325.1547; found 325.1548 (+0.4 ppm).

(2*R*,*E*)-methyl 2-(2-(4-fluorobenzoyl)-1-phenylhydrazinyl)pent-3-enoate

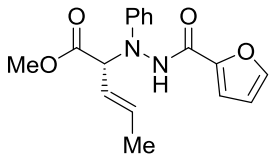


(2*R*)-**447**

Following general procedure N, (*E*)-pent-3-enoic acid (40.6 μL, 0.40 mmol), *i*-Pr$_2$NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%), diazene **580** (91.2 mg, 0.40 mmol) and *i*-Pr$_2$NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et$_2$O:petrol 40:60) a rotameric mixture (ratio 92:8) of (2*R*)-**447** as a white solid (109 mg, 79%); mp 102-104 °C; $[\alpha]_D^{20}$-57.8 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 13.2 min, t_R(2*R*): 17.1 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3522 (N-H), 2951 (C-H), 1751 (C=O ester), 1661 (C=O amide), 1599; Data for major rotamer δ_H (500 MHz, $CDCl_3$) 1.71 (3H, d, *J* 5.1, C*H*$_3$CH=), 3.78 (3H, s, OC*H*$_3$), 5.24 (1H, d, *J* 4.2, C(2)*H*), 5.77-5.87 (2H, m, C*H*=CHCH$_3$ and CH=C*H*CH$_3$), 6.94-6.97 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.17 (2H, t, *J* 8.4, NAr(3,5)*H*), 7.28 (2H, t, *J* 7.8, C(O)Ar(3,5)*H*), 7.87-7.90 (2H, m, C(O)Ar(2,6)*H*), 8.63 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 18.0 (*C*H$_3$CH=), 52.3 (O*C*H$_3$), 64.6 (*C*(2)), 114.7 (N*ArC*(2,6)), 115.9 (d, *J* 21.8, C(O)*ArC*(3,5)), 121.6 (N*ArC*(4)), 123.6 (*C*H=CHCH$_3$), 129.1 (d, *J* 3.0, C(O)*ArC*(1)), 129.4 (N*ArC*(3,5)), 129.6 (d, *J* 8.9, C(O)*ArC*(2,6)), 132.2 (CH=*C*HCH$_3$), 148.1 (N*ArC*(1)), 165.1 (d, *J* 251, C(O)*ArC*(4)), 166.3 (NH*C*=O), 173.3 (MeO*C*=O); Selected data for minor rotamer δ_H (500 MHz, $CDCl_3$) 1.64 (3H, d, *J* 6.1,

CH_3CH=), 3.67 (3H, s, OCH_3), 4.98 (1H, d, *J* 7.0, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 18.0 (*C*H_3CH=), 52.2 (O*C*H_3), 65.9 (*C*(2)), 115.0 (N*ArC*(2,6)); *m*/*z* (NSI^+) 343 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{19}H_{20}FN_2O_3^+$ ($[M+H]^+$) requires 343.1452; found 343.1458 (+1.6 ppm).

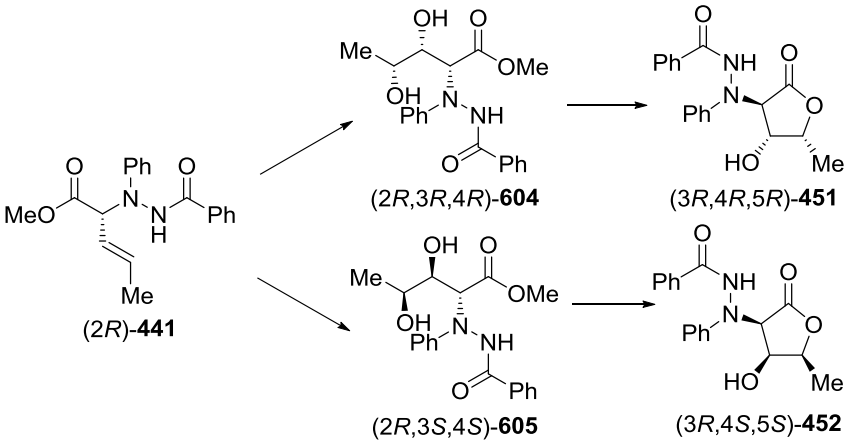
(2*R*,*E*)-methyl 2-(2-(furan-2-carbonyl)-1-phenylhydrazinyl)pent-3-enoate



(2*R*)-**448**

Following general procedure N, (*E*)-pent-3-enoic acid (40.6 μL, 0.40 mmol), *i*-Pr_2NEt (104 μL, 0.60 mmol) and pivaloyl chloride (74.0 μL, 0.60 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (1.23 mg, 0.004 mmol, 1 mol%), diazene **588** (80.0 mg, 0.40 mmol) and *i*-Pr_2NEt (174 μL, 1.00 mmol) for 15 min at rt, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 94:6) of (2*R*)-**448** as a colourless oil (109 mg, 87%); $[\alpha]_D^{20}$-82.4 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(2*S*): 16.0 min, t_R(2*R*): 22.2 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3335 (N-H), 2953 (C-H), 1730 (C=O ester), 1688 (C=O amide), 1589; Data for major rotamer δ_H (500 MHz, $CDCl_3$) 1.70 (3H, d, *J* 6.1, C*H*$_3$CH=), 3.70 (3H, s, OC*H*$_3$), 5.21 (1H, d, *J* 5.5, C(2)*H*), 5.75 (1H, dd, *J* 15.7, 5.6, C*H*=CHCH$_3$), 5.85 (1H, dt, *J* 14.5, 7.0, CH=C*H*CH$_3$), 6.56 (1H, s, C(O)Ar(4)*H*), 6.93-6.94 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.25-7.28 (3H, m, NAr(3,5)*H* and C(O)Ar(3)*H*), 7.52 (1H, s, C(O)Ar(5)*H*), 8.75 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 18.1 (*C*H$_3$CH=), 52.3 (O*C*H$_3$), 64.6 (*C*(2)), 112.2 (C(O)*ArC*(4)), 114.7 (N*ArC*(2,6)), 115.8 (C(O)*ArC*(3)), 121.6 (N*ArC*(4)), 123.3 (*C*H=CHCH$_3$), 129.3 (N*ArC*(3,5)), 132.7 (CH=*C*HCH$_3$), 144.6 (C(O)*ArC*(5)), 146.5 (C(O)*ArC*(2)), 148.0 (N*ArC*(1)), 158.2 (NH*C*=O), 173.0 (MeO*C*=O); Selected data for minor rotamer: δ_H (500 MHz, $CDCl_3$) 3.69 (3H, s, OC*H*$_3$), 5.10 (1H, d, *J* 6.9, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 52.4 (O*C*H$_3$), 65.5 (*C*(2)), 114.9 (N*ArC*(2,6)), 129.7 (N*ArC*(3,5)) *m*/*z* (NSI^+) 315 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{17}H_{19}N_2O_4^+$ ($[M+H]^+$) requires 315.1339; found 315.1335 (-1.4 ppm).

_N_'-((3_R_,4_R_,5_R_)-4-hydroxy-5-methyl-2-oxotetrahydrofuran-3-yl)-_N_'-phenylbenzohydrazide and _N_'-((3_R_,4_S_,5_S_)-4-hydroxy-5-methyl-2-oxotetrahydrofuran-3-yl)-_N_'-phenylbenzohydrazide



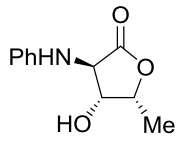
To a solution of hydrazide (2*R*)-**441** (1.12 g, 3.44 mmol) in acetone:water (9:1, 40 mL) was added 2,6-lutidine (0.80 mL, 6.88 mmol), *N*-methylmorpholine-*N*-oxide (0.60 g, 5.16 mmol) and OsO_4 (4% wt in H_2O, 0.44 mL, 0.07 mmol) and the reaction mixture was stirred at rt for 5 h after which time if was quenched by addition of sat. aq. $Na_2S_2O_3$. The reaction mixture as extracted with EtOAc (x 3) and the combined organic fractions were washed with HCl (2M in H_2O), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a mixture of crude diols (2*R*,3*R*,4*R*)-**604** and (2*R*,3*S*,4*S*)-**605** which were used directly in the next reaction without purification. The crude reaction mixture was dissolved in CH_2Cl_2 (50 mL) and treated with *p*-toluenesulfonic acid (0.65 g, 3.44 mmol). The reaction mixture was stirred at rt for 2 h before being quenched by addition of H_2O. The reaction mixture was extracted with CH_2Cl_2 (x 3) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude lactones (3*R*,4*R*,5*R*)-**451** and (3*R*,4*S*,5*S*)-**452** (70:30 dr).

Major diastereoisomer: Chromatographic purification (eluent Et_2O:petrol 60:40 to 100% Et_2O) gave a rotameric mixture (ratio 84:16) of lactone (3*R*,4*R*,5*R*)-**451** (>99:1 dr) as a white solid (0.59 g, 53%); mp 58-60 °C; $[\alpha]_D^{20}$+37.0 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralcel OJ-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*S*,4*S*,5*S*): 13.5 min, t_R(3*R*,4*R*,5*R*): 19.3 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3306 (N-H and O-H), 2980 (C-H), 1767 (C=O lactone), 1661 (C=O amide), 1597; Data for major rotamer δ_H (300 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.4, C*H*$_3$), 4.58-4.74 (3H, m, C(3)*H*, C(4)*H* and C(5)*H*), 6.83-6.86 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.16 (2H, t, *J* 8.0, NAr(3,5)*H*), 7.38 (2H, t,

J 7.6, C(O)Ar(3,5)*H*), 7.49-7.55 (1H, m, C(O)Ar(4)*H*), 7.73-7.75 (2H, m, C(O)Ar(2,6)*H*), 8.47 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 14.8 (*C*H_3), 66.5 (*C*(3)), 69.1 (*C*(4)), 77.2 (*C*(5)), 114.5 (N*ArC*(2,6)), 121.6 (N*ArC*(4)), 127.5 (*ArC*), 129.0 (*ArC*), 129.5 (*ArC*), 131.3 (C=O*ArC*(1)), 133.0 (C=O*ArC*(4)), 147.8 (N*ArC*(1)), 168.9 (NH*C*=O), 171.9 (MeO*C*=O); Selected data for minor rotamer δ_H (300 MHz, $CDCl_3$) 8.12 (1H, s, N*H*); δ_C (125 MHz, $CDCl_3$) 15.3 (*C*H_3), 114.2 (N*ArC*(2,6)), 121.7 (N*ArC*(4)), 127.2 (*ArC*), 128.8 (*ArC*), 129.2 (*ArC*), 132.3 (C=O*ArC*(4)); *m*/*z* (NSI^+) 327 ($[M+H]^+$, 86%); HRMS (NSI^+) $C_{18}H_{19}N_2O_4^+$ ($[M+H]^+$) requires 327.1339; found 327.1345 (+1.7 ppm).

Minor diastereoisomer: Chromatographic purification (eluent Et_2O:petrol 60:40 to 100% Et_2O) gave lactone (3*R*,4*S*,5*S*)-**452** (>99:1 dr) as a white solid (0.28 g, 25%); mp 110-112 °C; $[\alpha]_D^{20}$-266.4 (*c* 0.5, CH_2Cl_2); Chiral HPLC Chiralpak IA (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*S*,4*R*,5*R*): 8.9 min, t_R(3*R*,4*S*,5*S*): 14.8 min, 99% *ee*; ν_{max} (ATR)/cm^{-1} 3238 (N-H and O-H), 2938 (C-H), 1776 (C=O lactone), 1668 (C=O amide), 1597, 1510; δ_H (500 MHz, $CDCl_3$) 1.53 (3H, d, *J* 6.3, C*H*$_3$), 4.64-4.69 (2H, m, C(4)*H* and C(5)*H*), 4.79 (1H, d, *J* 8.1, C(3)*H*), 4.97 (1H, s, O*H*), 6.91 (2H, d, *J* 7.4, NAr(2,6)*H*), 6.99 (1H, t, *J* 7.4, NAr(4)*H*), 7.33 (2H, dd, *J* 8.7. 7.5, NAr(3,5)*H*), 7.52 (2H, t, *J* 7.7, C(O)Ar(3,5)*H*), 7.63 (1H, t, *J* 7.5, C(O)Ar(4)*H*), 7.92-7.93 (2H, m, C(O)Ar(2,6)*H*), 8.93 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 13.8 (*C*H_3), 67.7 (*C*(3)), 70.2 (*C*(4)), 79.3 (*C*(5)), 113.0 (N*ArC*(2,6)), 121.4 (N*ArC*(4)), 127.5 (*ArC*), 129.0 (*ArC*), 129.7 (*ArC*), 131.3 (C=O*ArC*(1)), 133.0 (C=O*ArC*(4)), 147.2 (N*ArC*(1)), 168.8 (NH*C*=O), 171.9 (MeO*C*=O); *m*/*z* (NSI^+) 327 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{18}H_{19}N_2O_4^+$ ($[M+H]^+$) requires 327.1339; found 327.1346 (+2.0 ppm).

(3*R*,4*R*,5*R*)-4-hydroxy-5-methyl-2-(phenylamino)dihydrofuran-2(3*H*)-one

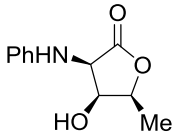


(3*R*,4*R*,5*R*)-**453**

To a solution of lactone (3*R*,4*R*,5*R*)-**451** (65.2 g, 0.20 mmol) in MeOH (2 mL) at –78 °C was added SmI_2 (0.1 M in THF, 6.00 mL, 0.60 mmol) and the reaction mixture was stirred at –78 °C for 10 minutes after which time if was quenched by addition of sat. aq. $NaHCO_3$. The reaction mixture was extracted with EtOAc (x 3) and the combined

organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 60:40) gave lactone (3*R*,4*R*,5*R*)-**453** as a colourless oil (29.0 mg, 70%); $[\alpha]_D^{20}$+18.0 (*c* 0.1, CH_2Cl_2); ν_{max} (ATR)/cm^{-1} 3381 (N-H or O-H), 2986 (C-H), 1761 (C=O), 1603, 1499; δ_H (500 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.8, CH_3), 2.74 (1H, d, *J* 4.9, O*H* or N*H*), 4.13 (1H, s, O*H* or N*H*), 4.18-4.19 (1H, m, C(3)*H*), 4.41 (1H, td, *J* 7.0, 4.8, C(4)*H*), 4.73 (1H, app. quintet, *J* 6.7, C(5)*H*), 6.80-6.85 (3H, m, NAr(2,6)*H* and NAr(4)*H*), 7.19-7.23 (2H, m, NAr(3,5)*H*); δ_C (125 MHz, $CDCl_3$) 14.7 (*C*H_3), 59.6 (*C*(3)), 74.9 (*C*(4)), 77.4 (*C*(5)), 114.1 (N*ArC*(2,6)), 119.6 (N*ArC*(4)), 129.6 (N*ArC*(3,5)), 146.8 (N*ArC*(1)), 174.2 (*C*=O); *m*/*z* (NSI^+) 208 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{11}H_{14}NO_3^+$ ($[M+H]^+$) requires 208.0968; found 208.0968 (-0.1 ppm).

(3*R*,4*S*,5*S*)-4-hydroxy-5-methyl-2-(phenylamino)dihydrofuran-2(3*H*)-one



(3*R*,4*S*,5*S*)-**454**

To a solution of lactone (3*R*,4*S*,5*S*)-**452** (65.2 g, 0.20 mmol) in MeOH (2 mL) at –78 °C was added SmI_2 (0.1 M in THF, 6.00 mL, 0.60 mmol) and the reaction mixture was stirred at –78 °C for 10 minutes after which time if was quenched by addition of sat. aq. $NaHCO_3$. The reaction mixture was extracted with EtOAc (x 3) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 60:40) gave lactone (3*R*,4*S*,5*S*)-**454** as a colourless oil (31.4 mg, 76%); $[\alpha]_D^{20}$-98.0 (*c* 0.1, CH_2Cl_2); ν_{max} (ATR)/cm^{-1} 3389 (N-H or O-H), 2982 (C-H), 1761 (C=O), 1603, 1506; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, d, *J* 6.5, CH_3), 2.76 (1H, br s, O*H* or N*H*), 4.08 (1H, d, *J* 4.4, C(3)*H*), 4.40 (1H, dd, *J* 4.4, 2.9, C(4)*H*), 4.58 (1H, qd, *J* 6.5, 2.9, C(5)*H*), 6.67-6.70 (2H, m, NAr(2,6)*H*), 6.84 (1H, tt, *J* 7.4, 1.0, NAr(4)*H*), 7.16-7.21 (2H, m, NAr(3,5)*H*); δ_C (100 MHz, $CDCl_3$) 13.8 (*C*H_3), 60.4 (*C*(3)), 69.8 (*C*(4)), 78.6 (*C*(5)), 114.2 (N*ArC*(2,6)), 120.5 (N*ArC*(4)), 129.6 (N*ArC*(3,5)), 146.0 (N*ArC*(1)), 174.6 (*C*=O); *m*/*z* (NSI^+) 208 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{11}H_{14}NO_3^+$ ($[M+H]^+$) requires 208.0968; found 208.0968 (-0.1 ppm).

9.5.2 References and Notes

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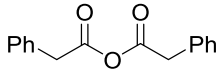
9.6 Experimental for Chapter 6

9.6.1 Experimental Procedures and Characterisation Data

General procedure O: *Formation of anhydrides.*

To a solution of carboxylic acid (1 eq) in toluene was added DCC (0.50-0.55 eq) and the solution was allowed to stir at rt for 15 minutes. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the crude reaction mixture.

2-phenylacetic anhydride

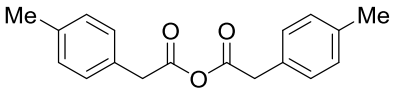


462

Following general procedure O, phenylacetic acid (1.00 g, 7.34 mmol) and DCC (0.83 g, 4.04 mmol) in toluene (20 mL) gave anhydride **462** as a white solid (1.68 g, 90%); mp 68-70 °C; {lit.[217] mp 72-72.5 °C}; δ_H (400 MHz, $CDCl_3$) 3.76 (4H, s, 2 CH_2), 7.23-7.25

(4H, m, Ar*H*), 7.32-7.38 (6H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[217]

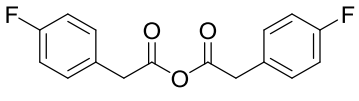
2-(*p*-tolyl)acetic anhydride



463

Following general procedure O, *p*-tolylacetic acid (1.00 g, 6.66 mmol) and DCC (0.70 g, 3.40 mmol) in toluene (20 mL) gave anhydride **463** as a white solid (1.00 g, 53%); mp 47-49 °C; {lit.[218] mp 56-57 °C}; δ_H (300 MHz, $CDCl_3$) 2.39 (6H, s, 2 C*H*$_3$), 3.72 (4H, s, 2 C*H*$_2$), 7.12-7.19 (8H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[218]

2-(4-fluorophenyl)acetic anhydride



464

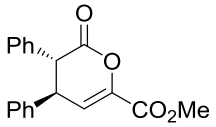
Following general procedure O, 4-fluorophenylacetic acid (1.00 g, 6.49 mmol) and DCC (0.74 g, 3.57 mmol) in toluene (20 mL) gave anhydride **464** as a white solid (1.48 g, 79%); mp 36-38 °C; ν_{max} (KBr)/cm^{-1} 3073, 2919 (C-H), 1821, 1750 (C=O), 1612, 1511; δ_H (400 MHz, $CDCl_3$) 3.63 (4H, s, 2 C*H*$_2$), 6.91-6.96 (4H, m, 2 Ar(3,5)*H*), 7.08-7.11 (4H, m, 2 Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 41.2 (2 *C*H$_2$), 115.7 (d, *J* 21.5, 2 *ArC*(3,5)), 127.6 (d, *J* 3.1, 2 *ArC*(1)), 131.0 (d, *J* 8.1, 2 *ArC*(2,6)), 162.3 (d, *J* 245, 2 *ArC*(4)), 166.7 (2 C=O); δ_F (376 MHz, $CDCl_3$) -115.1 (Ar*F*); *m*/*z* (ES$^+$) 313 ([M+Na]$^+$, 100%); HRMS (ES$^+$) $C_{16}H_{12}F_2NaO_3^+$ ([M+Na]$^+$) requires 313.0652; found 313.0655 (+1.0 ppm).

General procedure P: *Intermolecular Michael addition-lactonisations.*

To a solution of anhydride (1.25 eq) in CH_2Cl_2 (~2 mL per 0.2 mmol of anhydride) was added HBTM-2.1 **112** (5 mol%), Michael acceptor (1 eq) and *i*-Pr$_2$NEt (1.25 eq) at −78 °C in that order. The reaction mixture was stirred at −78 °C until complete by TLC and was subsequently quenched by addition of HCl (1 M in H_2O). Once warmed to rt, the reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude

reaction mixture. Note: Racemic samples for HPLC analysis were obtained *via* the same general procedure using HBTM-2.1 (±)-**112** as catalyst.

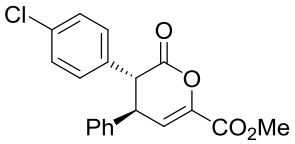
(3*R*,4*R*)-methyl 2-oxo-3,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**147**

Following general procedure P, anhydride **462** (63.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), keto ester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at –78 °C gave crude lactone (3*R*,4*R*)-**147** (98:2 dr). Chromatographic purification (eluent Et_2O:petrol 30:70) gave lactone (3*R*,4*R*)-**147** (>99:1 dr) as a white solid (47.8 mg, 78%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralpak AD-H (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*R*,4*R*): 11.1 min, t_R(3*S*,4*S*): 17.8 min, >99% *ee*.

(3*R*,4*R*)-methyl 3-(4-chlorophenyl)-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

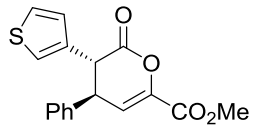


(3*R*,4*R*)-**465**

Following general procedure P, 2-(4-chlorophenyl)acetic anhydride[219] (80.8 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), keto ester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at –78 °C gave crude lactone (3*R*,4*R*)-**465** (90:10 dr). Chromatographic purification (eluent Et_2O:petrol 30:70) gave lactone (3*R*,4*R*)-**465** (>99:1 dr) as a white solid (53.3 mg, 79%); mp 138-140 °C; $[\alpha]_D^{20}$-193.0 (*c* 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*R*,4*R*): 13.2 min, t_R(3*S*,4*S*): 19.1 min, >99% *ee*; ν_{max} (ATR)/cm^{-1} 3059, 3030, 2957 (C-H), 1778 (C=O lactone), 1746 (C=O ester), 1663; δ_H (300 MHz, $CDCl_3$) 3.78-3.82 (4H, m, C(3)*H* and CH_3), 3.94 (1H, dd, *J* 10.1, 3.4, C(4)*H*), 6.60 (1H, d, *J* 3.5, C(5)*H*), 6.91-6.95 (4H, m, Ar*H*), 7.15-7.21 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 45.4 (*C*(4)), 52.0 (*C*(3)), 52.9 (*C*H_3), 118.2 (*C*(5)),

127.6 (*ArC*), 128.1 (*ArC*), 129.0 (*ArC*), 129.2 (*ArC*), 129.9 (*ArC*), 133.7 (4ry *ArC*), 133.9 (4ry *ArC*), 138.8 (4ry *ArC*), 142.0 (*C*(6)), 160.6 (*C*$O_2$$CH_3$), 166.6 (*C*(2)); *m*/*z* (NSI^+) 365 ($[M+Na]^+$, 70%); HRMS (NSI^+) $C_{19}H_{15}{}^{35}ClO_4{}^+$ ($[M+Na]^+$) requires 365.0551; found 365.0547 (-1.1 ppm).

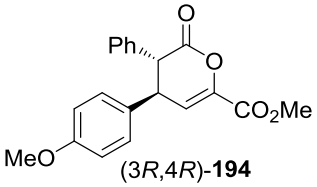
(3*R*,4*R*)-methyl 2-oxo-4-phenyl-3-(thiophen-3-yl)-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**466**

Following general procedure P, 2-(thiophen-3-yl)acetic anhydride[219] (66.6 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), keto ester **143** (38.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at –78 °C gave crude lactone (3*R*,4*R*)-**466** (93:7 dr). Chromatographic purification (eluent Et_2O:petrol 30:70) gave lactone (3*R*,4*R*)-**466** (>99:1 dr) as a white solid (52.3 mg, 83%); mp 128-130 °C; $[\alpha]_D^{20}$-209.5 (*c* 0.2, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*R*,4*R*): 11.1 min, t_R(3*S*,4*S*): 19.4 min, >99% *ee*; ν_{max} (ATR)/cm^{-1} 3105, 2951, 2924 (C-H), 1767 (C=O lactone), 1736 (C=O ester), 1661; δ_H (500 MHz, $CDCl_3$) 3.81 (3H, s, CH_3), 3.97 (1H, dd, *J* 7.1, 4.5, C(4)*H*), 4.01 (1H, d, *J* 7.1, C(3)*H*), 6.62 (1H, d, *J* 4.4, C(5)*H*), 6.90-6.91 (2H, m, Ar*H*), 7.01 (2H, d, *J* 6.8, Ar*H*), 7.19-7.25 (4H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 44.9 (*C*(4)), 48.0 (*C*(3)), 52.9 (*C*H_3), 117.2 (*C*(5)), 123.4 (*ArC*), 126.6 (*ArC*), 126.8 (*ArC*), 127.4 (*ArC*), 128.1 (*ArC*), 129.2 (*ArC*), 135.1 (4ry *ArC*), 139.0 (4ry *ArC*), 142.1 (*C*(6)), 160.7 (*C*$O_2$$CH_3$), 166.2 (*C*(2)); *m*/*z* (NSI^+) 332 ($[M+NH_4]^+$, 61%); HRMS (NSI^+) $C_{17}H_{18}NO_4S^+$ ($[M+NH_4]^+$) requires 332.0951; found 332.0955 (+1.2 ppm).

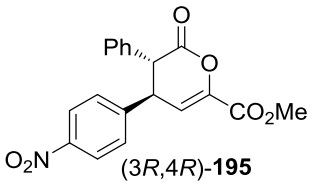
(3*R*,4*R*)-methyl 4-(4-methoxyphenyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**194**

Following general procedure P, anhydride **462** (63.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), keto ester **549** (44.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**194** (93:7 dr). Chromatographic purification (eluent Et_2O:petrol 30:70) gave lactone (3*R*,4*R*)-**194** (>99:1 dr) as a white solid (57.9 mg, 86%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralpak AD-H (40% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*R*,4*R*): 14.9 min, t_R(3*S*,4*S*): 35.5 min, >99% *ee*.

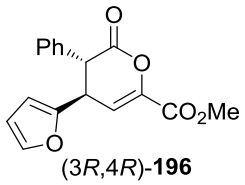
(3*R*,4*R*)-methyl 4-(4-nitrophenyl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate



(3*R*,4*R*)-**195**

Following general procedure P, anhydride **462** (63.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), (*E*)-methyl 4-(4-nitrophenyl)-2-oxobut-3-enoate[171] (49.8 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**195** (91:9 dr). Chromatographic purification (eluent Et_2O:petrol 40:60) gave lactone (3*R*,4*R*)-**195** (93:7 dr) as an off-white solid (60.6 mg, 86%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralcel OD-H (50% IPA:hexane, flow rate 1 mL min^{-1}, 254 nm, 30 °C) t_R(3*S*,4*S*): 18.5 min, t_R(3*R*,4*R*): 23.2 min, >99% *ee*.

(3*R*,4*R*)-methyl 4-(furan-2-yl)-2-oxo-3-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate

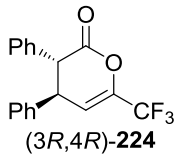


(3*R*,4*R*)-**196**

Following general procedure P, anhydride **462** (63.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), keto ester **174** (36.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**196** (95:5 dr). Chromatographic purification (eluent Et_2O:petrol 30:70) gave lactone (3*R*,4*R*)-**196** (>99:1 dr) as a white solid (47.6 mg, 80%) with identical physical

and spectroscopic data as previously reported; Chiral HPLC Chiralcel OJ-H (20% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C) t_R(3*R*,4*R*): 25.9 min, t_R(3*S*,4*S*): 29.1 min, >99% *ee*.

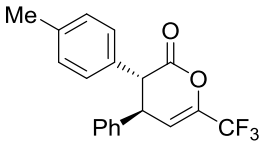
(3*R*,4*R*)-3,4-diphenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**224**

Following general procedure P, anhydride **462** (63.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**224** (94:6 dr). Chromatographic purification (eluent Et_2O:petrol 3.5:96.5) gave lactone (3*R*,4*R*)-**224** (>99:1 dr) as a white solid (51.8 mg, 81%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 10.9 min, t_R(3*S*,4*S*): 12.2 min, 98% *ee*.

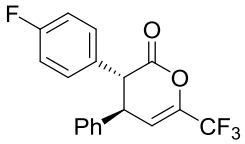
(3*R*,4*R*)-4-phenyl-3-(*p*-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**225**

Following general procedure P, anhydride **463** (70.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**225** (95:5 dr). Chromatographic purification (eluent Et_2O:petrol 3:97) gave lactone (3*R*,4*R*)-**225** (>99:1 dr) as a white solid (51.8 mg, 81%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*S*,4*S*): 14.0 min, t_R(3*R*,4*R*): 16.4 min, 99% *ee*.

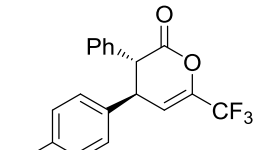
(3*R*,4*R*)-3-(4-fluorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**229**

Following general procedure P, anhydride **464** (72.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **220** (40.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**229** (87:13 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**229** (>99:1 dr) as a white solid (54.0 mg, 80%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 19.2 min, t_R(3*S*,4*S*): 39.4 min, >99% *ee*.

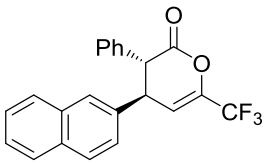
(3*R*,4*R*)-4-(4-chlorophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**253**

Following general procedure P, anhydride **462** (63.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **555** (46.9 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**253** (85:15 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**253** (>99:1 dr) as a white solid (59.8 mg, 85%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 10.2 min, t_R(3*S*,4*S*): 30.3 min, >99% *ee*.

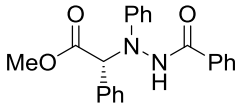
(3*R*,4*R*)-4-(naphthalen-2-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one



(3*R*,4*R*)-**257**

Following general procedure P, anhydride **462** (63.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), enone **559** (50.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 16 h at −78 °C gave crude lactone (3*R*,4*R*)-**257** (89:11 dr). Chromatographic purification (eluent Et_2O:petrol 5:95) gave lactone (3*R*,4*R*)-**257** (>99:1 dr) as a white solid (63.0 mg, 86%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min^{-1}, 211 nm, 20 °C) t_R(3*R*,4*R*): 11.1 min, t_R(3*S*,4*S*): 26.8 min, 99% *ee*.

(2*R*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-2-phenylacetate



(2*R*)-**321**

Following general procedure P, anhydride **462** (63.5 mg, 0.25 mmol) in CH_2Cl_2 (2 mL), HBTM-2.1 (2*S*,3*R*)-**112** (3.09 mg, 0.01 mmol, 5 mol%), diazene **313** (42.0 mg, 0.20 mmol) and *i*-Pr_2NEt (43.5 μL, 0.25 mmol) for 30 minutes at −78 °C, followed by addition of MeOH (2 mL) and stirring for 1 h at rt gave, after chromatographic purification (eluent Et_2O:petrol 50:50) a rotameric mixture (ratio 90:10) of hydrazide (2*R*)-**321** as a pale yellow solid (43.9 mg, 61%) with identical physical and spectroscopic data as previously reported; Chiral HPLC Chiralpak IB (10% IPA:hexane, flow rate 1 mL min^{-1}, 220 nm, 30 °C) t_R(2*S*): 10.5 min, t_R(2*R*): 12.2 min, 98% *ee*.

9.6.2 References and Notes

[171] This compound was kindly provided by Dr Stuart Leckie.

[217] J. A. Jenkins and T. Cohen, *J. Org. Chem.*, 1975, **40**, 3566-3571.

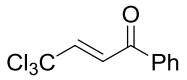
[218] A. A. M. Roof, H. F. van Woerden and H. Cerfontain, *Tetrahedron*, 1976, **32**, 2967-2971.

[219] This compound was kindly provided by Miss Lyndsay Anne Ledingham (MChem Student).

9.7 Experimental for Chapter 7

9.7.1 Experimental Procedures and Characterisation Data

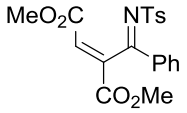
(*E*)-4,4,4-trichloro-1-phenylbut-2-en-1-one



501

To a solution of 1,3-diphenylpropan-1,3-dione (4.49 g, 20.0 mmol) in THF (15 mL) was added K_2CO_3 (4.15 g, 30.0 mmol) and chloral (2.53 mL, 24.0 mmol) and the reaction mixture was stirred at rt for 48 h before being diluted with H_2O and extracted with Et_2O (x 3). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 3:97), gave enone **501** as a white solid (3.34 g, 67%); mp 98-100 °C; {lit.[220] mp 98-99 °C}; δ_H (500 MHz, $CDCl_3$) 7.30 (1H, d, *J* 14.7, *C*(2)H), 7.44 (1H, d, *J* 14.6, C(3)*H*), 7.54-7.57 (2H, m, Ar(3,5)*H*), 7.65-7.68 (1H, m, Ar(4)*H*), 8.01-8.03 (2H, m, Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[221]

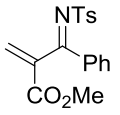
Dimethyl 2-(phenyl(tosylimino)methyl)fumarate



505

To a solution of *N*-benzylidene-4-methylbenzenesulfonamide (1.00 g, 3.86 mmol) in THF (25 mL) was added dimethyl acetylenedicarboxylate (0.56 mL, 4.63 mmol) and the reaction mixture was stirred at rt for 5 minutes. DMAP (94.0 mg, 0.77 mmol) was added and the reaction mixture was stirred at 60 °C for 16 h before being concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 40:60) gave imine **505** as a white solid (0.53 g, 34%); mp 124-126 °C; {lit.[222] mp 128-130 °C}; δ_H (300 MHz, $CDCl_3$) 2.46 (3H, s, ArCH_3), 3.61 (3H, s, CO_2CH_3), 3.87 (3H, s, CO_2CH_3), 7.23 (1H, s, C*H*), 7.35 (2H, d, *J* 8.0, SO_2Ar(3,5)*H*), 7.40-7.46 (2H, m, Ph(3,5)*H*), 7.54-7.60 (1H, m, Ph(4)*H*), 7.85-7.91 (4H, m, Ph(2,6)*H* and SO_2Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[222]

Methyl 2-(phenyl(tosylimino)methyl)acrylate

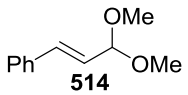


506

To a solution of *N*-benzylidene-4-methylbenzenesulfonamide (1.00 g, 3.86 mmol) and PPh_3 (202 mg, 0.77 mmol) in toluene (60 mL) at 80 °C was added a solution of methyl

propiolate (0.41 mL, 4.63 mmol) in toluene (20 mL) dropwise over 3 h. After complete addition the reaction mixture was cooled and concentrated *in vacuo*. Chromatographic purification (eluent Et_2O:petrol 25:75) gave imine **506** as a colourless oil (0.35 g, 27%); δ_H (500 MHz, $CDCl_3$) 2.47 (3H, s, ArC*H*$_3$), 3.81 (3H, s, CO_2C*H*$_3$), 5.96 (1H, s, =C*H*H), 6.86 (1H, s, =CH*H*), 7.37 (2H, d, *J* 8.1, SO_2Ar(3,5)*H*), 7.44 (2H, t, *J* 7.9, Ph(3,5)*H*), 7.59 (1H, t, *J* 7.4, Ph(4)*H*), 7.88-7.93 (4H, m, Ph(2,6)*H* and SO_2Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[223]

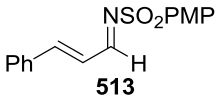
(*E*)-(3,3-dimethoxyprop-1-en-1-yl)benzene



514

To a solution cinnamaldehyde (3.90 mL, 31.0 mmol) in MeOH (100 mL) was added *p*-TSA monohydrate (178 mg, 0.93 mmol) and trimethyl orthoformate (6.80 mL, 62.0 mmol) and the reaction mixture was heated at 80 °C for 3 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and concentrated *in vacuo*. The reaction mixture was diluted with Et_2O and washed with H_2O. The organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual oil was purified by distillation to give acetal **514** as a colourless oil (4.49 g, 81%); bp 126-128 °C (22 mmHg); {lit.[5] bp 115 °C (20 mmHg)}; δ_H (500 MHz, $CDCl_3$) 3.41 (6H, s, 2 C*H*$_3$), 5.00 (1H, dd, *J* 4.9, 1.1, C(3)*H*), 6.19 (1H, dd, *J* 16.2, 4.9, C(2)*H*), 6.76 (1H, d, *J* 16.0, C(1)*H*), 7.28-7.31 (1H, m, Ar(4)*H*), 7.35-7.38 (2H, m, Ar(3,5)*H*), 7.44-7.45 (2H, m, Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[224]

(*E*)-4-methoxy-*N*-((*E*)-3-phenylallylidene)benzenesulfonamide



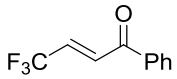
513

A flask was charged with acetal **514** (2.00 g, 11.2 mmol) 4-methoxybenzenesulfonamide (2.10 g, 11.2 mmol) and the contents were heated to 180 °C without a stopper for 30 minutes. Recrystallisation (EtOAc:Et_2O) gave imine **513** as a light yellow solid (1.86 g, 55%); mp 118-120 °C; δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, C*H*$_3$), 6.98-7.05 (3H, m, =C*H*CH=N and SO_2Ar(3,5)*H*), 7.44-7.52 (4H, m, Ph(3,5)*H*, Ph(4)*H* and PhC*H*=), 7.56-7.58 (2H, m, Ph(2,6)*H*), 7.92-7.94 (2H, m, SO_2Ar(2,6)*H*), 8.78 (1H, d, *J* 9.4, C*H*=N). Spectroscopic data are in accordance with the literature.[158]

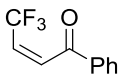
General Procedure Q*: Preparation of trifluoromethyl enones*.

To a solution of *i*-Pr_2NH (2.2 eq) in THF at −78 °C was added *n*-BuLi (2.2 eq) and the solution was allowed to stir for 20 minutes. A pre-cooled (−78 °C) solution of 2-bromo-3,3,3-trifluoroprop-1-ene (1 eq) in THF was added dropwise at −78 °C followed by a further 5 minutes of stirring. The desired aldehyde (1.2 eq) was added slowly followed by stirring at −78 °C for 30 minutes. The reaction mixture was quenched by addition of HCl (1 M in H_2O) and allowed to warm to rt. The reaction mixture was extracted with EtOAc (x 3) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude intermediate propargyl alcohol. The residual oil was dissolved in THF and Et_3N (4 eq) was added before the reaction mixture was heated at reflux for 16 h. Once cool the reaction mixture was quenched by addition of HCl (1 M in H_2O) and the reaction mixture was extracted with EtOAc (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture typically containing an 80:20 mixture of (*E*)- and (*Z*)-enones.

(*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-one and (*Z*)-4,4,4-trifluoro-1-phenylbut-2-en-1-one



488



489

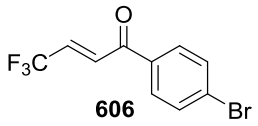
Following general procedure Q, diisopropylamine (15.42 mL, 110 mmol) and *n*-BuLi (2.5M in hexanes, 44.0 mL, 110 mmol) in THF (130 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (5.30 mL, 50.0 mmol) in THF (90 mL) and benzaldehyde (6.10 mL, 60.0 mmol) gave the intermediate alcohol. Subsequent treatment with Et_3N (27.9 mL, 200 mmol) in THF (280 mL) gave, after chromatographic purification (eluent Et_2O:petrol 5:95):

(*E*)-enone **488** as a light yellow solid (7.22 g, 72% over 2 steps); mp 26-28 °C; {lit.[225] mp 28 °C}; δ_H (500 MHz, $CDCl_3$) 6.85 (1H, dq, *J* 15.6, 6.6, C(3)*H*), 7.55-7.59 (3H, m, C(2)*H* and Ar(3,5)*H*), 7.66-7.69 (1H, m, Ar(4)*H*), 8.00-8.02 (2H, m, Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[225]

(*Z*)-enone **489** as a light yellow oil (1.72 g, 17% over 2 steps); δ_H (500 MHz, $CDCl_3$) 6.12 (1H, dq, *J* 12.8, 7.9, C(3)*H*), 6.90 (1H, d, *J* 12.8, C(2)*H*), 7.54 (2H, t, *J* 7.8, Ar(3,5)*H*),

7.65-7.68 (1H, m, Ar(4)*H*), 7.95-7.97 (2H, m, Ar(2,6)*H*). Spectroscopic data are in accordance with the literature.[226]

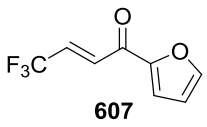
(2*E*)-1-(4-bromophenyl)-4,4,4-trifluorobut-2-en-1-one



606

Following general procedure Q, diisopropylamine (7.71 mL, 55.0 mmol) and *n*-BuLi (2.5M in hexanes, 22.0 mL, 55.0 mmol) in THF (65 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (2.65 mL, 25.0 mmol) in THF (45 mL) and 4-bromobenzaldehyde (5.55 g, 30.0 mmol) gave the intermediate alcohol. Subsequent treatment with Et_3N (13.9 mL, 100 mmol) in THF (140 mL) gave, after chromatographic purification (eluent Et_2O:petrol 3:97), enone **606** as a light yellow solid (3.75 g, 54% over 2 steps); mp 52-54 °C; {lit.[227] mp 51-52 °C}; δ_H (500 MHz, $CDCl_3$) 6.86 (1H, dq, *J* 15.5, 6.6, C(3)*H*), 7.51 (1H, dq, *J* 15.5, 2.0, C(2)*H*), 7.69-7.72 (2H, m, Ar*H*), 7.86-7.88 (2H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[227]

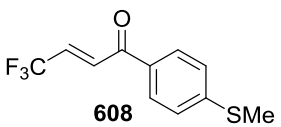
(*E*)-4,4,4-trifluoro-1-(furan-2-yl)but-2-en-1-one



607

Following general procedure Q, diisopropylamine (7.71 mL, 55.0 mmol) and *n*-BuLi (2.5M in hexanes, 22.0 mL, 55.0 mmol) in (65 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (2.65 mL, 25.0 mmol) in THF (45 mL) and furfural (2.50 mL, 30.0 mmol) gave the intermediate alcohol. Subsequent treatement with Et_3N (13.9 mL, 100 mmol) in THF (140 mL) gave, after chromatographic purification (eluent Et_2O:petrol 10:90), enone **607** as an off-white solid (2.48 g, 52% over 2 steps); mp 66-68 °C; {lit.[228] mp 64-66 °C}; δ_H (500 MHz, $CDCl_3$) 6.67 (1H, dd, *J* 3.65, 1.7, C(1)Ar(4)*H*), 6.92 (1H, dq, *J* 15.6, 6.7, C(3)*H*), 7.41-7.46 (2H, m, C(2)*H* and Ar*H*), 7.73 (1H, m, Ar*H*). Spectroscopic data are in accordance with the literature.[228]

(*E*)-4,4,4-trifluoro-1-(4-(methylthio)phenyl)but-2-en-1-one



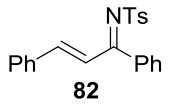
608

Following general procedure Q, diisopropylamine (7.71 mL, 55.0 mmol) and *n*-BuLi (2.5M in hexanes, 22.0 mL, 55.0 mmol) in THF (65 mL), 2-bromo-3,3,3-trifluoroprop-1-ene (2.65 mL, 25.0 mmol) in THF (45 mL) and 4-(methylthio)benzaldehyde (3.99 mL, 30.0 mmol) gave the intermediate alcohol. Subsequent treatement with Et_3N (13.9 mL, 100 mmol) in THF (140 mL) gave, after chromatographic purification (eluent Et_2O:petrol 10:90), enone **608** as a light yellow solid (3.48 g, 57% over 2 steps); mp 102-104 °C; ν_{max} (ATR) 3123 (C-H), 2967, 1682 (C=O), 1636, 1585; δ_H (500 MHz, $CDCl_3$) 2.57 (3H, s, C*H*$_3$), 6.84 (1H, dq, *J* 15.5, 6.7, C(3)*H*), 7.33-7.35 (2H, m, C(1)Ar(3,5)*H*), 7.54 (1H, dq, *J* 15.5, 2.0, C(2)*H*), 7.91-7.93 (2H, m, C(1)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 122.6 (q, *J* 268, *C*F$_3$), 125.1 (C(1)*ArC*(3,5)), 129.2 (C(1)*ArC*(2,6)), 130.0, (q, *J* 35.0, *C*(3)), 130.9 (q, *J* 5.5, *C*(2)), 132.4 (C(1)*ArC*(4)), 147.9 (C(1)*ArC*(1)), 168.7 (*C*(1)); *m*/*z* (APCI$^+$) 247 ([M+H]$^+$, 10%); HRMS (APCI$^+$) $C_{11}H_{10}F_3OS^+$ ([M+H]$^+$) requires 247.0399; found 247.0396 (-1.2 ppm).

General Procedure R*: Preparation of imines.*

To a solution of the desired enone (1 eq) and 4-toluenesulfonamide (1 eq) in CH_2Cl_2 at 0 °C was added Et_3N (2 eq) followed by $TiCl_4$ (1 eq) and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was quenched by addition of H_2O and extracted with EtOAc (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture.

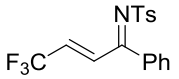
***N*-((*E*)-1,3-diphenylallylidene)-4-methylbenzenesulfonamide**



82

Following general procedure R, chalcone (2.08 g, 10.0 mmol) and 4-toluenesulfonamide (1.71 g, 10.0 mmol) in CH_2Cl_2 (20 mL), Et_3N (2.79 mL, 20.0 mmol) and $TiCl_4$ (1.10 mL, 10.0 mmol) gave, after recrystallisation (EtOAc:Petrol), imine **82** as a light yellow solid (1.68 g, 46%); mp 146-148 °C; {lit.[229] mp 147-149 °C}; δ_H (500 MHz, $CDCl_3$) 2.45 (3H, s, C*H*$_3$), 7.09 (1H, d, *J* 16.2, C(2)*H*), 7.34 (2H, m, Ar*H*), 7.43-7.47 (5H, m, Ar*H*), 7.55-7.68 (5H, m, Ar*H*), 7.94-8.10 (3H, m, Ar*H* and C(3)*H*). Spectroscopic data are in accordance with the literature.[229]

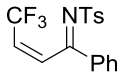
4-methyl-*N*-((*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-ylidine)benzenesulfonamide



486

Following general procedure R, trifluoromethyl enone **488** (7.22 g, 36.1 mmol) and 4-toluenesulfonamide (6.18 g, 36.1 mmol) in CH_2Cl_2 (200 mL), Et_3N (10.1 mL, 72.2 mmol) and $TiCl_4$ (3.98 mL, 36.1 mmol) gave, after recrystallisation (Et_2O:Petrol), imine **486** as a white solid (10.2 g, 80%); mp 102-104 °C; ν_{max} (ATR) 3053 (C-H), 1597, 1582, 1549, 1306 (S=O), 1146 (S=O); δ_H (500 MHz, $CDCl_3$) 2.47 (3H, s, CH_3), 6.15 (1H, dq, *J* 16.3, 6.1, C(3)*H*), 7.38 (2H, d, *J* 8.0, SO_2Ar(3,5)*H*), 7.48 (2H, t, *J* 7.7, C(1)Ar(3,5)*H*), 7.62 (1H, t, *J* 7.4, C(1)Ar(4)*H*), 7.67-7.80 (2H, m, SO_2Ar(2,6)*H*), 7.82-8.00 (3H, m, C(2)*H* and C(1)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 21.7 (*C*H_3), 121.9 (q, *J* 270, *C*F_3), 126.5 (*C*(3)), 127.5 (C(1)*ArC*(3,5)), 128.9 (C(1)*ArC*(4)), 129.7 (C(1)*ArC*(2,6)), 130.2 (SO_2*ArC*), 131.7 (SO_2*ArC*), 133.7 (*C*(2)), 135.5 (SO_2*ArC*(4)), 137.4 (C(1)*ArC*(1)), 144.3 (SO_2*ArC*(1)), 172.9 (*C*(1)); *m*/*z* (APCI$^+$) 354 ([M+H]$^+$, 100%); HRMS (APCI$^+$) $C_{17}H_{15}F_3NO_2S^+$ ([M+H]$^+$) requires 354.0770; found 354.0768 (-0.6 ppm).

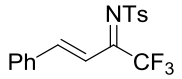
4-methyl-*N*-((*Z*)-4,4,4-trifluoro-1-phenylbut-2-en-1-ylidine)benzenesulfonamide



487

Following general procedure R, trifluoromethyl enone **489** (1.72 g, 8.60 mmol) and 4-toluenesulfonamide (1.47 g, 8.60 mmol) in CH_2Cl_2 (50 mL), Et_3N (2.40 mL, 17.2 mmol) and $TiCl_4$ (0.95 mL, 8.60 mmol) gave, after recrystallisation (Et_2O:Petrol), imine **487** (90% pure with 10% $TsNH_2$ impurity) as a white solid (0.64 g, 21%); mp 98-100 °C; ν_{max} (ATR) 2968 (C-H), 1587, 1557, 1310 (S=O), 1143 (S=O); δ_H (500 MHz, $CDCl_3$) 2.48 (3H, s, CH_3), 6.20 (1H, dq, *J* 12.8, 7.7, C(3)*H*), 7.18 (1H, d, *J* 12.8, C(2)*H*), 7.39 (2H, d, *J* 8.0, SO_2Ar(3,5)*H*), 7.47 (2H, t, *J* 7.9, C(1)Ar(3,5)*H*), 7.62 (1H, t, *J* 7.4, C(1)Ar(4)*H*), 7.92-7.95 (4H, m, C(1)Ar(2,6)*H* and SO_2Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 21.7 (*C*H_3), 121.7 (q, *J* 270, *C*F_3), 122.1 (q, *J* 34.8, *C*(3)), 127.6 (*ArC*), 128.9 (*ArC*), 129.5 (*ArC*), 129.6 (*ArC*), 132.7 (q, *J* 5.4, *C*(2)), 134.2 (C(1)*ArC*(4)), 134.5 (SO_2*ArC*(4)), 137.2 (C(1)*ArC*(1)), 144.2 (SO_2*ArC*(1)), 172.8 (*C*(1)); *m*/*z* (NSI$^+$) 354 ([M+H]$^+$, 12%); HRMS (NSI$^+$) $C_{17}H_{15}F_3NO_2S^+$ ([M+H]$^+$) requires 354.0770; found 354.0762 (-2.3 ppm).

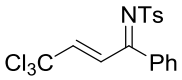
4-methyl-N-((*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-ylidene)benzenesulfonamide



492

Following general procedure R, trifluoromethyl enone **220** (1.50 g, 7.50 mmol) and 4-toluenesulfonamide (1.29 g, 7.50 mmol) in CH_2Cl_2 (20 mL), Et_3N (2.10 mL, 15.0 mmol) and $TiCl_4$ (0.83 mL, 7.50 mmol) gave, after recrystallisation (EtOAc:Petrol), imine **492** as a light yellow solid (404 mg, 19%); mp 140-142 °C; ν_{max} (ATR) 3053 (C-H), 1608, 1585, 1574, 1306 (S=O), 1146 (S=O); δ_H (500 MHz, $CDCl_3$) 2.49 (3H, s, C*H*$_3$), 7.40 (2H, d, *J* 8.1, SO_2Ar(3,5)*H*), 7.48-7.55 (3H, m, C(4)Ar(3,4,5)*H*), 7.66-7.70 (3H, m, C(4)Ar(2,6)*H* and =C*H*), 7.87 (1H, dd, *J* 16.7, 1.6, =C*H*), 7.94 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 21.7 (*C*H$_3$), 116.0 (*C*(4)), 119.1 (q, *J* 280, *C*F$_3$), 127.5 (*ArC*), 129.3 (*ArC*), 129.4 (*ArC*), 129.8 (*ArC*), 132.5 (C(4)*ArC*(4)), 133.9 (C(4)*ArC*(1)), 137.0 (SO_2*ArC*(4)), 144.7 (SO_2*ArC*(1)), 149.2 (q, *J* 2.5, *C*(3)), 161.2 (q, *J* 33.8, *C*(2)); *m*/*z* (APCI$^+$) 354 ([M+H]$^+$, 100%); HRMS (APCI$^+$) $C_{17}H_{14}F_3NO_2S^+$ ([M+H]$^+$) requires 354.0770; found 354.0766 (-1.2 ppm).

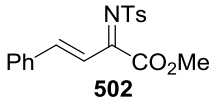
4-methyl-*N*-((*E*)-4,4,4-trichloro-1-phenylbut-2-en-1-ylidine)benzenesulfonamide



499

Following general procedure R, trichloromethyl enone **501** (2.84 g, 11.4 mmol) and 4-toluenesulfonamide (1.96 g, 11.4 mmol) in CH_2Cl_2 (30 mL), Et_3N (3.17 mL, 22.8 mmol) and $TiCl_4$ (1.25 mL, 11.4 mmol) gave, after recrystallisation (Et_2O:Petrol), imine **499** as a white solid (3.45 g, 75%); mp 126-128 °C; ν_{max} (ATR) 3059 (C-H), 1595, 1580, 1543, 1317 (S=O), 1153 (S=O); δ_H (500 MHz, $CDCl_3$) 2.47 (3H, s, C*H*$_3$), 6.60 (1H, d, *J* 15.3, C(3)*H*), 7.37 (2H, d, *J* 8.0, SO_2Ar(3,5)*H*), 7.49 (2H, t, *J* 7.7, C(1)Ar(3,5)*H*), 7.62 (1H, t, *J* 7.4, C(1)Ar(4)*H*), 7.70-7.80 (2H, m, SO_2Ar(2,6)*H*), 7.90-7.95 (3H, m, C(2)*H* and C(1)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 21.7 (*C*H$_3$), 92.4 (*C*Cl$_3$), 124.5 (*C*(2)), 127.5 (C(1)*ArC*(2,6)), 128.8 (C(1)*ArC*(3,5)), 129.7 (SO_2*ArC*(3,5)), 130.3 (SO_2*ArC*(2,6)), 133.5 (C(1)*ArC*(4)), 133.7 (*C*(2)), 137.6 (SO_2*ArC*(4)), 137.4 (C(1)*ArC*(1)), 144.2 (SO_2*ArC*(1)), 145.3 (*C*(3)), 173.8 (*C*(1); *m*/*z* (APCI$^+$) 402 ([M+H]$^+$, 75%); HRMS (APCI$^+$) $C_{17}H_{15}Cl_3NO_2S^+$ ([M+H]$^+$) requires 401.9884; found 401.9880 (-0.9 ppm).

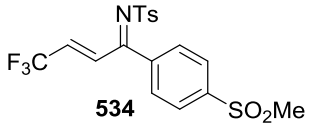
(3*E*)-methyl 4-phenyl-2-(tosylimino)but-3-enoate



502

Following general procedure R, keto ester **143** (1.60 g, 8.42 mmol) and 4-toluenesulfonamide (1.44 g, 8.42 mmol) in CH_2Cl_2 (20 mL), Et_3N (2.35 mL, 16.8 mmol) and $TiCl_4$ (0.93 mL, 8.42 mmol) gave, after chromatographic purification (eluent Et_2O:petrol 50:50), imine **502** as a yellow oil (1.59 g, 55%); ν_{max} (ATR) 3061 (C-H), 1736 (C=O), 1612, 1560, 1310 (S=O), 1145 (S=O); δ_H (500 MHz, $CDCl_3$) 2.46 (3H, s, ArC*H*$_3$), 4.10 (3H, s, CO_2C*H*$_3$), 6.86 (1H, d, *J* 16.4, C(3)*H*), 7.36-7.54 (8H, m, Ar*H* and C(4)*H*), 7.92 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 21.7 (Ar*C*H$_3$), 53.6 (CO_2*C*H$_3$), 123.4 (*C*(3)), 128.1 (*ArC*), 128.8 (*ArC*), 129.2 (*ArC*), 129.2 (*ArC*), 129.8 (*ArC*), 131.9 (C(4)*ArC*(4)), 133.9 (C(4)*ArC*(1)), 135.7 (SO_2*ArC*(4)), 149.7 (*C*(4)), 165.0 (*C*(2)), 167.5 (*C*(1)); *m*/*z* (NSI^+) 344 ($[M+H]^+$, 18%); HRMS (NSI^+) $C_{18}H_{18}NO_4S^+$ ($[M+H]^+$) requires 344.0951; found 344.0955 (+1.1 ppm).

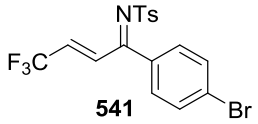
4-methyl-*N*-((*E*)-4,4,4-trifluoro-1-(4-(methylsulfonyl)phenyl)but-2-en-1-ylidine)benzenesulfonamide



534

To a solution of imine **611** (4.60 g, 11.5 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added *m*-CPBA (70% w/w, 5.70 g, 23.0 mmol) portionwise and the reaction mixture was allowed to stir at rt for 30 minutes. The reaction mixture was quenched by addition of sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallisation (Et_2O:Petrol) gave imine **534** as a white solid (2.85 g, 57%); mp 126-130 °C; ν_{max} (ATR) 3098 (C-H), 2920, 1584, 1558, 1309 (S=O), 1145 (S=O); δ_H (500 MHz, $CDCl_3$) 2.48 (3H, s, ArC*H*$_3$), 3.09 (3H, s, SO_2C*H*$_3$), 6.09-6.17 (1H, m, C(3)*H*), 7.38-7.40 (2H, m, NSO_2Ar(3,5)*H*), 7.66-8.05 (7H, m, Ar*H* and C(2)*H*); δ_C (125 MHz, $CDCl_3$) 21.7 (Ar*C*H$_3$), 44.3 (SO_2*C*H$_3$), 121.7 (q, *J* 270, *C*F$_3$), 124.0 (*C*(3)), 127.6 (*ArC*), 127.9 (*ArC*), 129.9 (*ArC*), 130.9, (*ArC*), 136.6 (4ry *C*), 138.2 (*C*(2)), 140.3 (4ry *C*), 144.4 (4ry *C*), 144.9 (4ry *C*), 171.0 (*C*(1)); *m*/*z* (NSI^+) 432 ($[M+H]^+$, 5%); HRMS (NSI^+) $C_{18}H_{17}F_3NO_4S_2^+$ ($[M+H]^+$) requires 432.0546; found 432.0543 (-0.6 ppm).

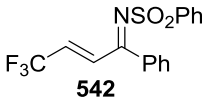
***N*-[(1*Z*,2*E*)-1-(4-bromophenyl)-4,4,4-trifluorobut-2-en-1-ylidine]-4-methylbenzene-1-sulfonamide**



541

Following general procedure R, trifluoromethyl enone **606** (3.75 g, 13.44 mmol) and 4-toluenesulfonamide (2.30 g, 13.4 mmol) in CH_2Cl_2 (60 mL), Et_3N Et_3N (3.76 mL, 26.9 mmol) and $TiCl_4$ (1.48 mL, 13.4 mmol) gave, after recrystallisation (Et_2O:Petrol) gave imine **541** as a white solid (2.96 g, 56%); mp 78-80 °C; ν_{max} (ATR) 3103 (C-H), 1574, 1549, 1305 (S=O), 1144 (S=O); δ_H (500 MHz, $CDCl_3$) 2.47 (3H, s, CH_3), 6.15 (1H, dq, *J* 16.3, 6.1, C(3)*H*), 7.38 (2H, d, *J* 8.0, C(1)Ar(2,6)*H*), 7.62 (4H, app. s, SO_2Ar*H*), 7.85-7.92 (3H, m, C(2)*H* and C(1)Ar(3,5)*H*); δ_C (125 MHz, $CDCl_3$) 21.7 (*C*H_3), 121.8 (q, *J* 282, *C*F_3), 127.5 (C(1)*ArC*(3,5)), 129.2 (C(1)*ArC*(4)), 129.7 (C(1)*ArC*(2,6)), 129.7, (*C*(2)), 131.5 (SO_2*ArC*), 131.5 (SO_2*ArC*), 132.2 (*C*(3)), 134.3 (SO_2*ArC*(4)), 137.1 (C(1)*ArC*(1)), 144.5 (SO_2*ArC*(1)), 171.7 (*C*(1)); *m*/*z* (APCI$^+$) 432 ([M+H]$^+$, 95%); HRMS (APCI$^+$) $C_{17}H_{14}{}^{79}BrF_3NO_2S^+$ ([M+H]$^+$) requires 431.9875; found 431.9875 (+0.0 ppm).

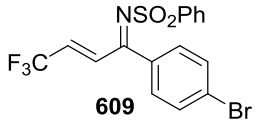
_N_-((_E_)-4,4,4-trifluoro-1-phenylbut-2-en-1-ylidine)benzenesulfonamide



542

Following general procedure R, trifluoromethyl enone **488** (7.22 g, 36.1 mmol) and benzenesulfonamide (5.67 g, 36.1 mmol) in CH_2Cl_2 (200 mL), Et_3N (10.1 mL, 72.2 mmol) and $TiCl_4$ (3.98 mL, 36.1 mmol) gave, after recrystallisation (Et_2O:Petrol), imine **542** as a white solid (6.98 g, 57%); mp 72-74 °C; ν_{max} (ATR) 3083 (C-H), 1551, 1304 (S=O), 1151 (S=O); δ_H (500 MHz, $CDCl_3$) 6.18 (1H, dq, *J* 16.3, 6.1, C(3)*H*), 7.48-7.68 (7H, m, Ar*H*), 7.70-7.80 (2H, m, Ar*H*), 7.85-7.95 (1H, m, C(2)*H*), 8.05 (2H, d, *J* 4.1, C(1)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 121.9 (q, *J* 270, *C*F_3), 126.4 (*C*(3)), 127.4 (C(1)*ArC*(3,5)), 128.9 (C(1)*ArC*(4)), 129.1 (C(1)*ArC*(2,6)), 130.2 (SO_2*ArC*), 131.7 (SO_2*ArC*), 133.4 (*C*(2)), 133.9 (SO_2*ArC*(4)), 135.3 (C(1)*ArC*(1)), 140.3 (SO_2*ArC*(1)), 173.3 (*C*(1)); *m*/*z* (NSI$^+$) 340 ([M+H]$^+$, 7%); HRMS (NSI$^+$) $C_{16}H_{13}F_3NO_2S^+$ ([M+H]$^+$) requires 340.0614; found 340.0615 (+0.4 ppm).

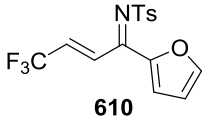
_N_-((_E_)-1-(4-bromophenyl)-4,4,4-trifluorobut-2-en-1-ylidine)-benzenesulfonamide



609

Following general procedure R, trifluoromethyl enone **606** (4.62 g, 16.6 mmol) and benzenesulfonamide (2.61 g, 16.6 mmol) in CH_2Cl_2 (70 mL), Et_3N (4.63 mL, 33.1 mmol) and $TiCl_4$ (1.82 mL, 16.6 mmol) gave, after chromatographic purification (eluent Et_2O:petrol 15:85), imine **609** as an orange oil (3.46 g, 50%); ν_{max} (ATR) 3110 (C-H), 1574, 1549, 1310 (S=O), 1147 (S=O); δ_H (500 MHz, $CDCl_3$) 6.17 (1H, dq, *J* 16.3, 6.1, C(3)*H*), 7.57-7.70 (7H, m, Ar*H*), 7.82-7.93 (1H, m, C(2)*H*), 8.04 (2H, d, *J* 5.8, C(1)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 121.8 (q, *J* 270, *C*F_3), 127.5 (C(1)*ArC*(3,5)), 129.2 (C(1)*ArC*(2,6)), 129.3 (C(1)*ArC*(4)), 130.1 (*C*(3)), 131.5 (SO_2*ArC*), 131.5 (SO_2*ArC*), 132.3 (*C*(2)), 134.5 (SO_2*ArC*), 134.3 (SO_2*ArC*(1)), 140.1 (C(1)*ArC*(1)), 172.1 (*C*(1)); *m*/*z* (NSI^+) 419 ($[M+H]^+$, 65%); HRMS (NSI^+) $C_{16}H_{11}{}^{81}BrF_3NO_2S^+$ ($[M+H]^+$) requires 419.9704; found 419.9694 (-1.2 ppm).

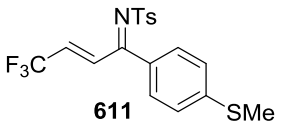
N-((*E*)-1-(furan-2-yl)-4,4,4-trifluorobut-2-en-1-ylidine)-4-methylbenzenesulfonamide



610

Following general procedure R, trifluoromethyl enone **607** (2.48 g, 13.1 mmol) and 4-toluenesulfonamide (2.23 g, 13.1 mmol) in CH_2Cl_2 (60 mL), Et_3N (3.65 mL, 26.1 mmol) and $TiCl_4$ (1.44 mL, 13.1 mmol) gave, after recrystallisation (Et_2O:Petrol), imine **610** as a light brown solid (2.79 g, 62%); mp 80-82 °C; ν_{max} (ATR) 3110 (C-H), 2989, 1595, 1566, 1539, 1305 (S=O), 1146 (S=O); δ_H (300 MHz, $(CD_3)_2S=O$, 80 °C) 2.32 (3H, s, CH_3), 6.61-6.73 (2H, m, C(3)*H* and C(1)Ar(4)*H*), 7.35 (2H, d, *J* 8.0, SO_2Ar(3,5)*H*), 7.40 (1H, d, *J* 3.7, C(1)Ar(3)*H*), 7.52 (1H, dq, *J* 16.3, 2.1, C(2)*H*), 7.73 (2H, d, *J* 8.3, SO_2Ar(2,6)*H*), 8.04 (1H, d, *J* 1.1, C(1)Ar(5)*H*); δ_C (75 MHz, $(CD_3)_2S=O$, 80 °C) 21.4 (*C*H_3), 114.6 (C(1)*ArC*(4)), 122.8 (q, *J* 269, *C*F_3), 125.5 (C(1)*ArC*(3)), 126.7 (q, *J* 34.0, *C*(3)), 127.3 (SO_2*ArC*(2,6)), 130.2 (SO_2*ArC*(3,5)), 132.1 (q, *J* 7.1, *C*(2)), 138.3 (SO_2*ArC*(1)), 144.4 (SO_2*ArC*(4)), 149.4 (C(1)*ArC*(2)), 151.6 (C(1)*ArC*(5)) 159.7 (*C*(1)); *m*/*z* ($APCI^+$) 344 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{15}H_{13}F_3NO_3S^+$ ($[M+H]^+$) requires 344.0563; found 344.0561 (-0.5 ppm).

4-methyl-*N*-((*E*)-4,4,4-trifluoro-1-(4-(methylthio)phenyl)but-2-en-1-ylidine)benzenesulfonamide



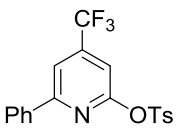
611

Following general procedure R, trifluoromethyl enone **608** (3.27 g, 13.3 mmol) and 4-toluenesulfonamide (2.28 g, 13.3 mmol) in CH_2Cl_2 (60 mL), Et_3N (3.73 mL, 26.6 mmol) and $TiCl_4$ (1.47 mL, 13.3 mmol) gave, chromatographic purification (eluent Et_2O:petrol 40:60), imine **611** as a yellow solid (4.60 g, 87%); mp 80-82 °C; ν_{max} (ATR) 3106 (C-H), 2924, 1560, 1535, 1306 (S=O), 1144 (S=O); δ_H (500 MHz, $CDCl_3$) 2.47 (3H, s, CH_3), 2.54 (3H, s, CH_3), 6.13 (1H, dq, *J* 16.5, 5.8, C(3)*H*), 7.27 (2H, d, *J* 8.5, SO_2Ar(3,5)*H*), 7.37 (2H, d, *J* 8.1, C(1)Ar(3,5)*H*), 7.67 (2H, d, *J* 7.2, SO_2Ar(2,6)*H*)), 7.81 (1H, br s, C(2)*H*), 7.92 (2H, d, *J* 8.1, C(1)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 14.7 (S*C*H$_3$), 21.7 (Ar*C*H$_3$), 121.9 (q, *J* 270, *C*F$_3$), 125.1 (*ArC*), 127.4 (*ArC*), 128.9 (*C*), 129.6 (*ArC*), 130.5 (*C*), 131.2 (C(1)*ArC*(1)), 131.9 (*C*), 137.6 (4ry *C*), 144.2 (4ry *C*), 148.0 (4ry *C*), 172.0 (*C*(1)); *m*/*z* (NSI^+) 400 ($[M+H]^+$, 45%); HRMS (NSI^+) $C_{18}H_{17}F_3NO_2S_2^+$ ($[M+H]^+$) requires 400.0647; found 400.0646 (-0.3 ppm).

General procedure S: *Intermolecular formal [4+2] cycloaddition.*

To a solution of (phenylthio)acetic acid (1 eq) in THF (~1 mL per 0.1 mmol of acid) were added *i*-Pr$_2$NEt (1.5 eq) and pivaloyl chloride (1.5 eq) at rt. The reaction mixture was allowed to stir at rt for 10 minutes. The requisite Michael acceptor (1 eq), DHPB (20 mol%) and *i*-Pr$_2$NEt (1 eq) were then added at rt and the reaction mixture was stirred at reflux for the required time for complete conversion to the pyridine. The reaction mixture was subsequently quenched by addition of H_2O and extracted with CH_2Cl_2 (x 3). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude reaction mixture.

6-phenyl-4-(trifluoromethyl)pyridin-2-yl 4-methylbenzene-1-sulfonate



491

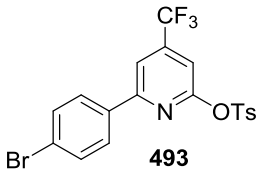
Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr$_2$NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **486**

(177 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 16 h at 80 °C gave, after chromatographic purification (eluent Et_2O:petrol 10:90), pyridine **491** as light yellow solid (113 mg, 58%) which was recrystallised (Et_2O:petrol) for an analytical sample; mp 100-102 °C; ν_{max} (ATR)/cm^{-1} 3109, 2940 (C-H), 1616, 1595, 1564, 1306 (S=O), 1142 (S=O); δ_H (500 MHz, $CDCl_3$) 2.51 (3H, s, CH_3), 7.26 (1H, s, C(3)*H*), 7.40 (2H, d, *J* 8.1, OSO_2Ar(3,5)*H*), 7.45-7.49 (3H, m, C(6)Ar(3,4,5)*H*), 7.78-7.79 (2H, m, C(6)Ar(2,6)*H*), 7.85 (1H, s, *C*(5)*H*), 7.99 (2H, d, *J* 8.2, OSO_2Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (*C*H_3), 109.8 (q, *J* 3.4, (*C*(3)), 114.3 (q, *J* 3.3, *C*(5)), 122.2 (q, *J* 272, *C*F_3), 127.1 (C(6)*ArC*(2,6)), 128.9 (*ArC*), 128.9 (*ArC*), 129.8 (*ArC*), 130.5 (C(6)*ArC*(4)), 134.0 (OSO_2*ArC*(1)), 136.2 (C(6)*ArC*(1)), 143.1 (q, *J* 34.2, C(4)), 145.6 (OSO_2*ArC*(4)), 157.5 (*C*(2) or *C*(6)), 158.0 (*C*(2) or *C*(6)); *m*/*z* ($APCI^+$) 394 ($[M+H]^+$, 100%); HRMS ($APCI^+$) $C_{19}H_{15}F_3NO_3S^+$ ($[M+H]^+$) requires 394.0719; found 394.0721 (+0.4 ppm).

Scale-up: Following general procedure S, (phenylthio)acetic acid (4.35 g, 25.9 mmol) in THF (250 mL), *i*-Pr_2NEt (6.73 mL, 38.9 mmol), pivaloyl chloride (4.80 mL, 38.9 mmol), imine **486** (9.13 g, 25.9 mmol), DHPB **108** (0.98 g, 5.18 mmol, 20 mol%) and *i*-Pr_2NEt (4.48 mL, 25.9 mmol) for 16 h at 80 °C gave, after chromatographic purification (eluent Et_2O:petrol 10:90), pyridine **491** as light yellow solid (5.18 g, 51%) with identical spectroscopic properties to above.

From (*Z*)-imine **487**: Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr_2NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **487** (177 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 16 h at 80 °C gave, after chromatographic purification (eluent Et_2O:petrol 10:90), pyridine **491** as light yellow solid (107 mg, 54%) with identical spectroscopic properties to above.

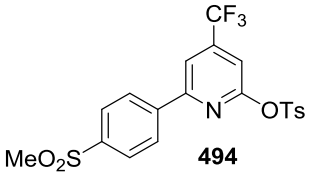
6-(4-bromophenyl)-4-(trifluoromethyl)pyridin-2-yl 4-methylbenzene-1-sulfonate



493

Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr_2NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **541** (216 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 16 h at 80 °C gave, chromatographic purification (eluent Et_2O:petrol 10:90), pyridine **493** as white solid (146.8 mg, 62%) which was recrystallised (Et_2O:petrol) for an analytical sample; mp 134-136 °C; ν_{max} (ATR)/cm^{-1} 3110 (C-H), 1614, 1591, 1564, 1306 (S=O), 1146 (S=O); δ_H (400 MHz, $CDCl_3$) 2.51 (3H, s, CH_3), 7.26 (1H, s, C(3)*H*), 7.40 (2H, d, *J* 8.6, OSO_2Ar(3,5)*H*), 7.56-7.60 (2H, m, C(6)Ar*H*), 7.65-7.68 (2H, m, C(6)Ar*H*), 7.81 (1H, s, *C*(5)*H*), 7.95-7.98 (2H, m, OSO_2Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (*C*H_3), 110.2 (q, *J* 3.5, (*C*(3)), 114.1 (q, *J* 3.2, *C*(5)), 122.0 (q, *J* 272, *C*F_3), 125.3 (C(6)*ArC*(4)), 128.6 (*ArC*), 128.8 (*ArC*), 129.8 (*ArC*), 132.1 (*ArC*), 134.0 (SO_2*ArC*(1)), 135.1 (C(6)*ArC*(1)), 143.3 (q, *J* 34.4, C(4)), 145.7 (SO_2*ArC*(4)), 156.7 (*C*(6)), 157.5 (*C*(2)); *m*/*z* ($APCI^+$) 472 ($[M+H]^+$, 100%); HRMS ($APCI^+$) $C_{19}H_{14}{}^{79}BrF_3NO_3S^+$ ($[M+H]^+$) requires 471.9824; found 471.9825 (+0.1 ppm).

6-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)pyridin-2-yl 4-methylbenzenesulfonate

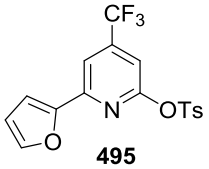


494

Following general procedure S, (phenylthio)acetic acid (0.39 g, 2.32 mmol) in THF (25 mL), *i*-Pr_2NEt (0.60 mL, 3.48 mmol), pivaloyl chloride (0.44 mL, 3.48 mmol), imine **534** (1.00 g, 2.32 mmol), DHPB **108** (88.3 mg, 0.46 mmol, 20 mol%) and *i*-Pr_2NEt (0.41 mL, 2.32 mmol) for 16 h at 80 °C gave, after chromatographic purification (eluent Et_2O:petrol 65:35), pyridine **494** as white solid (580 mg, 53%) which was recrystallised (Et_2O:petrol) for an analytical sample; mp 146-148 °C; ν_{max} (ATR)/cm^{-1} 3118 (C-H), 2934, 2912, 1599, 1562, 1306 (S=O), 1144 (S=O); δ_H (500 MHz, $CDCl_3$) 2.52 (3H, s, ArCH_3), 3.13 (3H, s, SO_2CH_3), 7.35 (1H, s, C(3)*H*), 7.42 (2H, d, *J* 8.0, OSO_2Ar(3,5)*H*), 7.91 (1H, s, *C*(5)*H*), 7.96-8.06 (6H, m, Ar*H*); δ_C (125 MHz, $CDCl_3$) 21.9 (Ar*C*H_3), 44.5 (SO_2*C*H_3), 111.3 (q, *J* 3.5, (*C*(3)), 115.0 (q, *J* 3.1, *C*(5)), 121.9 (q, *J* 272, *C*F_3), 128.1 (*ArC*), 128.1 (*ArC*), 128.7 (*ArC*), 129.9 (*ArC*), 133.8 (OSO_2*ArC*(1)), 141.2 (4ry *ArC*), 142.0 (4ry *ArC*), 143.7 (q, *J* 34.5, C(4)), 145.9 (OSO_2*ArC*(4)), 155.7 (*C*(6)), 157.7

(*C*(2)); *m*/*z* (NSI$^+$) 472 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{20}H_{17}F_3NO_5S_2^+$ ([M+H]$^+$) requires 472.0495; found 472.0485 (-2.1 ppm).

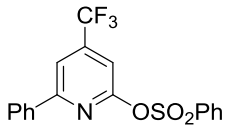
6-(furan-2-yl)-4-(trifluoromethyl)pyridin-2-yl 4-methylbenzene-1-sulfonate



495

Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr$_2$NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **610** (172 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr$_2$NEt (87.5 μL, 0.50 mmol) for 16 h at 80 °C gave, after chromatographic purification (eluent Et$_2$O:petrol 10:90), pyridine **495** as white solid (89.9 mg, 47%) which was recrystallised (Et$_2$O:petrol) for an analytical sample; mp 78-80 °C; ν_{max} (ATR)/cm^{-1} 3090 (C-H), 1624, 1570, 1305 (S=O), 1146 (S=O); δ_H (500 MHz, $CDCl_3$) 2.50 (3H, s, C*H*$_3$), 6.55 (1H, s, C(6)Ar*H*), 6.88 (1H, d, *J* 2.8, C(6)Ar*H*), 7.14 (1H, s, C(3)*H*), 7.42 (2H, d, *J* 7.9, OSO_2Ar(3,5)*H*), 7.56 (1H, s, C(6)Ar(5)*H*), 7.77 (1H, s, *C*(5)*H*), 7.99 (2H, d, *J* 8.0 OSO_2Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 21.8 (*C*H$_3$), 109.2 (q, *J* 3.6, (*C*(3)), 111.6 (C(6)*ArC*), 112.4 (q, *J* 3.4, *C*(5)), 112.6 (C(6)*ArC*), 122.0 (q, *J* 272, *C*F$_3$), 128.9 (SO_2*ArC*), 129.7 (SO_2*ArC*), 133.9 (SO_2*ArC*(1)), 143.1 (q, *J* 34.3, C(4)), 144.6 (C(6)*ArC*(5), 145.6 (SO_2*ArC*(4)), 149.4 (C(6)*ArC*(2)), 151.4 (*C*(6)), 157.4 (*C*(2)); *m*/*z* (APCI$^+$) 384 ([M+H]$^+$, 100%); HRMS (APCI$^+$) $C_{17}H_{13}F_3NO_4S^+$ ([M+H]$^+$) requires 384.0512; found 384.0509 (-0.8 ppm).

6-phenyl-4-(trifluoromethyl)pyridin-2-yl benzene-1-sulfonate

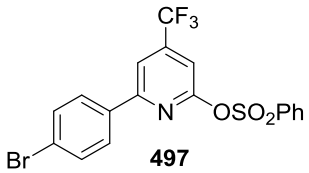


496

Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr$_2$NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **542** (170 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr$_2$NEt (87.5 μL, 0.50 mmol) for 16 h at 80 °C gave, after chromatographic purification (eluent Et$_2$O:petrol 10:90), pyridine **496** as white solid (103 mg, 54%) which was recrystallised

(Et_2O:petrol) for an analytical sample; mp 88-90 °C; ν_{max} (ATR)/cm^{-1} 3118 (C-H), 1570, 1371 (S=O), 1177 (S=O); δ_H (300 MHz, $CDCl_3$) 7.26 (1H, s, C(3)*H*), 7.43-7.50 (3H, m, OSO_2Ar(3,5)*H* and OSO_2Ar(4)*H*), 7.62 (2H, t, *J* 7.8, C(6)Ar(3,5)*H*), 7.72-7.78 (3H, m, C(6)Ar(2,6)*H* and C(6)Ar(4)*H*), 7.85 (1H, s, *C*(5)*H*), 8.11 (2H, d, *J* 8.3, OSO_2Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 109.8 (q, *J* 3.5, (*C*(3)), 114.4 (q, *J* 3.2, *C*(5)), 122.2 (q, *J* 272, *C*F_3), 127.1 (C(6)*ArC*(2,6)), 128.8 (*ArC*), 128.9 (*ArC*), 129.2 (*ArC*), 130.6 (C(6)*ArC*(4)), 134.3 (OSO_2*ArC*(4)), 136.2 (C(6)*ArC*(1)), 137.2 (OSO_2*ArC*(1)), 143.2 (q, *J* 34.1, C(4)), 157.4 (*C*(2) or *C*(6)), 158.0 (*C*(2) or *C*(6)); *m*/*z* (NSI^+) 380 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{18}H_{13}F_3NO_3S^+$ ($[M+H]^+$) requires 380.0563; found 380.0563 (+0.1 ppm).

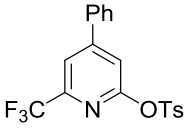
6-(4-bromophenyl)-4-(trifluoromethyl)pyridin-2-yl benzene-1-sulfonate



497

Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr_2NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **609** (209 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 16 h at 80 °C gave, chromatographic purification (eluent Et_2O:petrol 5:10), pyridine **497** as white solid (151 mg, 66%) which was recrystallised (Et_2O:petrol) for an analytical sample; mp 150-152 °C; ν_{max} (ATR)/cm^{-1} 3115 (C-H), 1616, 1564, 1373 (S=O), 1172 (S=O); δ_H (500 MHz, $CDCl_3$) 7.28 (1H, s, C(3)*H*), 7.54-7.65 (6H, m, Ar*H*), 7.75 (1H, t, *J* 7.2, OSO_2Ar(4)*H*), 7.82 (1H, s, *C*(5)*H*), 8.09 (2H, d, *J* 7.6, OSO_2Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 110.2 (q, *J* 3.6, (*C*(3)), 114.2 (q, *J* 3.2, *C*(5)), 122.1 (q, *J* 272, *C*F_3), 125.3 (C(6)*ArC*(4)), 128.6 (*ArC*), 128.7 (*ArC*), 129.2 (*ArC*), 132.1 (*ArC*), 134.3 (SO_2*ArC*(4)), 135.0 (C(6)*ArC*(1)), 137.2 (SO_2*ArC*(1)), 143.4 (q, *J* 34.3, C(4)), 156.8 (*C*(6)), 157.5 (*C*(2)); *m*/*z* (NSI^+) 457 ($[M+H]^+$, 97%); HRMS (NSI^+) $C_{18}H_{12}{}^{79}BrF_3N_2O_2S^+$ ($[M+H]^+$) requires 457.9668; found 457.9667 (-0.2 ppm).

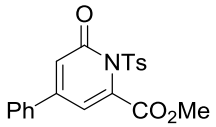
4-phenyl-6-(trifluoromethyl)pyridin-2-yl 4-methylbenzenesulfonate



498

Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr_2NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **492** (177 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 48 h at 80 °C gave, after chromatographic purification (eluent Et_2O:petrol 15:85), pyridine **498** as white solid (79.0 mg, 40%) which was recrystallised (Et_2O:petrol) for an analytical sample; mp 130-132 °C; ν_{max} (ATR)/cm^{-1} 3119 (C-H), 1614, 1597, 1553, 1303 (S=O), 1147 (S=O); δ_H (300 MHz, $CDCl_3$) 2.51 (3H, s, CH_3), 7.41 (2H, d, *J* 8.1, OSO_2Ar(3,5)*H*), 7.52-7.68 (6H, m, Ar*H* and C(3)*H*), 7.80 (1H, s, C(5)*H*), 8.03 (2H, d, *J* 8.0, OSO_2Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 21.8 (*C*H_3), 115.8 (*C*(3)), 117.1 (q, *J* 2.9, *C*(5)), 120.8 (q, *J* 273, *C*F_3), 127.2 (*ArC*), 129.3 (*ArC*), 129.5 (*ArC*), 129.6 (*ArC*), 130.5 (C(4)*ArC*(4)), 133.4 (4ry *ArC*), 135.9 (4ry *ArC*), 145.8 (OSO_2*ArC*(4)), 146.8 (q, *J* 35.7, C(6)), 154.9 (*C*(4)), 157.9 (*C*(2)); *m*/*z* (NSI^+) 394 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{19}H_{15}F_3NO_3S^+$ ($[M+H]^+$) requires 394.0719; found 394.0716 (-0.8 ppm).

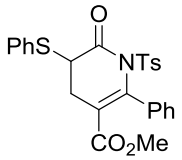
Methyl 6-oxo-4-phenyl-1-tosyl-1,6-dihydropyridine-2-carboxylate



504

Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr_2NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **502** (172 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 16 h at 80 °C gave, after chromatographic purification (eluent Et_2O:petrol 40:60), pyridone **504** as an off-white solid (86.0 mg, 45%); mp 150-152 °C; ν_{max} (ATR)/cm^{-1} 3071 (C-H), 2951, 1728 (C=O Ester), 1668 (C=O Lactam), 1612, 1595; δ_H (500 MHz, $CDCl_3$) 2.48 (3H, s, ArCH_3), 4.03 (3H, s, CO_2CH_3), 6.65 (1H, d, *J* 1.8, C(5)*H*), 6.81 (1H, d, *J* 1.8, C(3)*H*), 7.39 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.48-7.50 (3H, m, Ar*H*), 7.55-7.57 (2H, m, Ar*H*), 8.16 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 21.9 (Ar*C*H_3), 53.6 (CO_2CH_3), 110.7 (*C*(3)), 121.1 (*C*(5)), 126.7 (*ArC*), 129.3 (*ArC*), 129.4 (*ArC*), 130.2 (*ArC*), 130.7 (C(4)*ArC*(4)), 134.3 (4ry *ArC*), 135.2 (4ry *ArC*), 137.3 (4ry *ArC*), 146.2 (SO_2*ArC*(4)), 151.0 (*C*(4)), 161.1 (*C*(6)), 163.4 (*C*O_2CH_3); *m*/*z* (NSI^+) 384 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{20}H_{18}NO_5S^+$ ($[M+H]^+$) requires 384.0900; found 384.0900 (-0.1 ppm).

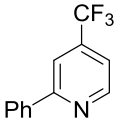
Methyl 6-oxo-2-phenyl-5-(phenylthio)-1-tosyl-1,4,5,6-tetrahydropyridine-3-carboxylate



(±)-**510**

Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr_2NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **506** (172 mg, 0.5 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 16 h at 80 °C gave, after chromatographic purification (eluent Et_2O:petrol 40:60), lactam **510** as a white solid (130 mg, 53%); mp 128-130 °C; ν_{max} (ATR)/cm^{-1} 2930 (C-H), 1717 (C=O Ester), 1636 (C=O Lactam), 1597; δ_H (500 MHz, $CDCl_3$) 2.42 (3H, s, ArC*H*$_3$), 2.99 (1H, dd, *J* 15.8, 5.6, C(4)*H*H), 3.14 (1H, dd, *J* 15.8, 4.2, C(4)H*H*), 3.55 (3H, s, CO_2CH_3), 4.00 (1H, dd, *J* 5.5, 4.3, C(5)*H*), 7.17 (2H, d, *J* 8.2, SO_2Ar(3,5)*H*), 7.25-7.34 (7H, m, Ar*H*), 7.40 (1H, m, Ar*H*), 7.47 (2H, d, *J* 8.4, SO_2Ar(2,6)*H*), 7.51-7.53 (2H, m, C(2)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 21.8 (Ar*C*H$_3$), 29.0 (*C*(4)), 50.9 (CO_2CH_3 or *C*(5)), 52.1 (CO_2CH_3 or *C*(5)), 119.2 (*C*(3)), 127.5 (*ArC*), 128.5 (*ArC*), 128.8 (*ArC*), 129.0 (*ArC*), 129.2 (*ArC*), 129.3 (*ArC*), 129.4 (*ArC*), 132.2 (4ry *ArC*), 133.1 (C(2)*ArC*(2,6)), 133.8 (4ry *ArC*), 136.0 (4ry *ArC*), 145.2 (4ry *ArC*), 145.2 (4ry *ArC*), 166.4 (*C*O_2CH_3), 169.6 (*C*(6)); *m*/*z* (NSI^+) 494 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{26}H_{24}NO_5S_2^+$ ($[M+H]^+$) requires 494.1090; found 494.1080 (-2.1 ppm).

2-phenyl-4-(trifluoromethyl)pyridine

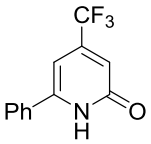


516

To a screw cap glass test tube was charged $Pd(OAc)_2$ (3.37 mg, 15.0 μmol), 1,3-Bis(diphenylphosphino)propane (6.19 mg, 15.0 μmol), Et_3N (0.21 mL, 1.50 mmol), pyridine **491** (118 mg, 0.30 mmol), DMF (2 mL) and formic acid (34.0 μL, 0.90 mmol) and the reaction mixture was heated at 60 °C for 1 h. Once cooled, the reaction mixture was quenched with brine and extracted with EtOAc (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification

(eluent 10% Et_2O:petrol) gave pyridine **516** as a colourless oil (59.8 mg, 89%); δ_H (300 MHz, $CDCl_3$) 7.48-7.59 (4H, m, C(2)Ar(3,5)*H*, C(2)Ar(4)*H* and C(5)*H*), 7.97 (1H, s, C(3)*H*), 8.05-8.09 (2H, m, C(2)Ar(2,6)*H*), 8.91 (1H, d, *J* 5.1, C(6)*H*). Spectroscopic data are in accordance with the literature.[230]

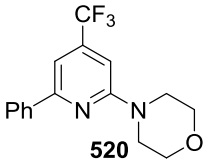
6-phenyl-4-(trifluoromethyl)pyridin-2(1*H*)-one



517

To a solution of pyridine **491** (118 mg, 0.30 mmol) in EtOH (10 mL) was added *n*-Bu_4NOH (1.5 M in H_2O, 2 mL, 3.00 mmol) and the reaction mixture was stirred at rt for 15 minutes. The reaction mixture was extracted with CH_2Cl_2 (x 3) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent 100% Et_2O) gave pyridone **517** as a white solid (63.9 mg, 89%); mp 174-176 °C; ν_{max} (ATR)/cm^{-1} 3063 (C-H), 1667 (C=O), 1612, 1506; δ_H (300 MHz, $CDCl_3$) 6.66 (1H, d, *J* 1.5, C(5)*H*), 6.84 (1H, s, C(3)*H*), 7.55-7.60 (3H, m, C(6)Ar(3,5)*H* and C(6)Ar(4)*H*), 7.78-7.82 (2H, m, C(6)Ar(2,6)*H*); δ_C (125 MHz, $CDCl_3$) 100.4 (q, *J* 2.4, *C*(5)), 115.8 (q, *J* 3.0, *C*(3)), 122.3 (q, *J* 273, *C*F_3), 127.0 (C(6)*ArC*(2,6)), 129.4 (C(6)*ArC*(3,5)), 131.0 (C(6)*ArC*(4)), 132.5 (C(6)*ArC*(1)), 143.2 (q, *J* 33.3, C(4)), 149.1 (*C*(6)), 164.8 (*C*(2)=O); *m*/*z* (NSI^+) 240 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{12}H_9F_3NO^+$ ($[M+H]^+$) requires 240.0631; found 240.0631 (+0.1 ppm).

4-(6-phenyl-4-(trifluoromethyl)pyridin-2-yl)morpholine

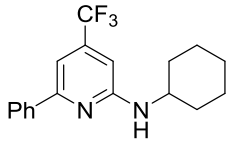


520

To a solution of pyridine **491** (78.6 mg, 0.20 mmol) in toluene (2 mL) was added Et_3N (55.8 μL, 0.40 mmol) and morpholine (172 μL, 2.00 mmol) and the reaction mixture was heated at 120 °C for 16 h. Once cooled, the reaction mixture was concentrated *in vacuo*. Chromatographic purification (eluent 15% Et_2O:petrol) gave pyridine **520** as a white solid (52.6 mg, 85%); mp 98-100 °C; ν_{max} (ATR)/cm^{-1} 2988 (C-H), 2968, 2860, 1611, 1568; δ_H (500 MHz, $CDCl_3$) 3.71 (4H, t, *J* 4.9, 2 NCH_2), 3.90 (4H, t, *J* 4.9, 2

OC*H*$_2$), 6.78 (1H, s, C(3)*H*), 7.32 (1H, s, C(5)*H*), 7.44-7.52 (3H, m, C(6)Ar(3,5)*H* and C(6)Ar(4)*H*), 8.04-8.06 (2H, m, C(6)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 45.3 (2 N*C*H$_2$), 66.7 (2 O*C*H$_2$), 100.8 (q, *J* 3.9, *C*(3)), 105.3 (q, *J* 3.2, *C*(5)), 123.4 (q, *J* 272, *C*F$_3$), 126.9 (C(6)*ArC*(2,6)), 128.7 (C(6)*ArC*(3,5)), 129.5 (C(6)*ArC*(4)), 138.6 (C(6)*ArC*(1)), 140.7 (q, *J* 32.7, C(4)), 156.8 (*C*(6)), 159.2 (*C*(2)); *m*/*z* (NSI$^+$) 309 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{16}H_{16}F_3N_2O^+$ ([M+H]$^+$) requires 309.1209; found 309.1210 (+0.2 ppm).

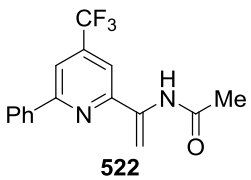
_N_-cyclohexyl-6-phenyl-4-(trifluoromethyl)pyridin-2-amine



521

To a solution of pyridine **491** (78.6 mg, 0.20 mmol) in toluene (2 mL) was added Et_3N (55.8 μL, 0.40 mmol) and cyclohexylamine (115 μL, 1.00 mmol) and the reaction mixture was heated at 120 °C for 16 h. A further portion of cyclohexylamine (115 μL, 1.00 mmol) was added and the reaction mixture was heated at 120 °C for a further 24 h. Once cooled, the reaction mixture was concentrated *in vacuo*. Chromatographic purification (eluent 10% Et_2O:petrol) gave pyridine **521** as a colourless oil (50.7 mg, 79%); ν_{max} (ATR)/cm^{-1} 2930 (C-H), 2855, 1616, 1572, 1510; δ_H (500 MHz, $CDCl_3$) 1.27-1.33 (3H, m, cyclohexyl C*H*), 1.43-1.52 (2H, m, cyclohexyl C*H*), 1.69-1.85 (3H, m, cyclohexyl C*H*), 2.11-2.14 (2H, m, cyclohexyl C*H*), 3.71-3.72 (1H, m, NHC*H*), 4.82 (1H, d, *J* 7.6, N*H*), 6.50 (1H, s, C(3)*H*), 7.19 (1H, s, C(5)*H*), 7.43-7.51 (3H, m, C(6)Ar(3,5)*H* and C(6)Ar(4)*H*), 7.99-8.01 (2H, m, C(6)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 24.9 (cyclohexyl *C*H$_2$), 25.8 (cyclohexyl *C*H$_2$), 33.2 (cyclohexyl *C*H$_2$), 50.4 (NH*C*H), 100.8 (*C*(3)), 104.4 (q, *J* 3.3, *C*(5)), 123.4 (q, *J* 271, *C*F$_3$), 126.9 (C(6)*ArC*(2,6)), 128.7 (C(6)*ArC*(3,5)), 129.2 (C(6)*ArC*(4)), 138.9 (C(6)*ArC*(1)), 140.4 (q, *J* 32.5, C(4)), 157.5 (*C*(2) or *C*(6)), 158.0 (*C*(2) or *C*(6)); *m*/*z* (NSI$^+$) 321 ([M+H]$^+$, 97%); HRMS (NSI$^+$) $C_{18}H_{20}F_3N_2^+$ ([M+H]$^+$) requires 321.1573; found 321.1573 (+0.0 ppm).

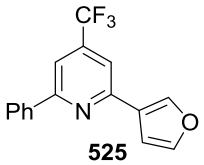
_N_-(1-(6-phenyl-4-(trifluoromethyl)pyridine-2-yl)vinyl)acetamide



522

To a screw cap glass test tube was charged $Pd(dba)_2$ (8.60 mg, 15.0 μmol), 1,1'-bis(diphenylphosphino)ferrocene (8.30 mg, 15.0 μmol), dicyclohexylamine (0.19 mL, 0.90 mmol), *N*-vinylacetamide (102 mg, 1.2 mmol), pyridine **491** (118 mg, 0.30 mmol) and 1,4-dioxane (3 mL) and the reaction mixture was heated 100 °C for 16 h. Once cooled, the reaction mixture filtered through Celite using CH_2Cl_2 as eluent and concentrated *in vacuo*. Chromatographic purification (eluent 30% Et_2O:petrol) gave pyridine **522** as a white solid (69.7 mg, 76%); mp 130-132 °C; ν_{max} (ATR)/cm^{-1} 3310 (N-H), 3082 (C-H), 1692 (C=O), 1566, 1506; δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 5.72 (1H, s, =CH*H*), 6.70 (1H, s, =C*H*H), 7.56-7.63 (3H, m, C(6)Ar(3,5)*H* and C(6)Ar(4)*H*), 7.91 (1H, s, C(3)*H* or C(5)*H*), 7.92 (1H, s, C(3)*H* or C(5)*H*), 8.02-8.05 (2H, m, C(6)Ar(2,6)*H*), 9.30 (1H, s, N*H*); δ_C (75 MHz, $CDCl_3$) 25.2 (*C*H_3), 101.1 (=*C*HH), 113.2 (q, *J* 3.5, *C*(3) or *C*(5)), 115.5 (q, *J* 3.3, *C*(3) or *C*(5)), 122.8 (q, *J* 272, *C*F_3), 127.0 (C(6)*ArC*(2,6)), 129.2 (C(6)*ArC*(3,5)), 130.3 (C(6)*ArC*(4)), 136.8 (C(2)*C*=CHH), 137.5 (C(6)*ArC*(1)), 140.4 (q, *J* 33.7, C(4)), 153.3 (*C*(2)), 157.2 (*C*(6)), 169.1 (*C*=O); *m*/*z* (NSI^+) 307 ($[M+H]^+$, 57%); HRMS (NSI^+) $C_{16}H_{14}F_3N_2O^+$ ($[M+H]^+$) requires 307.1053; found 307.1052 (-0.2 ppm).

2-(furan-3-yl)-6-phenyl-4-(trifluoromethyl)pyridine

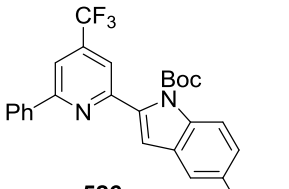


525

To a screw cap glass test tube was charged $Pd(OAc)_2$ (2.25 mg, 0.01 mmol), 2-(Dicyclohexylphospino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (10.7 mg, 0.02 mmol), pyridine **491** (197 mg, 0.50 mmol), 3-furanylboronic acid (112 mg, 1.00 mmol), $K_3PO_4.H_2O$ (345 mg, 1.50 mmol) and toluene (1 mL) and the reaction mixture was heated at 110 °C for 2 h. Once cooled, the reaction mixture was quenched with H_2O and extracted with EtOAc (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent 5% Et_2O:petrol) gave pyridine **525** as a colourless oil (101 mg, 70%); ν_{max} (ATR)/cm^{-1} 3012, 2988 (C-H), 2959, 1616, 1572, 1508; δ_H (500 MHz, $CDCl_3$) 7.05 (1H, s, C(2)Ar(4)*H*), 7.50-7.59 (5H, m, Ar*H*), 7.82 (1H, s, C(3)*H*), 8.15 (2H, d, *J* 7.3, C(6)Ar(2,6)*H*), 8.22 (1H, s, C(5)*H*); δ_C (125 MHz, $CDCl_3$) 108.7 (C(2)*ArC*(4)), 113.6 (q, *J* 3.4, *C*(3), 113.6 (q, *J* 3.4, *C*(5)), 123.1 (q, *J* 272, *C*F_3), 126.6 (C(2)*ArC*(3)), 127.1 (C(6)*ArC*(2,6)), 128.9

(C(6)*ArC*(3,5)), 129.9 (C(6)*ArC*(4)), 138.1 (C(6)*ArC*(1)), 139.7 (q, *J* 33.3, C(4)), 142.3 (C(2)*ArC*(2)), 144.2 (C(2)*ArC*(5)), 152.9 (*C*(2)), 158.3 (*C*(6)); *m*/*z* (NSI^+) 290 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{16}H_{11}F_3NO^+$ ($[M+H]^+$) requires 290.0787; found 290.0789 (+0.6 ppm).

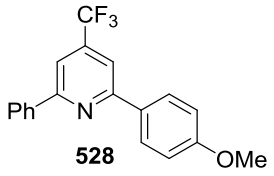
tert-butyl 5-methoxy-2-(6-phenyl-4-(trifluoromethyl)pyridine-2-yl)-1*H*-indole-1-carboxylate



526

To a screw cap glass test tube was charged $Pd(OAc)_2$ (2.25 mg, 0.01 mmol), 2-(Dicyclohexylphospino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl (10.7 mg, 0.02 mmol), pyridine **491** (197 mg, 0.50 mmol), (1-(*tert*-butoxycarbonyl)5-methoxy-1*H*-indol-2-yl)boronic acid (291 mg, 1.00 mmol), $K_3PO_4.H_2O$ (345 mg, 1.50 mmol) and toluene (1 mL) and the reaction mixture was heated at 110 °C for 2 h. Once cooled, the reaction mixture was quenched with H_2O and extracted with EtOAc (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent 5% Et_2O:petrol) gave pyridine **526** as a colourless oil (190 mg, 81%); ν_{max} (ATR)/cm^{-1} 2978 (C-H), 2936, 1732 (C=O), 1612, 1572; δ_H (300 MHz, $CDCl_3$) 1.37 (9H, s, C(CH_3)$_3$), 3.92 (3H, s, OCH_3), 6.91 (1H, s, C(2)Ar(3)*H*), 7.06-7.12 (2H, m, C(2)Ar(4)*H* and C(2)Ar(6)*H*), 7.47-7.60 (3H, m, C(6)Ar(3,5)*H* and C(6)Ar(4)*H*), 7.70 (1H, s, C(3)*H*), 7.96 (1H, s, C(5)*H*), 8.16-8.19 (3H, m, C(6)Ar(2,6)*H* and C(2)Ar(7)*H*); δ_C (75 MHz, $CDCl_3$) 27.6 (C(*C*H_3)$_3$), 55.7 (O*C*H_3), 83.7 (*C*(CH$_3$)$_3$), 103.4 (C(2)*ArC*(4)), 112.2 (C(2)*ArC*(3)), 114.0 (q, *J* 3.2, *C*(5)), 114.6 (C(2)*ArC*(6)), 116.1 (C(2)*ArC*(7)), 117.1 (q, *J* 3.3, *C*(3)), 123.1 (q, *J* 271, *C*F_3), 127.2 (C(6)*ArC*(2,6)), 129.0 (C(6)*ArC*(3,5)), 129.5 (C(2)*ArC*(7a)), 130.0 (C(6)*ArC*(4)), 132.8 (C(2)*ArC*(3a)), 137.7 (C(6)*ArC*(1)), 138.9 (C(2)*ArC*(2)), 139.3 (q, *J* 33.5, C(4)), 149.9 (*C*=O), 154.3 (*C*(2)), 156.2 (C(2)*ArC*(5)), 157.8 (*C*(6)); *m*/*z* (NSI^+) 469 ($[M+H]^+$, 70%); HRMS (NSI^+) $C_{26}H_{24}F_3N_2O_3^+$ ($[M+H]^+$) requires 469.1734; found 469.1727 (-1.4 ppm).

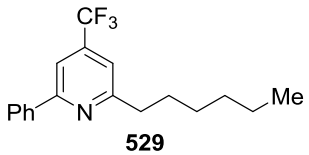
2-(4-methoxyphenyl)-6-phenyl-4-(trifluoromethyl)pyridine



528

To a screw cap glass test tube was charged $Pd(dba)_2$ (7.20 mg, 12.5 μmol), 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide (4.10 mg, 25.0 μmol) and 1,4-dioxane (2 mL) and the reaction mixture was stirred at rt for 5 minutes. 4-Methoxylphenylmagnesium bromide solution (0.5 M in THF, 1.5 mL, 0.75 mmol) was added and the reaction mixture was stirred at rt for 5 minutes. Pyridine **491** (197 mg, 0.50 mmol) was added and the reaction was heated at 80 °C for 16 h. Once cooled, the reaction mixture was quenched with HCl (1M in H_2O) and extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent 3% Et_2O:petrol) gave pyridine **528** as a colourless oil (109 mg, 66%); ν_{max} (ATR)/cm^{-1} 3042, 2961 (C-H), 1609, 1566, 1516; δ_H (300 MHz, $CDCl_3$) 3.78 (3H, s, OC*H*$_3$), 6.91-6.96 (2H, m, C(2)Ar(3,5)*H*), 7.34-7.46 (3H, m, C(6)Ar(3,5)*H* and C(6)Ar(4)*H*), 7.70 (2H, app. s, C(3)*H* and C(5)*H*), 8.01-8.08 (4H, m, C(2)Ar(2,6)*H* and C(6)Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 55.4 (O*C*H$_3$), 113.3 (app. t, *J* 3.6, *C*(3) and *C*(5)), 114.3 (C(2)*ArC*(3,5)), 123.3 (q, *J* 272, *C*F$_3$), 127.1 (C(6)*ArC*(2,6)), 128.5 (C(2)*ArC*(2,6)), 128.9 (C(6)*ArC*(3,5)), 129.8 (C(6)*ArC*(4)), 132.8 (C(2)*ArC*(1)), 138.4 (C(6)*ArC*(1)), 139.9 (q, *J* 33.1, C(4)), 157.8 (*C*(2) or *C*(6)), 158.0 (C(2) or *C*(6)), 161.2 (*C*(2)*ArC*(4)); *m*/*z* (NSI^+) 330 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{19}H_{15}F_3NO^+$ ($[M+H]^+$) requires 330.1100; found 330.1102 (+0.5 ppm).

2-hexyl-6-phenyl-4-(trifluoromethyl)pyridine



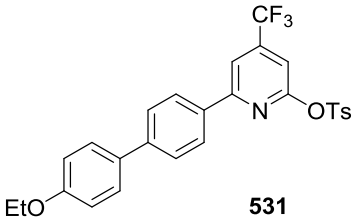
529

To a flask containing Mg turnings (486 mg, 20.0 mmol) in Et_2O (10 ml) under an argon atmosphere was added 2 drops of bromohexane and the reaction mixture was heated to intiate grigard formation. Bromohexane (2.81 mL, 20.0 mmol) was added dropwise to maintain autoreflux. Once all bromide was added the reaction mixture was stirred at rt for 30 minutes until all Mg was consumed.

To a screw cap glass test tube was charged pyridine **491** (197 mg, 0.50 mmol), $FeCl_3$ (4.06 mg, 0.025 mmol) and THF (2 mL). *N*-Methyl-2-pyrrolidone (0.43 mL, 4.50 mmol)

was added and the reaction mixture was cooled to –10 °C before the freshly prepared hexylmagnesium bromide (2.0 M in Et_2O, 0.38 mL, 0.75 mmol) was added dropwise. The reaction mixture was stirred at –10 °C for 15 minutes before being quenched with MeOH and diluted with H_2O. The reaction mixture was extracted with Et_2O (x 3). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification (eluent 3% Et_2O:petrol) gave pyridine **529** as a colourless oil (114 mg, 74%); ν_{max} (ATR)/cm^{-1} 2957 (C-H), 2928, 1574; δ_H (400 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.0, C*H*$_3$), 1.22-1.35 (6H, m, 3 C*H*$_2$), 1.70-1.78 (2H, m, C(2)CH$_2$C*H*$_2$C$_4$H$_9$), 2.84 (2H, t, *J* 7.8, C(2)C*H*$_2$C$_5$H$_{11}$), 7.20 (1H, s, C(3)), 7.34-7.43 (3H, m, C(6)Ar(3,5)*H* and C(6)Ar(4)*H*), 7.64 (1H, s, C(5)*H*), 7.94-7.97 (2H, m, C(6)Ar(2,6)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*H$_3$) 22.6 (CH$_3$*C*H$_2$), 29.1 (*C*H$_2$), 29.6 (*C*H$_2$), 31.7 (*C*H$_2$), 38.6 (C(2)*C*H$_2$C$_5$H$_{11}$), 113.3 (q, *J* 3.5, *C*(5)), 116.4 (q, *J* 3.4, *C*(3)), 123.2 (q, *J* 272, *C*F$_3$), 127.1 (C(6)*ArC*(2,6)), 128.9 (C(6)*ArC*(3,5)), 129.6 (C(6)*ArC*(4)), 138.5 (C(6)*ArC*(1)), 139.1 (q, *J* 33.2, C(4)), 158.1 (*C*(6)), 164.0 (C(2)); *m/z* (NSI$^+$) 308 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{18}H_{21}F_3N^+$ ([M+H]$^+$) requires 308.1621; found 308.1621 (+0.1 ppm).

6-(4'-ethoxy-[1,1'-biphenyl-4-yl)-4-(trifluoromethyl)pyridine-2-yl 4-methylbenzenesulfonate

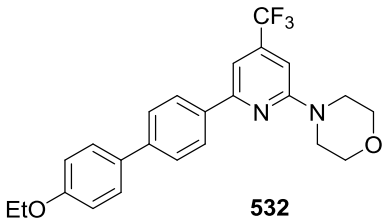


531

To a screw cap glass test tube was charged Pd(OAc)$_2$ (4.49 mg, 0.02 mmol), tris(2,4-di-tertbutylphenyl)phoshite (25.9 mg, 0.04 mmol), pyridine **493** (944 mg, 2.00 mmol), 4-ethoxyphenylboronic acid (0.50 g, 3.00 mmol), KF (349 mg, 6.00 mmol) and THF (2 mL) and the reaction mixture was stirred at rt for 2 h. The reaction mixture was filtered through Celite using CH_2Cl_2 as eluent and concentrated *in vacuo*. Chromatographic purification (eluent 20% Et_2O:petrol) gave pyridine **531** as a white solid (890 mg, 87%); mp 150-152 °C; ν_{max} (ATR)/cm^{-1} 3042, 2976 (C-H), 2936, 1605, 1574, 1503, 1306 (S=O), 1146 (S=O); δ_H (500 MHz, $CDCl_3$) 1.49 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 2.51 (3H, s, C*H*$_3$), 4.13 (2H, m, C*H*$_2$CH$_3$), 7.03 (2H, d, *J* 8.7, C(6)Ar(3',5')*H*), 7.24 (1H, s, C(3)*H*), 7.41 (2H, d, *J* 8.1, OSO$_2$Ar(3,5)*H*), 7.60 (2H, d, *J* 8.7, C(6)Ar(2',6')*H*), 7.64 (2H, d, *J* 8.5, C(6)Ar(3,5)*H*), 7.84 (2H, d, *J* 8.5, C(6)Ar(2,6)*H*), 7.87 (1H, s, C(5)*H*), 8.00 (2H, d, *J*

8.3, $OSO_2Ar(2,6)H$); δ_C (100 MHz, $CDCl_3$) 14.9 (CH_3CH_2O), 21.8 (CH_3Ar), 63.6 (CH_3CH_2O), 109.6 (q, *J* 3.4, *C*(3)), 114.0 (q, *J* 3.0, *C*(5)), 114.9 (C(6)*ArC*(3',5'), 122.2 (q, *J* 272, CF_3), 127.0 (C(6)*ArC*(3,5)), 127.5 (C(6)*ArC*(2,6)), 128.2 (C(6)*ArC*(2',6')), 128.9 ($OSO_2ArC(2,6)$), 129.8 ($OSO_2ArC(3,5)$), 132.3 (C(6)*ArC*(1')), 134.0 ($OSO_2ArC(1)$), 134.4 (C(6)*ArC*(4)), 143.0 (C(6)*ArC*(1)), 143.1 (q, *J* 34.1, C(4)), 145.5 ($OSO_2ArC(4)$), 157.5 (*C*(2) or *C*(6)), 157.7 (*C*(2) or *C*(6)), 159.1 (*C*(6)*ArC*(4')); *m*/*z* (NSI^+) 514 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{27}H_{23}F_3NO_4S^+$ ($[M+H]^+$) requires 514.1294; found 514.1287 (-1.4 ppm).

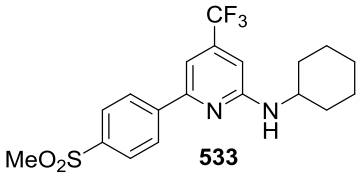
6-(4'-ethoxy-[1,1'-biphenyl-4-yl)-4-(trifluoromethyl)pyridine-2-yl 2-morpholine



532

To a solution of pyridine **531** (240 mg, 0.47 mmol) in toluene (4 mL) was added Et_3N (131 μL, 0.94 mmol) and morpholine (0.40 mL, 4.68 mmol) and the reaction mixture was heated at 120 °C for 16 h. Once cooled, the reaction mixture was concentrated *in vacuo*. Chromatographic purification (eluent 30% Et_2O:petrol) gave pyridine **532** as a white solid (163 mg, 82%); mp 178-180 °C; ν_{max} (ATR)/cm^{-1} 2982 (C-H), 2853, 1603, 1574; δ_H (300 MHz, $CDCl_3$) 1.36 (3H, t, *J* 7.0, CH_2CH_3), 3.60 (4H, t, *J* 4.9, 2 NCH_2), 3.79 (4H, t, *J* 4.9, 2 OCH_2), 4.00 (2H, q, *J* 7.0, CH_2CH_3), 6.66 (1H, s, C(3)*H*), 6.88-6.93 (2H, m, C(6)Ar(3',5')*H*), 7.24 (1H, s, C(5)*H*), 7.47-7.52 (2H, m, C(6)Ar(2',6')*H*), 7.54-7.58 (2H, m, C(6)Ar(3,5)*H*), 7.96-8.00 (2H, m, C(6)Ar(2,6)*H*); δ_C (75 MHz, $CDCl_3$) 14.9 (CH_3CH_2O), 45.4 (NCH_2), 63.6 (CH_3CH_2O), 66.7 (OCH_2), 100.7 (q, *J* 3.8, *C*(3)), 105.1 (q, *J* 3.2, *C*(5)), 114.9 (C(6)*ArC*(3',5'), 123.4 (q, *J* 272, CF_3), 126.9 (C(6)*ArC*(3,5)), 127.3 (C(6)*ArC*(2,6)), 128.1 (C(6)*ArC*(2',6')), 132.8 (C(6)*ArC*(1')), 136.9 (C(6)*ArC*(4)), 140.7 (q, *J* 32.3, *C*(4)), 141.9 (C(6)*ArC*(1)), 157.5 (*C*(6)), 158.9 (*C*(6)*ArC*(4')), 159.3 (*C*(2)); *m*/*z* (NSI^+) 429 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{24}H_{24}F_3N_2O_2^+$ ($[M+H]^+$) requires 429.1784; found 429.1782 (-0.6 ppm).

***N*-cyclohexyl-6-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)pyridin-2-amine**



533

To a solution of pyridine **494** (335 mg, 0.71 mmol) in toluene (5 mL) was added Et_3N (0.20 mL, 1.42 mmol) and cyclohexylamine (0.40 mL, 3.56 mmol) and the reaction mixture was heated at 120 °C for 16 h. A further portion of cyclohexylamine (0.40 mL, 3.56 mmol) was added and the reaction mixture was heated at 120 °C for a further 24 h. Once cooled, the reaction mixture was concentrated *in vacuo*. Chromatographic purification (eluent 100% Et_2O) gave pyridine **533** as white solid (260 mg, 92%); mp 130-132 °C;[3] δ_H (400 MHz, $CDCl_3$) 1.27-1.55 (5H, m, cyclohexyl C*H*), 1.69-1.74 (1H, m, cyclohexyl C*H*), 1.80-1.86 (2H, m, cyclohexyl C*H*), 2.10-2.14 (2H, m, cyclohexyl C*H*), 3.11 (3H, s, SO_2CH_3), 3.72-3.76 (1H, m, NHC*H*), 4.86 (1H, d, *J* 7.1, N*H*), 6.58 (1H, s, C(3)*H*), 7.21 (1H, s, *C*(5)*H*), 8.03-8.06 (2H, m, Ar*H*), 8.17-8.20 (2H, m, Ar*H*).

Crossover Experiment

Following general procedure S, (phenylthio)acetic acid (84.1 mg, 0.50 mmol) in THF (5 mL), *i*-Pr_2NEt (130 μL, 0.75 mmol), pivaloyl chloride (92.5 μL, 0.75 mmol), imine **542** (85.0 mg, 0.25 mmol), imine **541** (108 mg, 0.25 mmol), DHPB **108** (19.0 mg, 0.1 mmol, 20 mol%) and *i*-Pr_2NEt (87.5 μL, 0.50 mmol) for 30 minutes at rt followed by heating at reflux for 16 h gave, by analysis of the crude ^1H NMR, a crude reaction mixture containing 50% of both pyridines **493** and **496**.

9.7.2 References and Notes

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