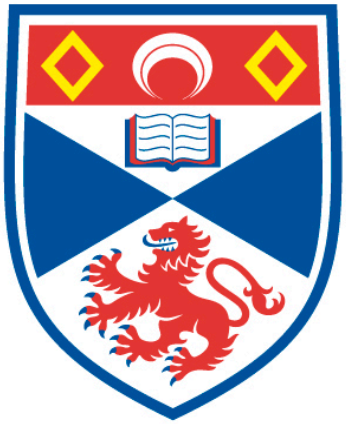
α,β-UNSATURATED ACYL AMMONIUM INTERMEDIATES IN ENANTIOSELECTIVE ORGANOCATALYSIS

Anastassia Matviitsuk

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



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St Andrews

This thesis is submitted in partial fulfilment for the degree of

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Acknowledgements

The work outlined in this thesis would have not been feasible without the great mentorship, enthusiasm, friendship and constant support throughout my PhD.

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I would finally like to thank my family and friends, especially my parents, without whose emotional support in these challenging three-and-a-half years of my PhD this thesis would not be possible.

Abstract

The research outlined in this thesis focuses on the study of the reactivity of α,β-unsaturated acyl ammonium intermediates and their utility in the development of new enantioselective processes exploiting isothiourea organocatalysts.

Chapter 2: A novel isothiourea-catalysed domino process has been developed demonstrating the synthetic power of α,β-unsaturated acyl ammonium intermediates to generate a library of complex heterocyclic compounds.
The use of these intermediates, generated *in situ* from trichlorophenol-activated ester and HyperBTM, proved successful in the development of an asymmetric Michael-Michael-lactonisation reaction with 1,3-dicarbonyls. This method gives a quick and simple approach to a wide range of highly functionalised lactones (20 examples) bearing three contiguous stereocentres in moderate to good yields (46-79%). Excellent diastereo- and enantioselectivities (up to >95:5 dr, up to >99:1 er) were obtained due to the catalyst controlled nucleophilic addition. Resulting indane derivatives represent potential biologically and pharmaceutically relevant molecules.

Chapter 3: The scope of the new domino reaction was extended employing benzazoles as an alternative pro-nucleophile class. Utilising acyl benzothiazoles selective *N*-cyclisation was observed through the operation of a domino Michael-lactamisation-Michael reaction, whilst the use of acyl benzimidazoles gave an alternative domino reaction pathway and selective access to quaternary stereocentres. The stereodivergence of these domino processes was studied by varying the electronic properties of the benzothiazole nucleophiles. A broad scope of complex fused polycycles (26 examples) was synthesised using this methodology with good to excellent yields (up to 94%) and high levels of stereocontrol (up to >95:5 dr; up to 97:3 er).

Chapter 4: A new general concept for α,β-unsaturated acyl ammonium catalysis has been developed which exploits 4-nitrophenoxide release from an α,β-unsaturated 4-nitrophenyl ester substrate to facilitate catalyst turnover. This method was used for the enantioselective isothiourea-catalysed Michael addition of nitroalkanes to α,β-unsaturated 4-nitrophenyl esters (27 examples, up to 79% yield, 99:1 er). The synthetic utility of this methodology was demonstrated through a simple synthesis of highly enantioenriched pyrrolidinones. Mechanistic investigations including kinetic analysis, catalyst labelling and crossover studies have delivered a fundamental understanding of this process, with the application of a recently reported variable time normalisation graphical analysis method used to allow the complex reaction kinetics to be probed.

Chapter 5: Alternative catalyst turnover within α,β-unsaturated acyl ammonium catalysis was further explored. A novel approach to highly enantioenriched γ-nitro esters was developed, which exploits the use of silyl nitronates to both undergo enantioselective Michael addition and facilitate catalyst turnover, through a silyl migration/[3,3]-rearrangement pathway, unprecedented in enantioselective catalysis. Application of silyl nitronates, as more active surrogates than their parent nucleophiles nitroalkanes, allows their use as stoichiometric reagents with a wide range of resulting γ-nitro-substituted silyl esters (25 examples) obtained with good to excellent diastereo- and enantioselectivity (up to >95:5 dr, up to >99:1 er).

Publications

The research described in this thesis has formed the basis of the following peer reviewed publications:

"Enantioselective Stereodivergent Nucleophile-Dependent Isothiourea-Catalysed Domino Reactions"
A. Matviitsuk, J. E. Taylor, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Chem. Eur. J.* **2016**, *22*, 17748–17757

"Aryloxide-Facilitated Catalyst Turnover in Enantioselective α,β-Unsaturated Acyl Ammonium Catalysis"
A. Matviitsuk, M. D. Greenhalgh, D.-J. B. Antúnez, Prof. A. M. Z. Slawin, Prof. A. D. Smith, *Angew. Chem*. *Int Ed.* **2017**, 40, 12282–12287 (highlighted in Synfacts, B008717SF)

Abbreviations

Å	Ångström(s) (1 x 10^{-10} m)
Ac	Acetyl
app.	Apparent
aq	Aqueous
Ar	Aromatic
PS-BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene
Bn	Benzyl
Boc	*N*-*tert*-Butoxycarbonyl
br	Broad
BTM	Benzotetramisole
Bu	Butyl
c	Concentration
C	Celsius
cal	Calorie(s)
cat.	Catalyst
cm	Centimetre(s)
COSY	Correlation spectroscopy
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
dr	Diasteroisomeric ratio
E	Electrophile
ee	Enantiomeric excess
equiv.	Equivalent molar quantity
er	Enantiomeric ratio
ES	Electrospray
ESI	Electrospray ionisation
Et	Ethyl
g	Gram(s)
h	Hour(s)
HBTM	Homobenzotetramisole
HMDS	Hexamethyldisilazide
HOMO	Highest occupied molecular orbital

HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
i	*Iso*
IR	Infrared
k	Rate constant
LB	Lewis base
LG	Leaving group
Lit	Literature
LUMO	Lowest unoccupied molecular orbital
M	Molar (i.e. mol dm^{-3})
m	Multiplet
MS	Molecular sieves
m/z	Mass / charge
MAL	Michael-Aldol-Lactonisation
Me	Methyl
Mes	Mesityl
mg	Milligram(s)
MHz	Megahertz
min	minute(s)
mL	Millilitre(s)
MML	Michael-Michael-Lactonisation
mol	Mole(s)
mp	Melting point
MS	Mass spectrometry
o/n	overnight
NCMAL	nucleophile-catalysed Michael-aldol-β-lactonisation
NHC	N-heterocyclic carbene
ν_{max}	Frequency
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
NSI	Nanospray ionization
Nu	Nucleophile
o	*Ortho*
p	*Para*
PG	Protecting group

Ph	Phenyl
Piv	Pivaloyl
ppm	Parts per million
PPY	4-Pyrrolidinopyridine
Pr	Propyl
PS	Polymer supported
q	Quartet
quant.	Quantitative
quint	Quintuplet
R	Alkyl
recryst	Recrystallisation/recrystallised
rt	Ambient (room) temperature
s	Singlet
sat.	Saturated
sept	Septet
SOMO	Singly Occupied Molecular Orbital
t	Triplet/time
T	Temperature
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TM	Tetramisole
TMS	Trimethylsilyl
TOF	Turnover frequency
Tol	Tolyl = Methylphenyl
TS	Transition state
Ts	Tosyl
V	Volume
µL	Microlitre(s)

Table of contents

1 Introduction

1.1 Role of enantioselective organocatalysis

The continually increasing challenges associated with the treatment of new and existing diseases necessitates that potential therapeutics contain higher levels of molecular complexity to achieve potency, selectivity and desirable physical properties. Moreover, potential drug candidates often possess one or more stereogenic centres or elements. [1] The selective synthesis of one enantiomer of a compound is of great relevance since there are many cases where the therapeutic action of the effective enantiomer is affected by the action of its antipode. A compelling example was provided by thalidomide **1** that was administered to pregnant women in the 1960's. (*R*)-Thalidomide **1a** has desirable sedative properties, while its (*S*)-enantiomer **1b** is teratogenic and induces fetal transformations (Figure 1).[2,3] Exposure of thalidomide to pregnant women has been restricted, as it is difficult to determine exactly the pharmacological effect of each enantiomer due to its *in vivo* interconversion of (*R*) and (*S*)-enantiomers.

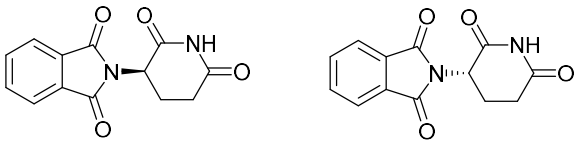


Figure 1. *R*-and *S*-enantiomers of thalidomide.

Single-enantiomer drugs are difficult to synthesise using conventional synthetic methods. Over the last decades a wide variety of enantioselective methods have been developed to meet this challenge for both academia and industry.[1] Asymmetric synthesis is often possible using readily accessible, naturally occurring chiral starting materials from the amino acids, carbohydrates, terpenes, or alkaloids. This approach can be highly efficient as the chirality built-in to the starting materials is preserved in the remainder of the reaction sequence, but synthetic pathways are restricted to the use of available substrates.[4]

Alternatively, a chemical approach allows for the flexible synthesis of a wide array of enantiopure organic substances from achiral precursors. Enantiomerically pure compounds can be obtained from racemic samples by classical chiral resolution. This involves the isolation of one enantiomer of a racemate by, for example, selective crystallisation. However, such methods provide a maximum yield of 50% of a single enantiomer,[5a] unless a dynamic process is employed, which involves the interconversion of enantiomers resulting in a maximum yield of 100% of a single enantiomer.[5b]

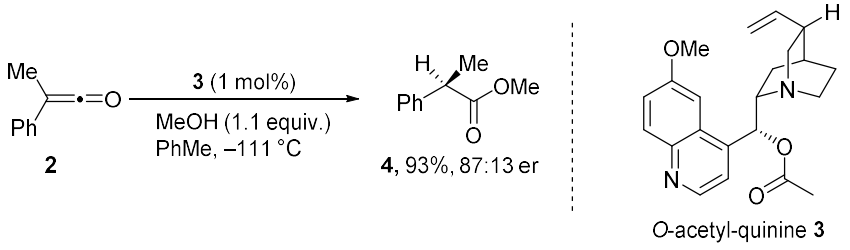
Beyond separation techniques, chiral metal complexes have been used for the enantioselective preparation of molecules from achiral precursors.[6] For example, enantioselective hydrogenation

of alkenes[1,7] has been crucial for development of many commercial therapeutics. Metal-based catalysts can exhibit remarkable structural diversity through variation of the bound ligands, which control both reactivity and selectivity.[8] Despite the great value of metal-catalysed transformations in the pharmaceutical industry, the use of such processes can require specific expertise and equipment that is expensive and not always available. Some metal-based catalysts are unstable to air and moisture, making them difficult to handle. The removal of metals from reaction mixtures and toxicity of metal residues are further challenges associated with metal catalysis.[9]

Enantioselective organocatalysis offers an alternative mild, practical, and often simple method of making small, functionalised molecules with high enantiopurity. Organocatalysis refers to the "acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom".[10] The advantages of organocatalysts include their typical lack of sensitivity to moisture and oxygen, their ready availability, low cost, low toxicity and ability to generate molecular complexity through a variety of reaction modes. Organocatalysis may provide a significant benefit over conventional metal catalysts in synthetic chemistry.[3]

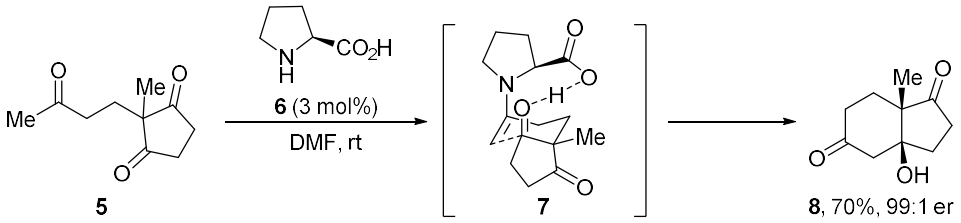
1.2 Historical perspective of enantioselective organocatalysis

The first enantioselective organocatalytic reaction dates back to 1912 when two German chemists, Bredig and Fiske, reported that addition of hydrogen cyanide to benzaldehyde catalysed by a cinchona alkaloid yields cyanohydrins in ~55:45 er.[11] In 1960 Pracejus reported the enantioselective synthesis of ester **4** from phenyl methyl ketene **2** and methanol using 1 mol% *O*-acetylquinine **3** as a catalyst in a quite remarkable 93% yield and 87:13 er (Scheme 1).[12]



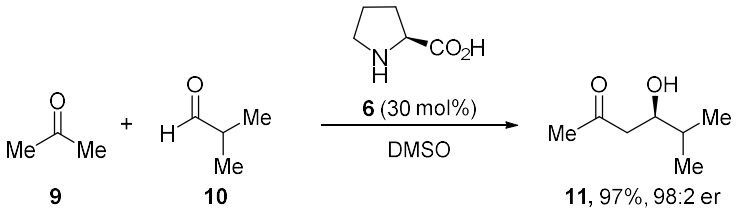
Scheme 1. First highly enantioselective organocatalytic reaction.

The next breakthrough that showed the great potential of organocatalysis was a proline-catalysed intramolecular aldol process developed independently by Hajos and Parrish, as well as Eder, Sauer and Wiechert in the 1970's.[13] Ketone **5** is activated by (*S*)-proline **6** to form enamine intermediate **7**, which undergoes intramolecular cyclisation to generate product **8** in 70% yield and 99:1 er (Scheme 2). Central to the success of this aldol transformation is a proposed hydrogen bond between the carbonyl electrophile and the carboxylic acid moiety of the proline catalyst.[14]



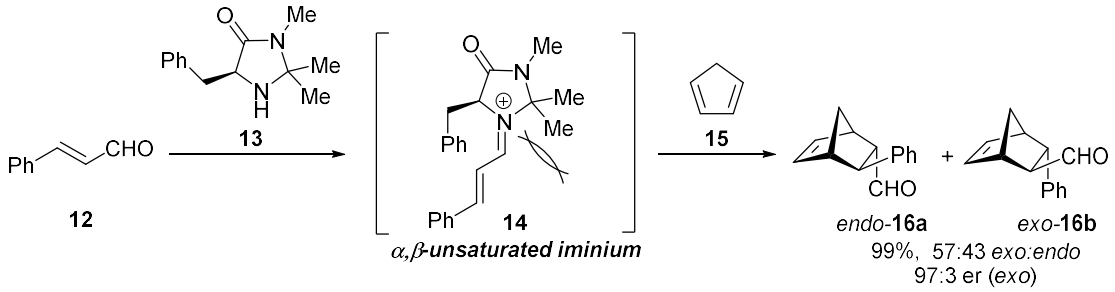
Scheme 2. Proline-catalysed intramolecular aldol reaction.

The true significance of this discovery was not realised until 2000 when List, Barbas and Lerner published a related intermolecular process between acetone **9** and aldehyde **10** to give corresponding aldol product **11** in excellent yield and enantioselectivity (Scheme 3).[15]



Scheme 3. Proline-catalysed intermolecular aldol reaction.

Another important discovery in enantioselective organocatalysis, reported by MacMillan in 2000,[16] was the organocatalytic Diels-Alder reaction using imidazolidinone catalyst **13**. Activated iminium ion **14**, formed through condensation of imidazolidinone **13** and α,β-unsaturated aldehyde **12**, undergoes [4+2]-cycloaddition with diene **15** to yield a mixture of *endo*- and *exo*-products **16a** and **16b** in excellent yield and enantioselectivity (Scheme 4).



Scheme 4. Enantioselective organocatalytic Diels-Alder reaction.

Both the initial proline aldol research and MacMillan's iminium ion catalysis concept highlighted the potential generality of organocatalysis and opened many further avenues of research.

1.3 Classification of enantioselective organocatalysis

Since the seminal reports of enantioselective organocatalysis a range of processes has been developed using a wide variety of modes of activation of small-molecule substrates. However, the classification of enantioselective modes of activation in organocatalytic reactions is challenging. A general distinction can be made between organocatalytic processes that form *covalent* intermediates between catalyst and substrate, and processes that rely on *non-covalent* interactions such as Brønsted acid and hydrogen bonding catalysis.[17,18] Further differentiation within each category is possible by considering the modes of substrate activation, such as Highest Occupied Molecular Orbital (HOMO) activation (e.g., enamine,[19] azolium enolate,[20] etc.) or Lowest Unoccupied Molecular Orbital (LUMO) activation (e.g., iminium,[21] acyl ammonium,[22] etc.) (Figure 2).

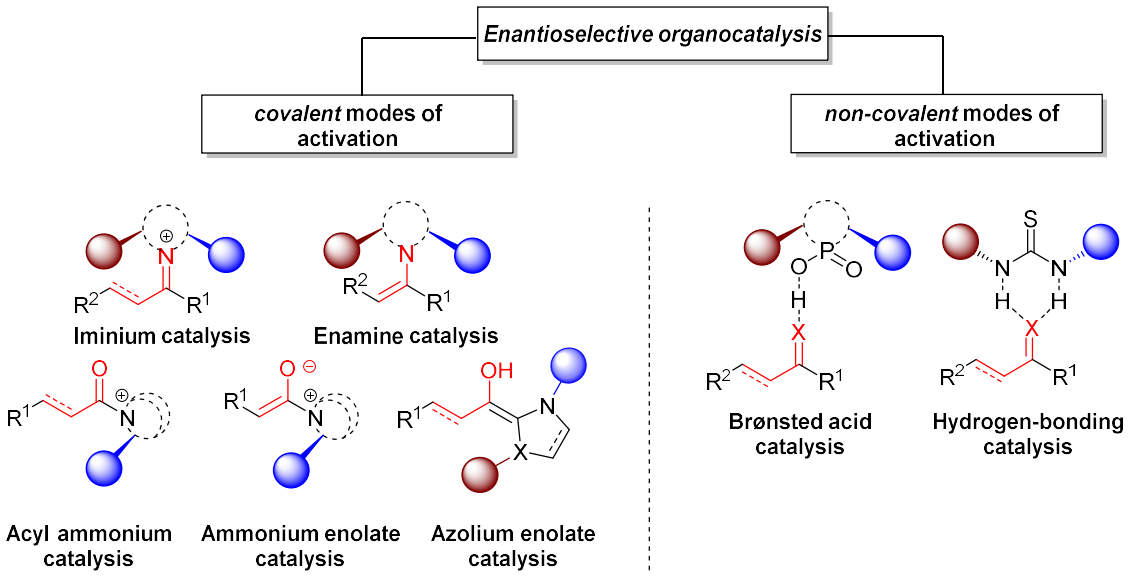


Figure 2. Classification of enantioselective organocatalysis.

It should be noted that a single organocatalyst may promote reactions by several modes of activation and thus can be classified a multifunctional catalyst.[23,24] In this regard, many different activation modes can be facilitated by Lewis base organocatalysts. As an example, isothiourea catalysts have been shown to exhibit remarkable catalytic activity in various transformations employing (i) acyl ammonium, (ii) ammonium enolate and (iii) α,β-unsaturated acyl ammonium intermediates. Whilst in acyl ammonium and α,β-unsaturated acyl ammonium catalysis the substrate is activated to nucleophilic attack by lowering of the LUMO energy relative to the parent carbonyl, ammonium enolate catalysis activates the substrate by raising the energy of the HOMO and thus increasing its nucleophilicity (Figure 3). These activation modes have been successfully investigated within the Smith group and will be considered in detail as the main subject of the work in this thesis.

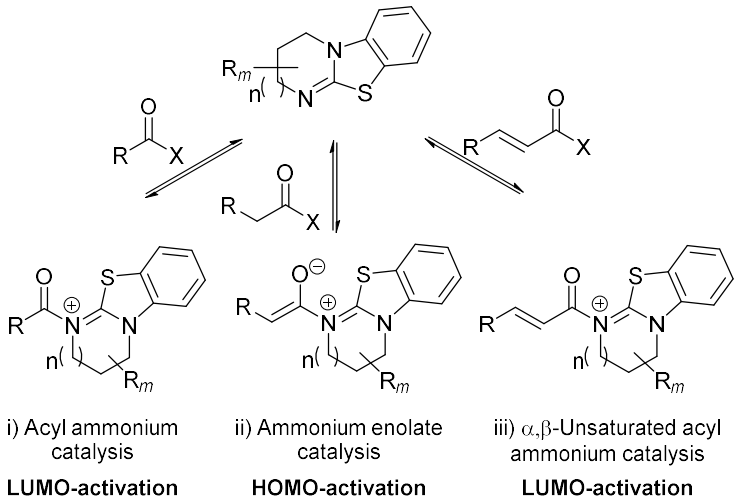
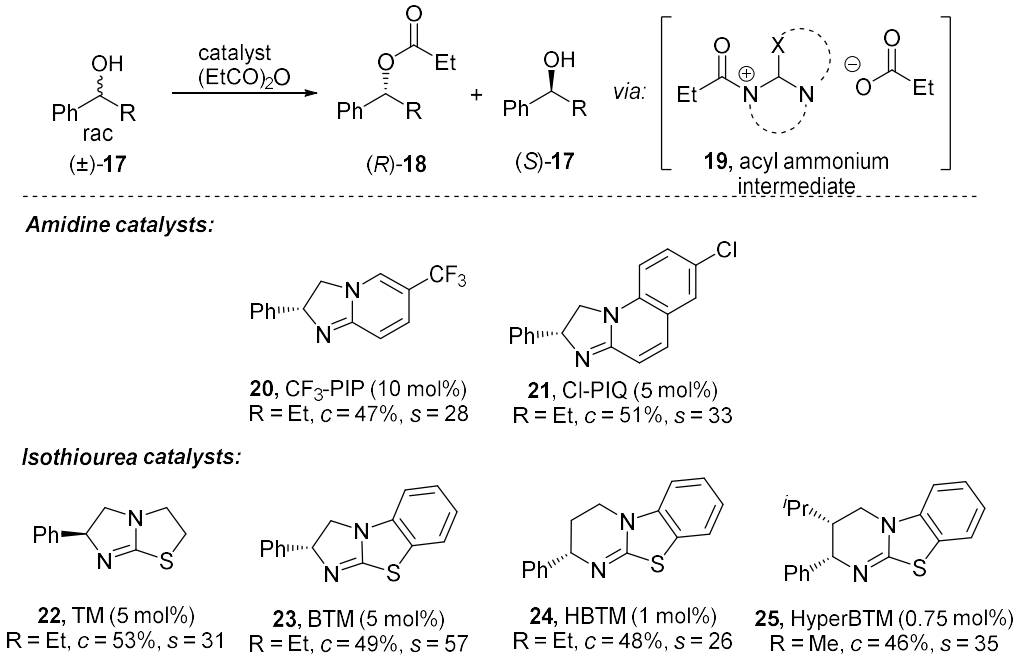


Figure 3. Activation modes in isothiourea catalysis.

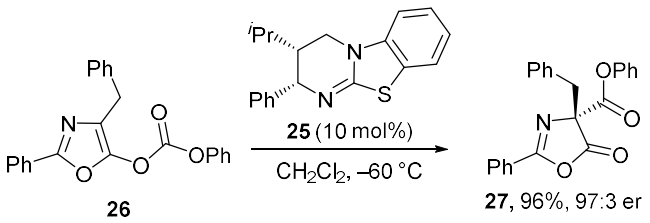
1.3.1 Acyl ammonium catalysis

The initial reports of acyl ammonium catalysis using isothioureas date back to 2004, with the development of an effective series of acylation catalysts in the kinetic resolution of secondary alcohols. Using anhydrides as acylating reagents, a racemic mixture of alcohol **17** can be separated into ester (*R*)-**18** and enantioenriched unreacted alcohol (*S*)-**17** due to preferential acylation of one enantiomer of the racemic starting material by chiral acyl ammonium intermediate **19**. The parameters reported are the reaction conversion (the percentage of ester (*R*)-**18** compared with alcohol (*S*)-**17**), and the *s*-factor, which takes into account the relative rates of acylation of the two enantiomers of alcohol **17** and can be calculated from the enantioselectivity of the process (Scheme 5).[25,26] Based upon the structure of amidines, Birman reported that 2-phenyl-6-trifluoromethyl-dihydroimidazo[1,2-*a*]pyridine **20** (CF_3-PIP) gave promising enantioselectivities for this process. Extending the π-system in the catalyst to give **21 (**Cl-PIQ) gave significant improvement in selectivity.[27,28] Further investigation led to the use of isothioureas as catalytic acylating agents, with commercially available tetramisole **22** (TM), its benzannulated analogue benzotetramisole **23** (BTM) and their derivatives, including homobenzotetramisole **24** (HBTM) and HyperBTM **25**[29,31] affording the kinetic resolution of secondary alcohols with excellent selectivity at very low catalyst loadings.



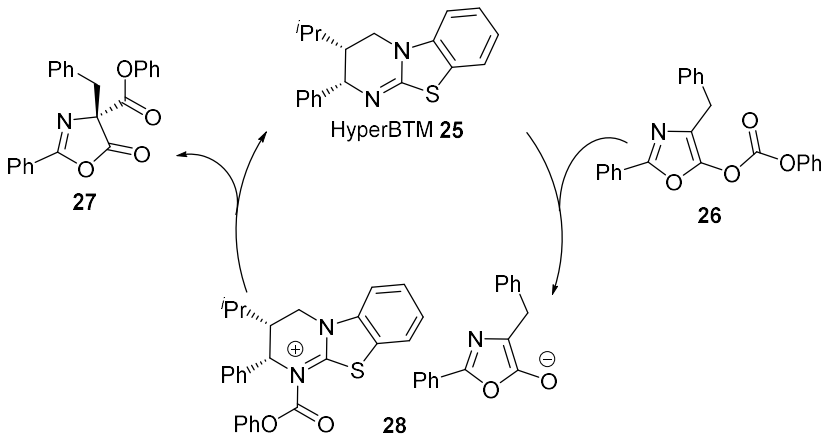
Scheme 5. Evolution of amidine and isothiourea catalysts for kinetic resolution.

The great potential of acyl ammonium catalysis with isothioureas was also shown by Smith who developed an isothiourea-promoted Steglich rearrangement in which *O*- to *C*-carboxyl transfer generates quaternary stereocentres with high enantioselectivity (Scheme 6).[32] HyperBTM **25** was evaluated as the best catalyst to transfer the phenoxycarbonyl group of oxazolyl carbonate **26** to give product **27** with excellent yield and enantiocontrol. The reaction is well tolerated for a range of alkyl- and aryl-substituted oxazole substrates.



Scheme 6. Enantioselective Steglich rearrangement.

In the proposed mechanism (Scheme 7) nucleophilic attack of isothiourea **25** into carbonate **26** generates ion pair **28** of *N*-carboxy intermediate and the azlactone enolate. Subsequent *C*-carboxylation is more favoured upon the *Re*-face of the enolate to give (*R*)-**27** and regenerate Lewis base catalyst **25**.



Scheme 7. Catalytic cycle of enantioselective Steglich rearrangement.

1.3.2 Ammonium enolate catalysis

C1-Ammonium enolate intermediates **29** can be accessed from the treatment of either a ketene [33] or a suitable activated carboxylic acid derivative with a nucleophilic tertiary amine catalyst, followed by deprotonation if required. Due to the inherent instability of ketenes, the development of alternative routes to C1-ammonium enolates from bench-stable materials, namely anhydrides, carboxylic acids or activated esters, is an active field of research (Figure 4).[34,35] Tertiary amines used for the generation of ammonium enolates include isothiourea-derived catalysts studied extensively within the Romo[36] and Smith groups.[37]

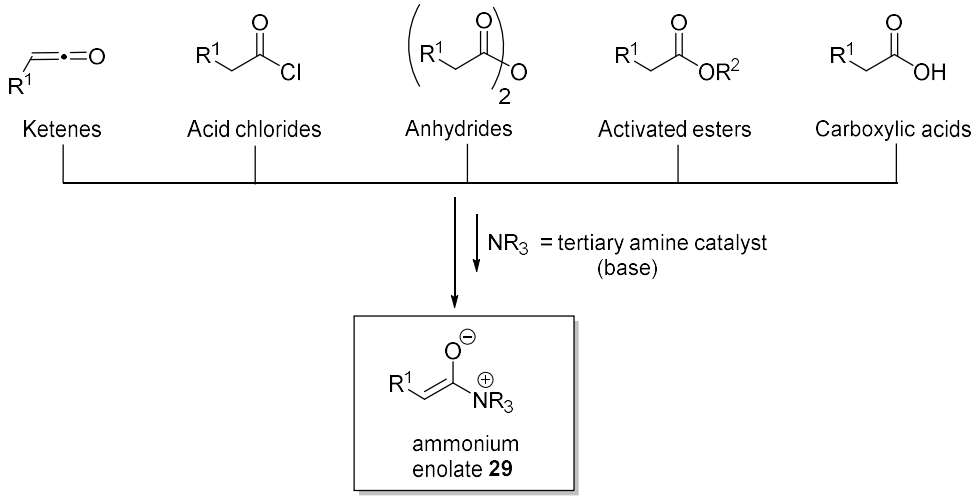
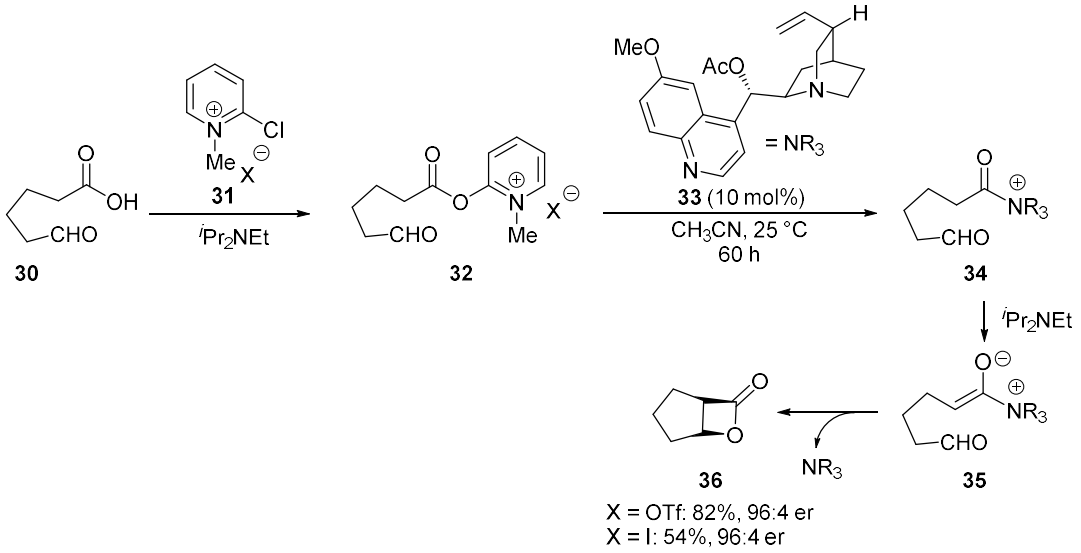


Figure 4. Organocatalytic C1-ammonium enolate generation.

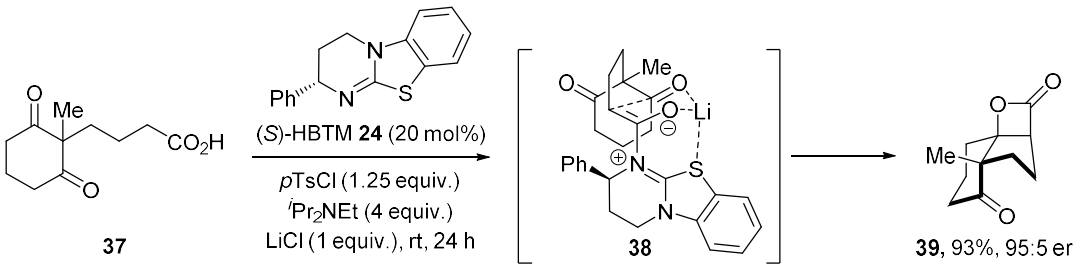
Inspired by the pioneering studies of Wynberg in generating β-lactones from the cinchona alkaloid-catalysed reaction of ketenes with aldehydes,[33] Romo's group has developed an alternative method employing *in situ* carboxylic acid **30** activation using Mukaiyama's reagent **31**.[38,41] Activated ester **32** is intercepted by tertiary amine cinchona alkaloid *O*-acetylquinidine

catalyst **33** to generate acyl ammonium species **34.** Deprotonation of **34** affords C1-ammonium enolate **35**, which undergoes intramolecular aldol reaction to form bicyclic β-lactone **36** in high er and moderate-to-good yields using 10 mol% of **33** (Scheme 8).[38]



Scheme 8. Generation of ammonium enolates from carboxylic acids.

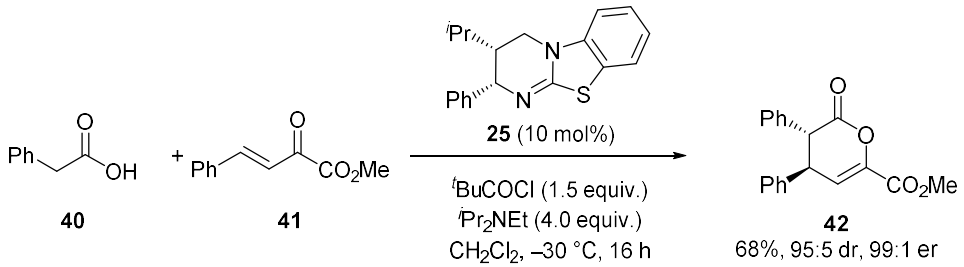
In a significant breakthrough, Romo extended this approach to the use of isothiourea (*S*)-HBTM **24**,[42] in an intramolecular desymmetrisation of ketoacid **37** with *p*-TsCl as an activating agent giving tricyclic β-lactone **39**. The use of LiCl as a Lewis acid additive results in a Li-chelated bicyclic chair-like transition state **38**, affording both excellent yield and enantioselectivity (Scheme 9).[36] The same strategy was applied towards the enantioselective synthesis of the spirocyclic sesquiterpene natural product (−)-curcumalactone.[43]



Scheme 9. Isothiourea-catalysed intramolecular β-lactone formation.

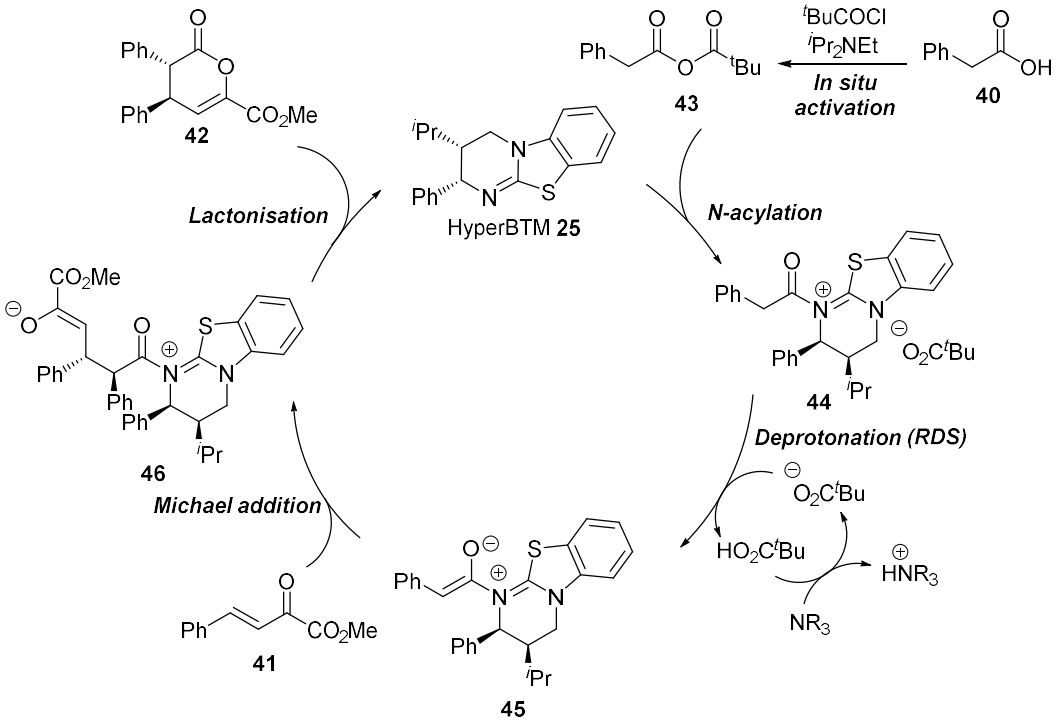
Extension of this methodology to intermolecular processes remained challenging until 2011 when the Smith group reported the use of carboxylic acids as ammonium enolate precursors in an intermolecular Michael addition-lactonisation.[44] Using pivaloyl chloride to activate aryl acetic acid **40**, the reaction with α-keto-β,γ-unsaturated ester **41** was efficiently catalysed by HyperBTM

25. The resulting *anti*-dihydropyranone **42** was obtained with high levels of diastereo- and enantiocontrol (Scheme 10).



Scheme 10. HyperBTM-catalysed intermolecular Michael addition-lactonisation.

In the proposed mechanism (Scheme 11) the reaction proceeds *via* initial *in situ* formation of mixed anhydride **43**, which readily undergoes *N*-acylation by HyperBTM **25** to form corresponding acyl ammonium ion **44**. Rate-determining deprotonation[47] by pivalate generates (*Z*)-ammonium enolate **45**. Subsequent intermolecular Michael addition to acceptor **41** in the *s-cis* conformation gives enolate **46**. The final lactonisation step affords enantioenriched product **42** and regenerates the isothiourea catalyst.



Scheme 11. Proposed catalytic cycle for isothiourea-catalysed Michael addition-lactonisation.

A simple model consistent with the observed stereoselectivity shows the isothiouronium heterocycle adopting a half-chair type conformation with the *C*(2)-phenyl substituent pseudoaxial to minimise 1,2 steric interactions and the *C*(3)-^{i}Pr unit pseudoequatorial (Figure 5).[45] Within

the (*Z*)-ammonium enolate, the oxygen atom preferentially lies *syn* to the sulfur atom within the isothiouronium ion, allowing a stabilising n_o to σ^*_{C-S} interaction previously suggested[46,47] and observed[48] by several groups. The reaction proceeds though the transition state shown in Figure 5 to give the observed *anti*-diastereoisomer (from (*E*)-enone) or *syn*-diastereoisomer (from (*Z*)-enone) in high enantiomeric excess and diastereomeric ratio.

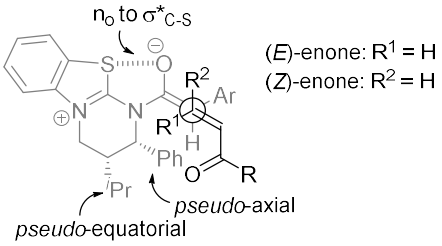


Figure 5. Stereochemical rationale.

The strategy of ammonium enolate chemistry has been successfully employed in both inter- and intramolecular processes to give a plethora of asymmetric products including β-lactones[33,36,49] and β-lactams,[50,52] δ-lactones,[44] substituted pyrrolidines[53] and pyridines[54] α-halogenated esters,[55] and *O*- and *N*-diquinones.[56,57]

1.3.3 α,β-Unsaturated acyl ammonium catalysis

Beyond acyl ammonium and ammonium enolate chemistry, the ability of isothioureas, as multifunctional catalysts, to display diverse modes of reactivity was further developed in the use of α,β-unsaturated acyl ammonium intermediates. While acyl ammonium and ammonium enolates have been the most extensively studied to date and utilised in a number of stereoselective processes, the use of α,β-unsaturated acyl ammonium intermediates of the type **47**, has received relatively little attention. These species contain electrophilic centres at the C1 and C3 positions, and a latent nucleophilic centre at C2 (Figure 6), providing new opportunities for reaction design to target previously inaccessible product architectures. Given the high potential of this intermediate within the Lewis base catalysis, the ways to expand the area of α,β-unsaturated acyl ammonium catalysis were sought in course of this work. At the outset of the research outlined in this thesis, three distinct domino reactions with high stereodivergence of these processes have been developed using multiple catalytic intermediates. These include α,β-unsaturated acyl ammonium, ammonium enolate and acyl ammoniums, which in combination with suitable nucleophilic components allowed to generate highly stereodefined indane-derived polycycles bearing multiple stereocentres. Furthermore, a new general concept within α,β-unsaturated acyl ammonium catalysis has been established utilising the aryloxide release from an α,β-unsaturated aryl ester substrate to facilitate catalyst turnover. This methodology allowed the use of

nitroalkanes as simple nucleophiles for the synthesis of enantioenriched γ-nitro derivatives. Finally, alternative catalyst turnover within α,β-unsaturated acyl ammonium catalysis was further investigated exploiting a unique reactivity of silyl nitronates to undergo enantioselective Michael addition and facilitate turnover of the Lewis base catalyst affording a wide range of γ-nitro-substituted silyl esters in high diastereo- and enantioselectivity.

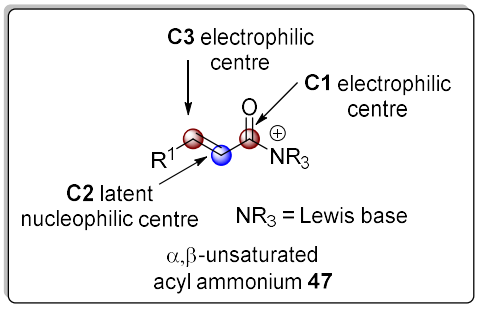


Figure 6. Structure of α,β-unsaturated acyl ammonium **47**.

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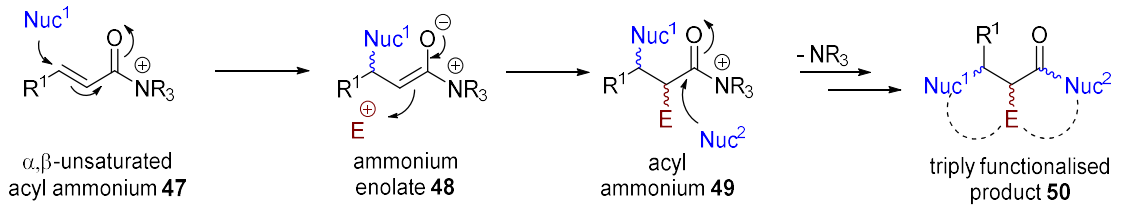
2 1,3-Dicarbonyls in isothiourea-catalysed domino reactions

2.1 Background

2.1.1 α,β-Unsaturated acyl ammonium catalysis in domino reactions

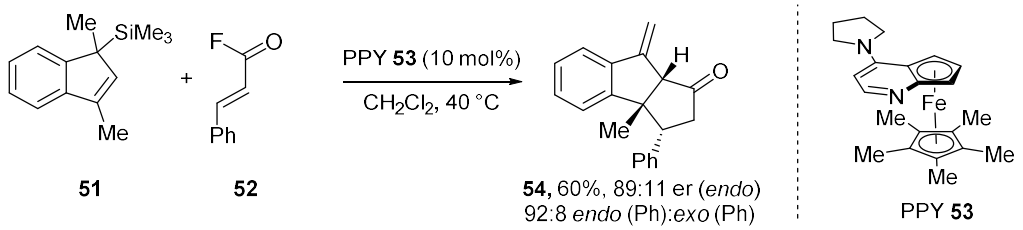
Synthetic transformations that rapidly assemble molecular complexity are actively being pursued given the importance of these processes for achieving improvements in synthetic efficiency.[1] In this regard, domino reactions[2] or organocascade processes[3,4] that generate multiple bonds and stereocentres in a single operation have emerged as some of the most useful strategies for quickly generating structural complexity.[5]

The α,β-unsaturated acyl ammonium intermediate **47** possesses multiple active sites (Chapter 1, Figure 6), which can be revealed sequentially to induce tandem-bond forming events. As depicted in Scheme 12, it can be first attacked by a nucleophile (Nuc^1) in a conjugate addition to form a chiral ammonium enolate **48**, which then enables α-addition of an electrophile (E) to deliver acyl ammonium **49**. Final acyl substitution by a second nucleophile (Nuc^2) leads to overall functionalisation of three carbons with up to two new stereocentres to form product **50** and regenerate the catalyst.[1]



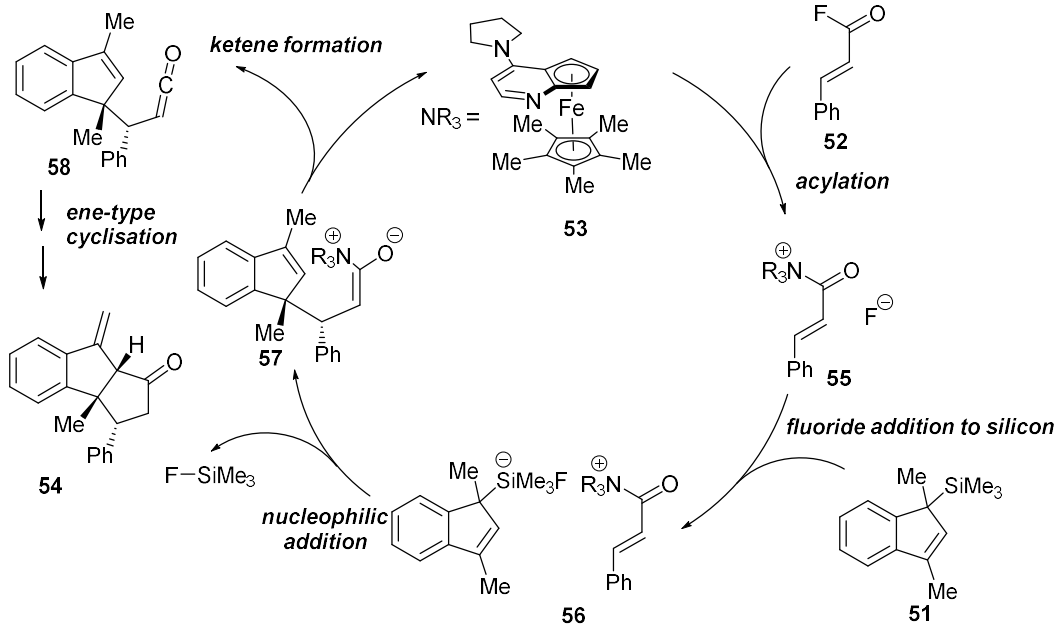
Scheme 12. Reactivity of the chiral unsaturated acyl ammonium.

A pioneering report from Fu[6] showed the great potential of α,β-unsaturated acyl ammonium intermediates to induce formation of multiple bonds and stereocentres. Employing a silylated indane **51** and cinnamoyl fluoride **52** delivers a [3 + 2] annulation reaction catalysed by chiral 4-pyrrolidinopyridine DMAP derivative **53**. The resulting diquinane **54** was obtained with moderate yields and enantioselectivities (Scheme 13).



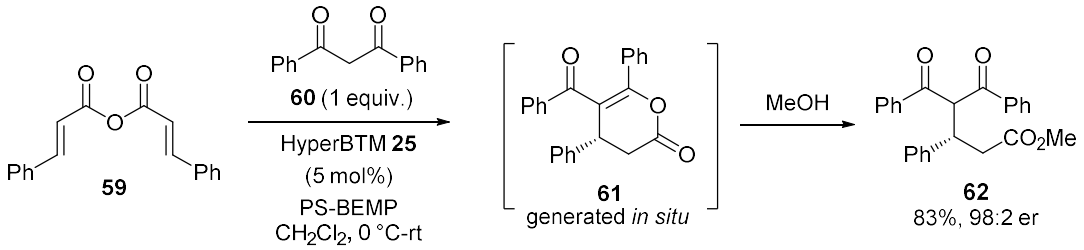
Scheme 13. [3 + 2] Asymmetric annulation employing α,β-unsaturated acyl ammonium.

A proposed mechanism for this transformation is illustrated in Scheme 14. Nucleophilic catalyst **53** is proposed to react with acid fluoride **52** to furnish ion pair **55**. The fluoride ion then binds to the silyl group of indene **51** to provide a new ion pair **56**. Conjugate addition of the indenyl nucleophile to its α,β-unsaturated acyl pyridinium counterion produces enolate **57** that bears two new stereocentres. Next, fragmentation releases the catalyst and affords ketene **58**, which is thought to cyclise *via* an ene-type process to generate the observed product **54**.



Scheme 14. Mechanism for enantioselective annulation of indenes with α,β-unsaturated carbonyl compounds.

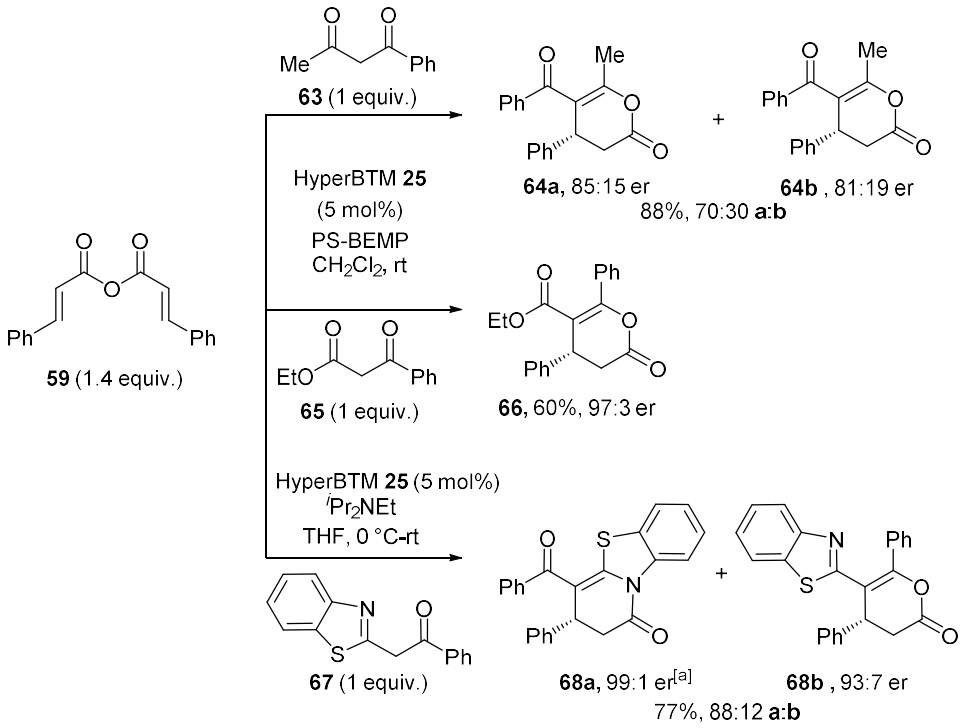
In 2013 Smith reported an isothiourea-promoted Michael-lactonisation process employing an α,β-unsaturated acyl ammonium species.[7] Using unsaturated homoanhydride **59** in combination with 1,3-diketone **60** provided dihydropyranone **61**, which was isolated as functionalised ester product **62** after *in situ* ring-opening with methanol in 83% yield and 98:2 er (Scheme 15).



Scheme 15. Isothiourea-catalysed enantioselective Michael addition-lactonisation with unsaturated aryl anhydrides.

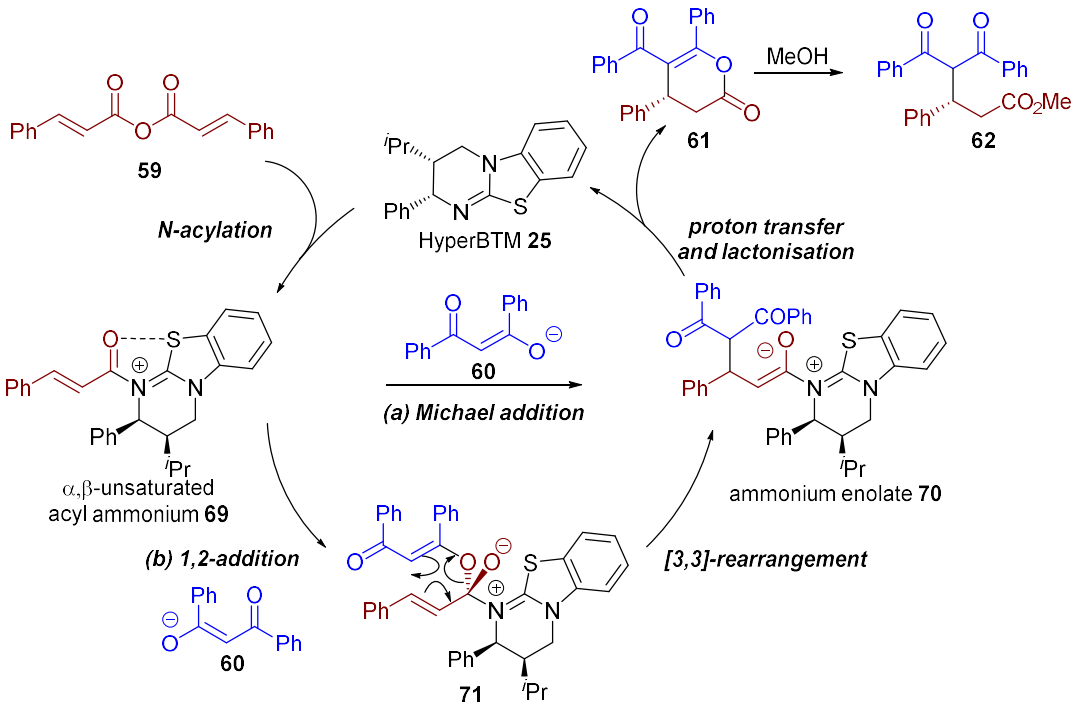
This method tolerates a range of 2-, 3- and 4-substituted β-aryl groups containing either electron-rich or electron-deficient groups, as well as heteroaryl substituents both in the anhydride and diketone components to give the corresponding esters in good yields (up to 86%) and excellent

enantioselectivities (95:5–99:1 er). The reaction can also be performed with ketoesters and non-symmetric diketones. Notably, dicarbonyl **63** gave a mixture of regioisomeric dihydropyranones **64a** and **64b**, while in the case of ethyl benzoylacetate **65** a single regioisomer **66** was obtained (Scheme 16). Intriguing reactivity was observed upon extending the nucleophile scope to azaaryl ketone **67**. Cyclisation occurs preferentially through the benzothiazole nitrogen, generating the enantioenriched dihydropyridone **68a** as a major product in addition to lactone **68b** (88:12 **a**:**b** ratio).



Scheme 16. Observed regioselectivity employing different nucleophiles. [a] er obtained upon single recrystallisation.

In this isothiourea-promoted annulation two possible catalytic cycles can be proposed (Scheme 17). Both cycles involve an initial *N*-acylation of the catalyst **25** with an anhydride to give an α,β-unsaturated acyl ammonium intermediate. In pathway (a) Michael addition of diketone enolate **60** to the *Re*-face of the α,β-unsaturated acyl ammonium **69** gives ammonium enolate **70**. Subsequent proton transfer followed by lactonisation generates the desired dihydropyranone **61**, which can be either isolated or subsequently ring-opened *in situ* with methanol to generate the functionalised ester **62** in high er. Alternatively, the reaction could proceed *via* 1,2-addition to the α,β-unsaturated acyl ammonium to form the intermediate **71**, followed by a [3,3]-rearrangement to give enolate intermediate **70**. In related NHC-processes pathway (a) was suggested by Studer and Mayr,[8] while pathway (b) was favoured by Bode.[9]



Scheme 17. Proposed mechanism for the isothiourea-promoted annulation process.

Mechanistic experiments[7,10e] showed that reacting cinnamoyl chloride with stoichiometric HyperBTM **25** gives α,β-unsaturated acyl ammonium chloride salt **72**, which was successfully used as a precatalyst in the reaction, consistent with the potential intermediacy of an acyl ammonium species. The obtained X-ray structure of **72** (Figure 7) supported the expected "conformational lock" between the acyl O and S of the isothiouronium heterocycle due to non-covalent 1,5-S···O interactions[10a] (Chapter 1, Figure 5). The internuclear distance (2.3 Å) is significantly less than the sum of the van der Waals radii (3.4 Å),[10b] which is consistent with an attractive force between the S- and O- atoms and in line with previous computations by Tantillo and Romo[10c] as well as by Houk and Birman[10d]. Facial stereoselectivity in the assumed conjugate addition mode is facilitated by the more favoured nucleophilic attack of the diketone enolate **60** to the *Re*-face of the α,β-unsaturated acyl ammonium intermediate *anti* to the stereodirecting groups of HyperBTM **25**.

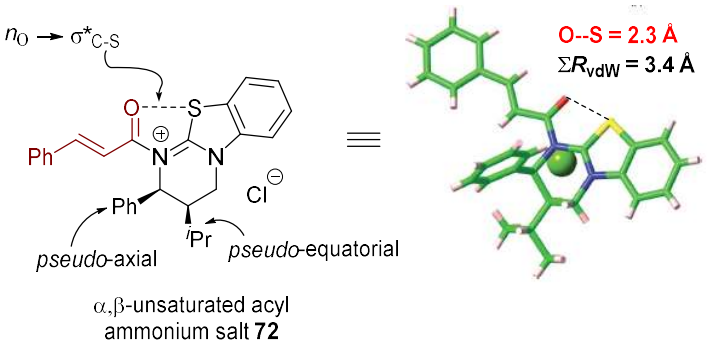
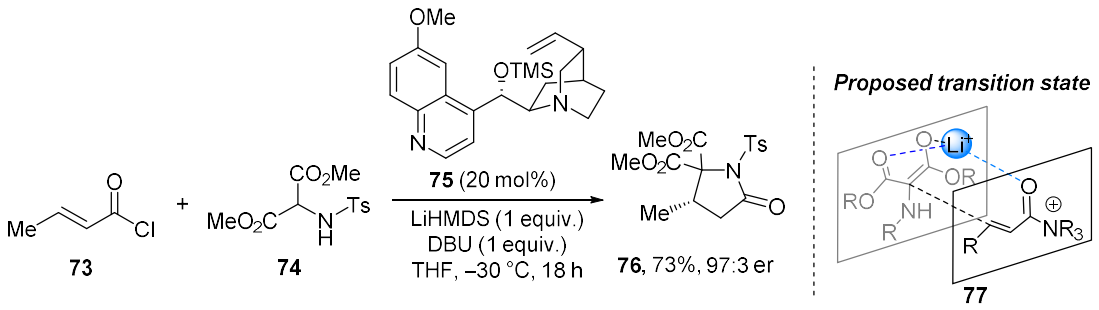


Figure 7. X-ray crystal structure of α,β-unsaturated acyl ammonium salt **72**.

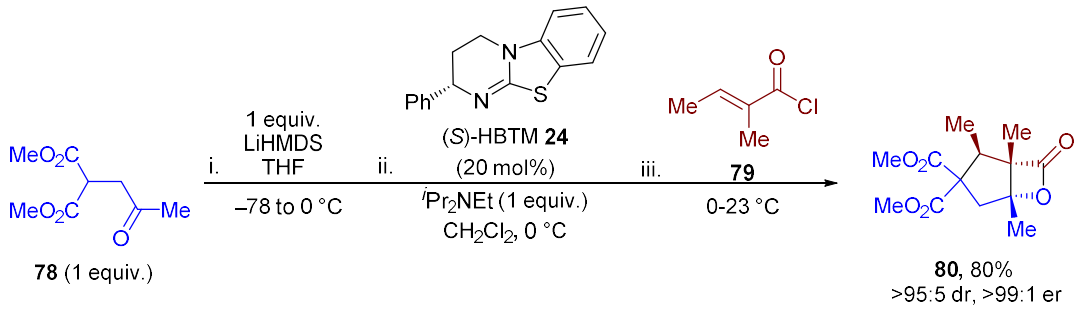
A further example using α,β-unsaturated acyl ammonium catalysis was reported by Romo in the synthesis of enantioenriched *N*-heterocycles.[11] Nucleophilic addition of a bisnucleophile **74** into an α,β-unsaturated acyl ammonium intermediate generated *in situ* by acylation of α,β-unsaturated acid chloride **73** with *O*-trimethylsilylquinidine **75** (Scheme 18) delivered pyrrolidinone **76** in good yield and enantioselectivity. In this instance, using LiHMDS to deprotonate amino ester **74** is crucial for reactivity and enantioselectivity. Romo postulated that the lithium cation chelates both the α,β-unsaturated acyl ammonium species and the nucleophile, thus lowering the energy of proposed transition state **77** and rationalising the observed absolute configuration of the pyrrolidinone products.



Scheme 18. Synthesis of pyrrolidinones *via* α,β-unsaturated acyl ammonium intermediates.

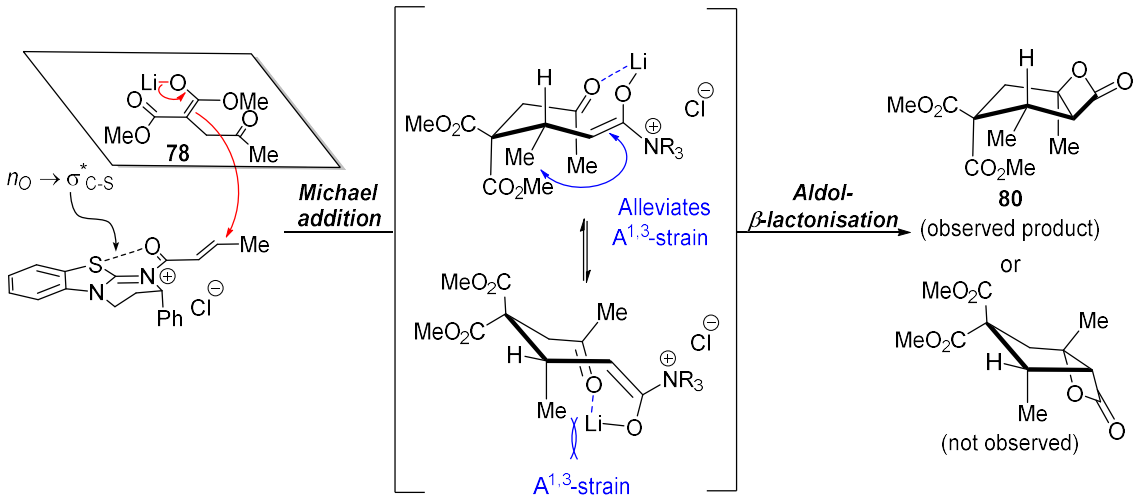
Successful application of α,β-unsaturated acyl ammonium intermediates provided precedent for the design of more complex tandem processes involving these species. In 2013, Romo developed an isothiourea-catalysed Michael-aldol-β-lactonisation (NCMAL) organocascade that gives access to stereochemically complex cyclopentanes from α,β-unsaturated acid chlorides.[12] Pro-nucleophile **78**, bearing two electron-withdrawing groups, reacts as a soft enolate with an α,β-unsaturated acyl ammonium formed *via* nucleophilic addition of (*S*)-HBTM **24** into acid chloride **79**. The construction of two C–C-bonds, one C–O bond, two rings and three contiguous

stereocentres delivers complex cyclopentane **80** with high diastereo- and enantiocontrol (Scheme 19).



Scheme 19. Isothiourea-catalysed NCMAL organocascade.

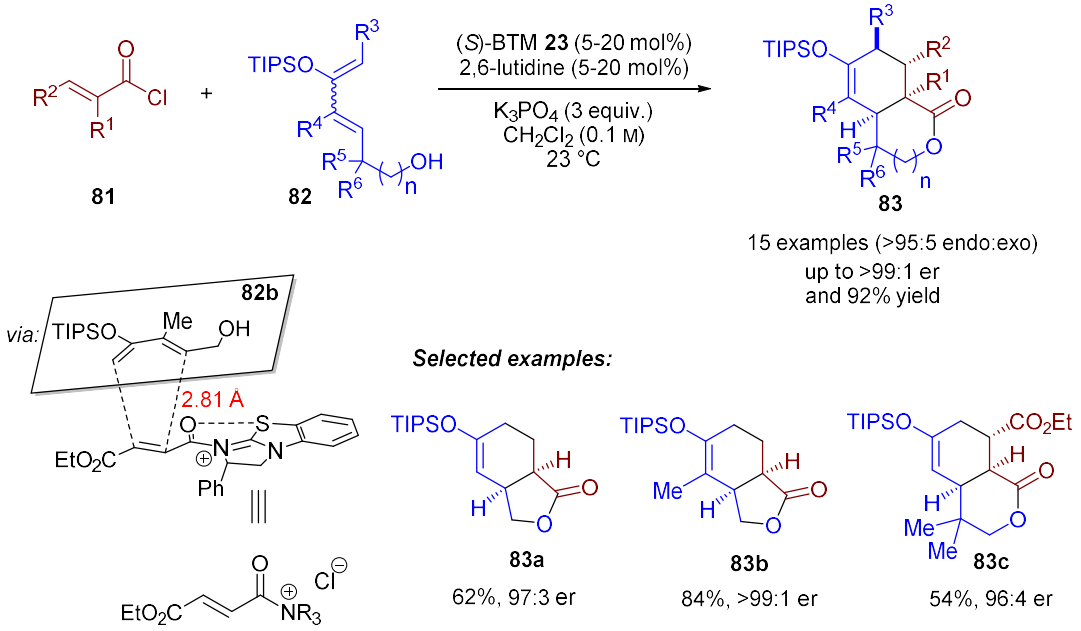
The origin of the facial selectivity during the nucleophilic attack is based on the same conformational features as observed by Smith[7] in the X-ray structure of **72** (Figure 7), with the initial Michael addition occurring to the *Re*-face of the Michael-acceptor. The high diastereoselectivity observed during the aldol step is proposed to derive from minimisation of allylic 1,3-strain in the pre-transition state assembly (Scheme 20).



Scheme 20. Transition-state arrangement rationalising the enantio- and diastereoselective outcome.

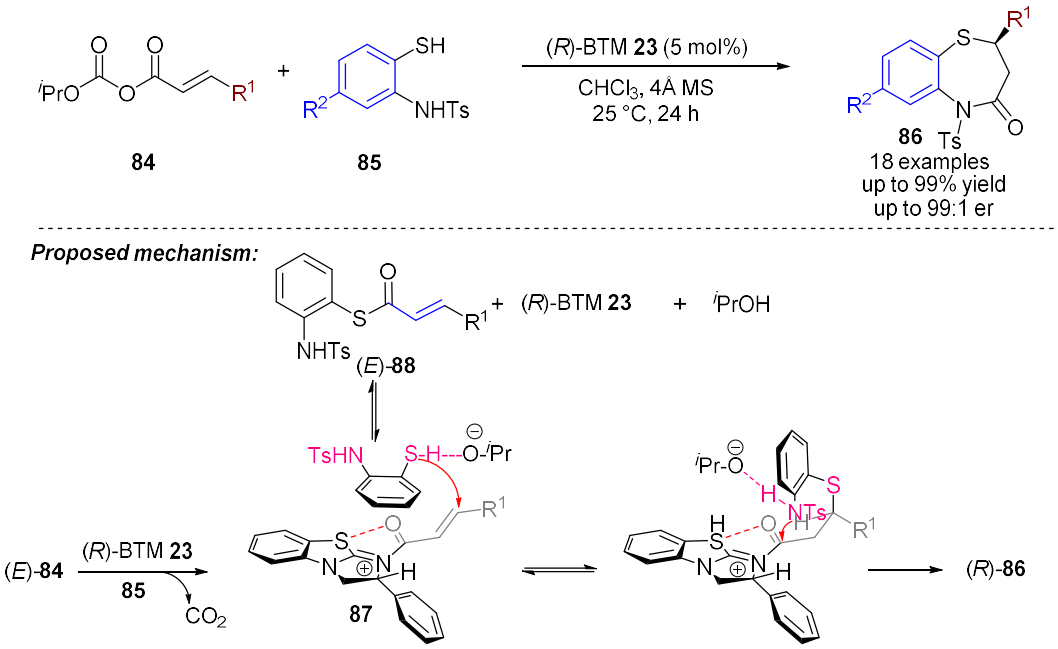
The Diels-Alder (DA) reaction is a versatile method to construct multiple bonds and generate complex, densely functionalised heterocycles or carbocycles. Enantioselective DA variants have recently been established using iminium,[13] enamine,[14] bifunctional acid-base catalysis,[15] and hydrogen-bonding catalysis.[16] The only enantioselective organocatalytic DA reaction employing chiral α,β-unsaturated acyl ammoniums was reported by Romo in 2014.[10c] Readily available acid chlorides **81** are activated by isothiourea derivative (*S*)-BTM **23** to generate α,β-unsaturated acyl ammonium species of the type **47** (Scheme 12). The ammonium salt reacts as a dienophile with

diene **82** in a DA-lactonisation organocascade. Resulting *cis*-fused bicyclic γ- and δ-lactones **83** bearing up to four contiguous stereocentres are formed with high enantio- and diastereoselectivities. A wide scaffold of DA-adducts was reported in this work with selected examples depicted in Scheme 21. Computational results suggest a kinetic preference for an *endo* transition state with enantiocontrol ascribed to stereoelectronic and conformational preferences of the acyl ammonium salt dienophiles.



Scheme 21. Diels-Alder-lactonisation organocascade promoted by (*S*)-BTM.

Matsubara and co-workers have recently prepared enantiomerically enriched 1,5-benzothiazepines through the domino reaction of 2-aminothiophenols **85** as *bis*-nucleophiles with α,β-unsaturated acyl ammoniums generated from mixed anhydrides **84** and an isothiourea organocatalyst (Scheme 22).[17] Mechanistic studies suggested that the reversibility of the nucleophilic attack by sulfur-centred nucleophiles to α,β-unsaturated acyl ammonium intermediates **87** imparts the high regio- and enantioselectivity of the transformation. In addition, in the event where (*E*)-**88** is generated during the course of the reaction, it could be incorporated back into the main catalytic process and ultimately lead to the formation of the desired product (*R*)-**86** in high enantioselectivity.



Scheme 22. Reaction of α,β-unsaturated acyl ammonium with 2-aminothiophenols.

2.1.2 α,β-Unsaturated acyl azolium catalysis in domino reactions

While the chemistry of α,β-unsaturated acyl ammoniums is relatively underexplored, the reactivity of the corresponding conjugated acyl azolium intermediates of the type **89** (Figure 8) has been well studied within N-heterocyclic carbene (NHC) catalysis. α,β-Unsaturated acyl azoliums can be used in stereoselective domino addition-cyclisation reactions to form biologically interesting compounds such as lactones and lactams.[18]

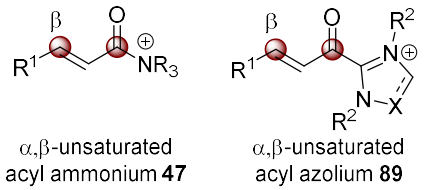
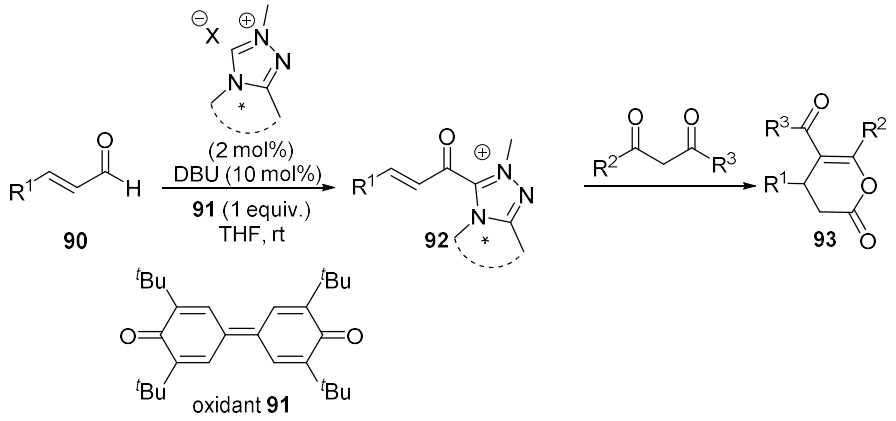


Figure 8. α,β-Unsaturated acyl ammonium and acyl azolium intermediates.

Unsaturated azolium intermediates can be generated from acid halides[19] or, using oxidative methods, from aldehydes,[20,21] enals,[22] haloenals,[23] and ynals.[24] However, poor stability of the starting materials and the use of relatively expensive oxidants are major disadvantages of this strategy.

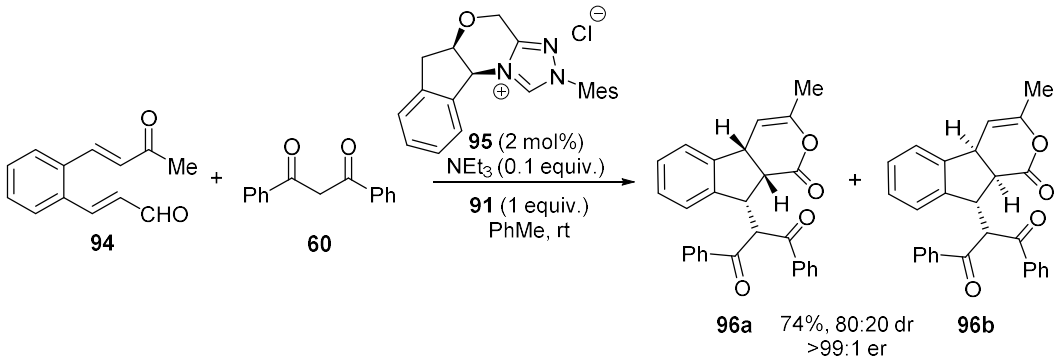
Studer developed an intermolecular Michael-addition-lactonisation organocascade *via* NHC-catalysed redox activation of enal **90** using oxidant **91** to generate α,β-unsaturated acyl azolium

intermediate **92**. It reacts as a Michael acceptor with β-diketones or β-ketoesters to give dihydropyranones **93** in good to excellent yields under mild conditions (Scheme 23).[25]



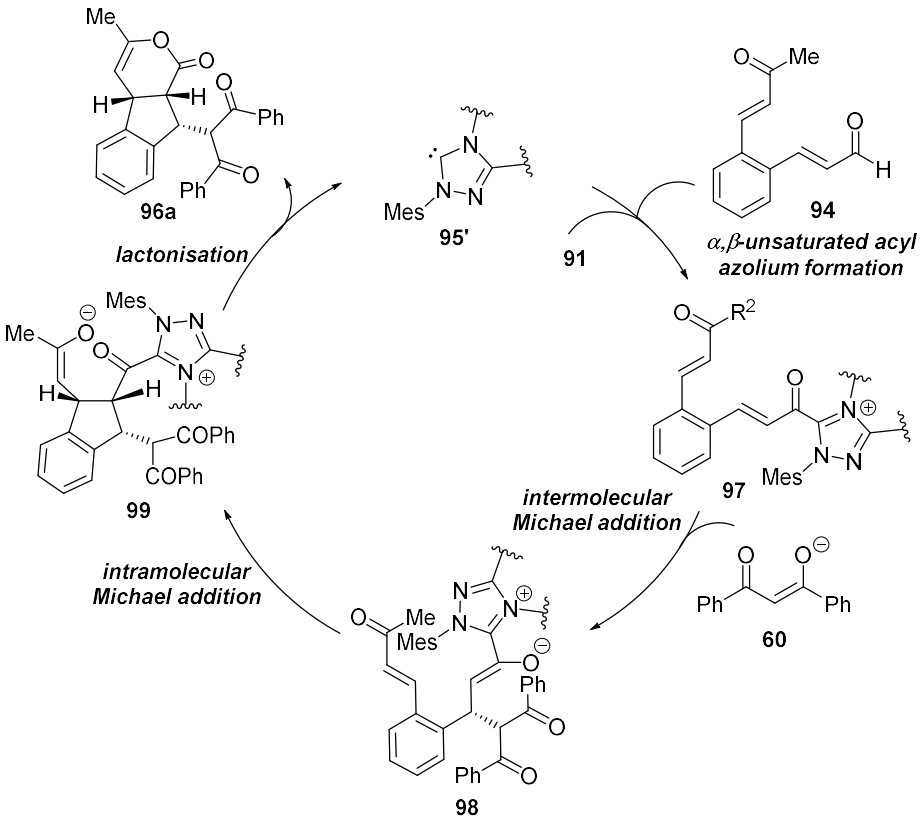
Scheme 23. NHC-catalysed oxidative domino Michael addition-lactonisation reaction.

They have also shown that a Michael-Michael-lactonisation cascade under similar conditions is successful, affording highly complex product architectures.[26] The reaction between aldehyde **94** and β-diketone **60** using chiral triazolium salt **95** as a precatalyst delivers trisubstituted indane derivatives **96a** and **96b** with three contiguous stereocentres in good yield and high levels of enantio- and diastereocontrol (Scheme 24).



Scheme 24. NHC-catalysed oxidative Michael-Michael-lactonisation cascade.

The reaction is proposed to occur *via* the catalytic cycle depicted in Scheme 25. Reaction of enal **94** with carbene **95'** in the presence of oxidant **91** generates α,β-unsaturated acyl azolium intermediate **97**. Conjugate addition of deprotonated 1,3-dicarbonyl compound **60** to the redox-activated Michael acceptor provides **98**. Enolate **98** can undergo intramolecular 1,4-addition to generate **99**, which undergoes intramolecular acylation to afford product **96** and catalyst **95'**.



Scheme 25. Proposed catalytic cycle for the NHC-catalysed oxidative MML cascade.

The authors assume that initial selectivity occurring in the first C-C-bond formation is increased by a subsequent second stereoselective reaction that funnels the minor isomer into a product which is not an enantiomer of the targeted compound, resulting in high enantioselectivity observed in this transformation. This phenomenon of correcting the "stereochemical error" is well established in asymmetric synthesis.[27]

2.2 Aims and objectives

Lewis base catalysis is being actively explored given its power for generating valuable synthetic building blocks. In particular, isothiourea catalysts are demonstrated to be successful in a variety of transformations employing acyl ammonium and ammonium enolate intermediates. Expanding the role of isothioureas as a multifunctional catalyst architecture, isothiourea-derived α,β-unsaturated acyl ammonium moieties have been used in the design of new organocascade processes that rapidly generate complex molecules, as shown by the Romo, Matsubara and Smith groups.

Studer's synthesis of indanes (Scheme 24) is an important contribution to the Lewis base catalysis, affording quick access to complex structures. Indane skeletons occur in various natural products and serve as valuable synthons for the synthesis of interesting complex organic compounds.[28] In

particular, chiral indane units constitute core structural elements that are ubiquitous in a large number of biologically and pharmaceutically active molecules. For example, indatraline **100** is a drug used in the treatment of depression and addiction.[85] Rasagiline **101** is an irreversible inhibitor of monoamine oxidase used as a monotherapy in early Parkinson's disease.[29] PNU-99194A **102** was reported to be a selective dopamine D3 receptor antagonist with potential antipsychotic properties in animal models.[30] Last but not least, Indinavir **103** is a protease inhibitor used as a component of highly active antiretroviral therapy to treat HIV infection and AIDS (Figure 9).[31]

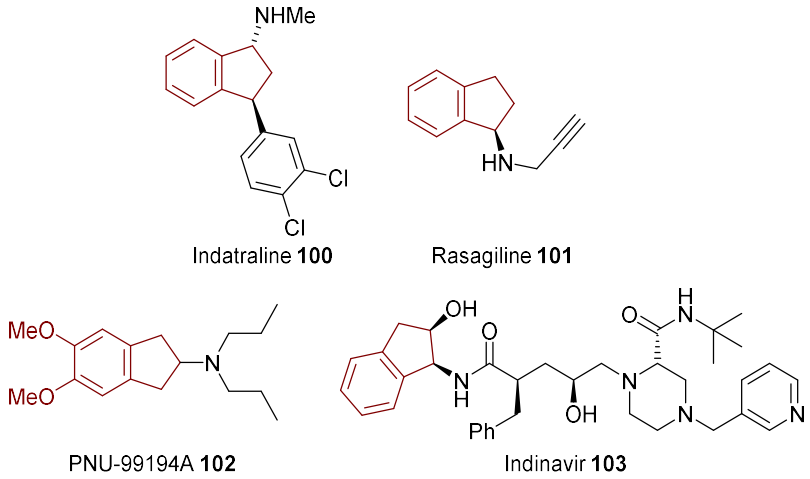
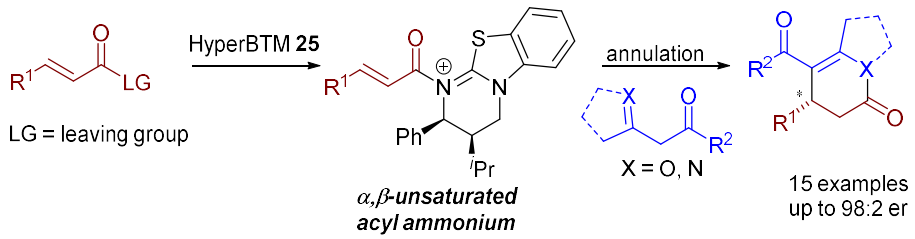


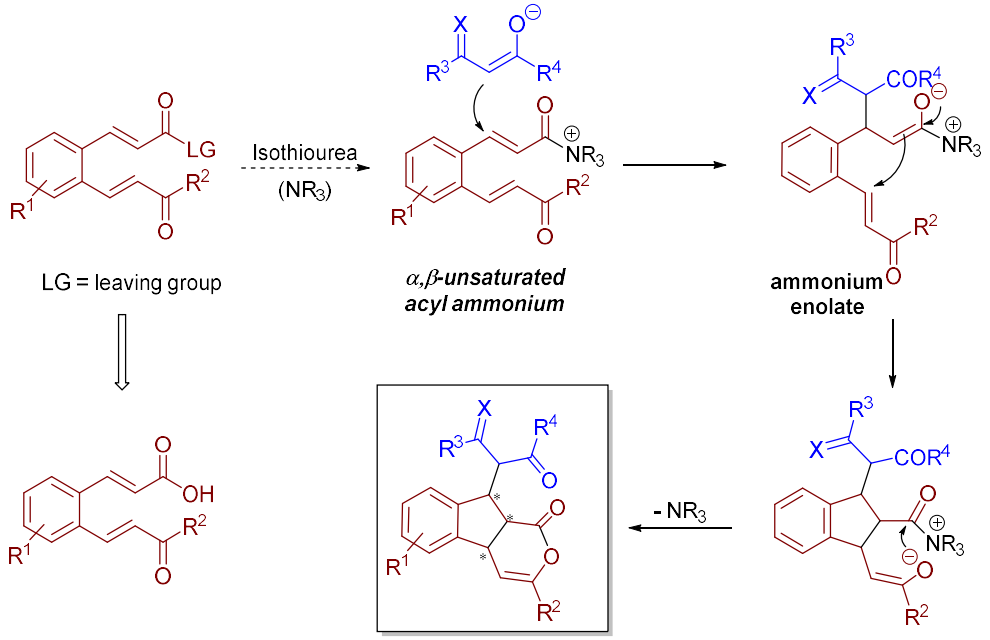
Figure 9. Indane skeletons in various therapeutic agents.

Despite the great importance of chiral indane motifs, only a few methods have been developed for the stereoselective construction of disubstituted and/or trisubstituted indanes by the use of chiral secondary amines,[32] chiral transition-metal complexes,[33,34] and NHCs [25,35,36] as catalysts. Application of isothiourea-derived α,β-unsaturated acyl ammonium species for the synthesis of valuable chiral indanes may provide a useful alternative to NHCs avoiding the use of unstable starting materials and relatively expensive stoichiometric oxidants. The aim of this project is to extend the previous work of the Smith group (Scheme 26a) employing α,β-unsaturated acyl ammonium intermediates[7] by introduction of a second Michael acceptor into the substrate, which would lead to overall functionalisation of three carbons. (Scheme 12). This first demonstration of an acyl ammonium intermediate in a domino Michael-Michael-lactonisation (MML) reaction was hoped to provide quick access to biologically relevant indanes with three contiguous stereocentres (Scheme 26b).

a) Previous work: *Michael-lactonisation reaction via α,β-unsaturated acyl ammoniums*



b) This project: *Domino Michael-Michael-lactonisation (MML) reaction via α,β-unsaturated acyl ammoniums. One-pot synthesis of chiral, functionalised indane derivatives*

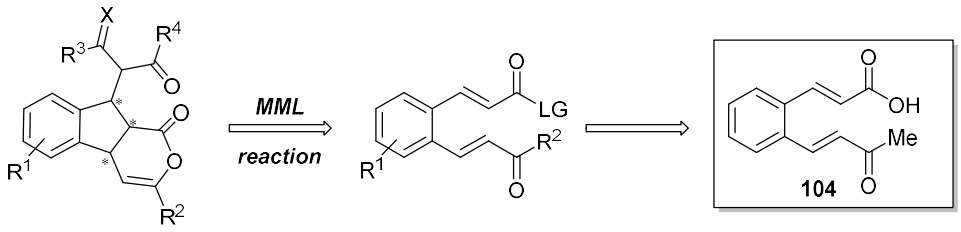


Scheme 26. Design of the isothiourea-promoted Michael-Michael-lactonisation cascade.

2.3 Domino Michael-Michael-lactonisation reaction using 1,3-dicarbonyls

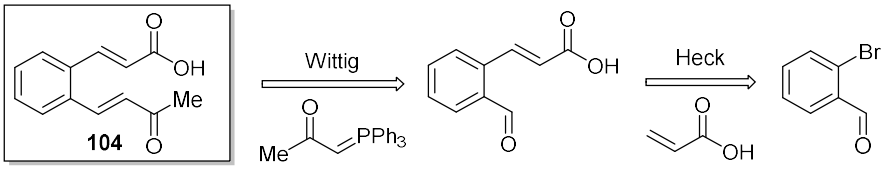
2.3.1 Synthesis of the starting material

Having set the aim of this project to develop a novel domino Michael-Michael-lactonisation (MML) reaction *via* α,β-unsaturated acyl ammonium intermediates and access enantiopure indane derivatives with three contiguous stereocentres, we required a starting point for studying the target transformation. Substrate **104** was chosen as a target starting material for the model reaction (Scheme 27).



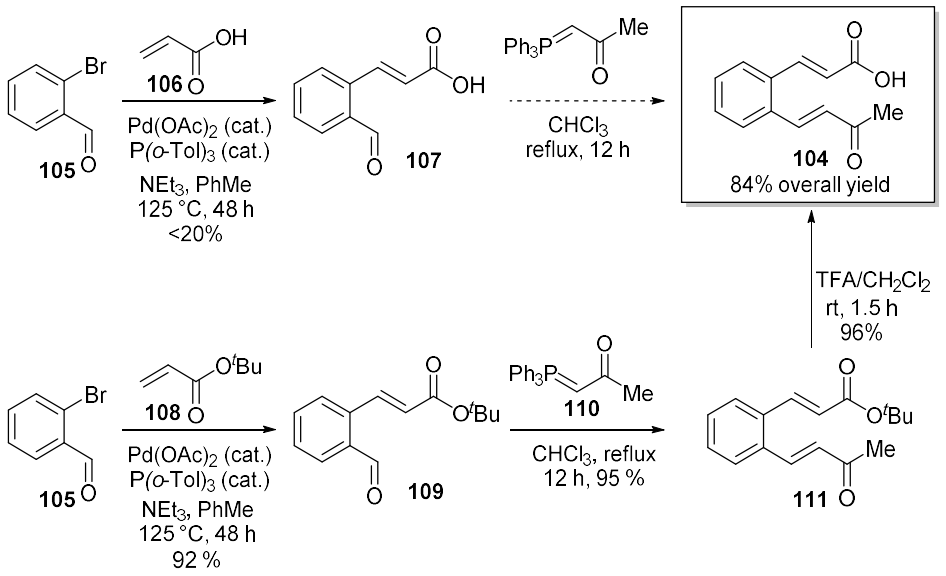
Scheme 27. α,β-Unsaturated acrylic acid as a target substrate.

The proposed two-step retrosynthetic analysis is depicted in Scheme 28. Acid **104** contains an enone that can be furnished *via* a Wittig reaction between an aldehyde and a corresponding phosphorane. The unsaturated carboxylic acid function can be synthesised in a Heck reaction between acrylic acid and 2-bromobenzaldehyde.



Scheme 28. Retrosynthetic analysis of the target acid **104**.

A facile and efficient method has been developed for the construction of desired α,β-unsaturated acid **104** (Scheme 29). The synthetic route commenced from commercially available 2-bromobenzaldehyde **105**, which was subjected to the Heck reaction with acrylic acid **106**. However, less than 20% of the unsaturated acid **107** was isolated after difficult purification by flash silica column chromatography. Alternatively, the use of *tert*-butyl acrylate **108** as an activated alkene in the Heck reaction gave acrylic ester **109** in 92% yield. The subsequent Wittig reaction of **104** with phosphorane **110** delivered ester **111** in excellent yield. Ester hydrolysis under acidic conditions led to the formation of acid **104** in 84% overall yield over the three steps.



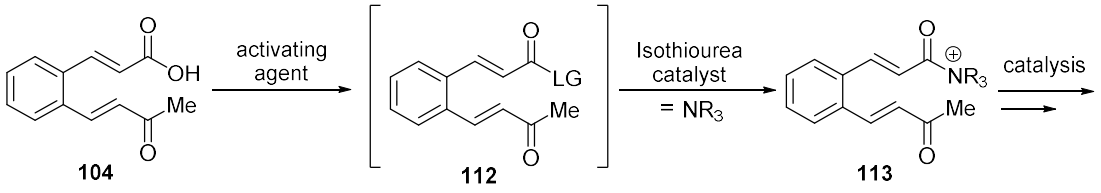
Scheme 29. Forward synthesis of the α,β-unsaturated acid **104**.

With the starting material in hand, optimisation of the target reaction including choosing an appropriate base and activating agent, finding a suitable catalyst and solvent for the reaction, alongside other parameters, was investigated.

2.3.2 Reaction optimisation

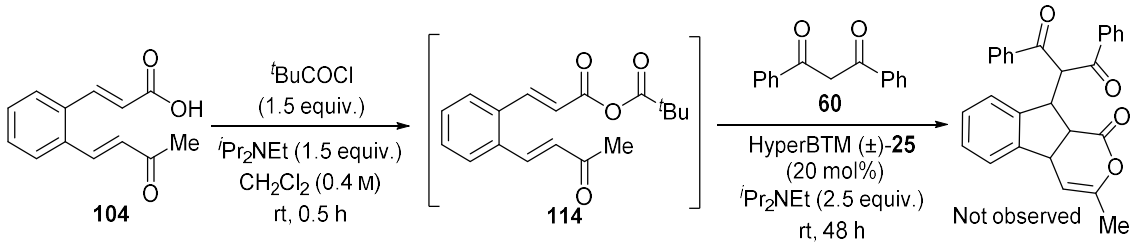
2.3.2.1 Activating agent and base screening

The first parameter to consider was the best activating agent for the generation of α,β-unsaturated acyl ammonium **113** from acid **104**. Acid substrates must firstly be "activated" to generate a reactive anhydride or ester species **112**, which are more susceptible to nucleophilic attack of the catalyst (Scheme 30).[37]



Scheme 30. General scheme for activation of the target acid **104.**

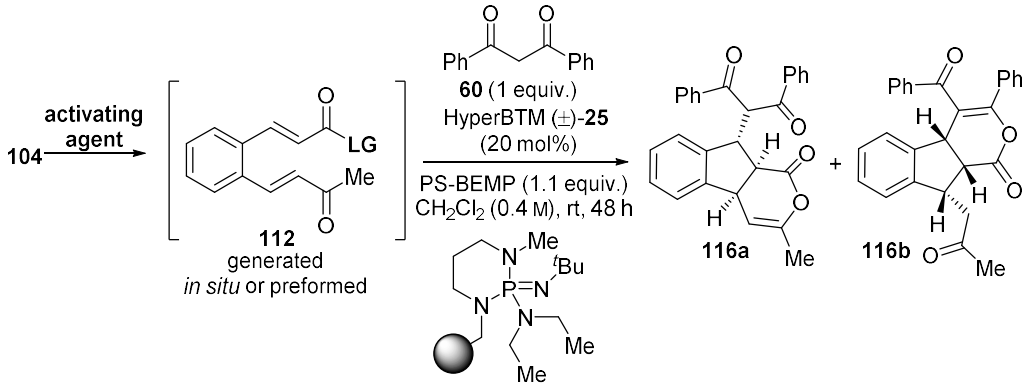
Previous work in the Smith group has used pivaloyl chloride as a useful activating agent, however the corresponding mixed anhydride **114** did not give any product using 1,3-diphenylpropane-1,3-dione **60** as a model nucleophile in the presence of racemic HyperBTM (±)-**25** as a catalyst (Scheme 31).



Scheme 31. Use of pivaloyl chloride as an activating agent.

No formation of the desired product was observed under these reaction conditions with starting material **104** being returned unreacted. For screening several alternative activating agents, a strong phosphazene base PS-BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene, loading of ~2.0–2.2 mmol/g loading, pK_a of BEMP = 27.6) was employed. Phosphazene bases represent a family of extremely strong, non-ionic, non-charged nitrogen-bases with an impressive list of advantages. The particular ability of phosphazene bases to produce highly reactive anions together with their low nucleophilicity and inertness towards the electrophilic component enables reactions of very weak C-H acidic substrates *via* deprotonation in typically excellent yields. Easier work-up, possible recovery of the BEMP, reaction rate enhancement and often better diastereoselectivity in reactions with BEMP due to its sterically hindered nature are further typical benefits of using phosphazene bases.[38,39]

In the Michael-lactonisation reaction reported by Smith, homoanhydrides proved the most suitable activated acids.[7] However, in this work other activation modes were pursued due to the complex structure of acid **104** and its corresponding homoanhydride. First, activated species **112** were generated *in situ* using several activating agents (Table 1). Applying the Mukaiyama reagent, no product formation was observed and starting materials were returned (entry 1). Thionyl chloride and carbonyldiimidazole were also unsuccessful and the activated species in both cases showed very poor stability (entries 2-3). More success was achieved using preformed activated esters. Some traces of the desired product were detected by ^{1}H NMR using a 4-nitrophenol activated ester, although with only poor conversion of the starting material (entry 4). However, using 2,4,6-trichlorophenol (TCP) activated ester **115** gave lactone **116a** along with its isomer **116b** in a promising 46% combined yield, **a**:**b** ratio of 75:25 and >95:5 dr for both lactones (entry 5). The structure of **116a** and **116b** was identified using 2D-NMR experiments (COSY, HSQC and HMBC). The **a**:**b** ratio was determined by ^{1}H NMR analysis of the crude mixture. Several alternative organic (^{i}Pr$_2$NEt, DBU, NEt$_3$) and inorganic (K_2CO_3) bases were screened. However, only low consumption of activated TCP-ester **115** (>20%) was observed, which made the product isolation more complicated and, therefore, these bases were not further investigated.



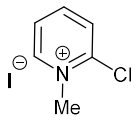
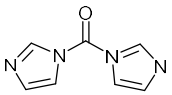
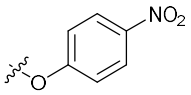
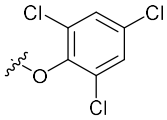
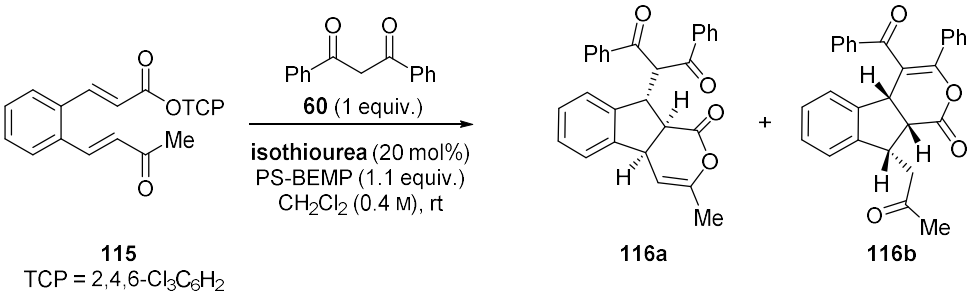
Entry	Activating Agent (*in situ*)		Yield (%)[a]	**116a**:**116b**[b]	dr[b]
1	Mukaiyama reagent		-	-	
2	Preformed acid chloride		-	-	
3	Carbonyldiimidazole		-	-	
	Activating Agent (preformed)	LG	Yield (%)[a]	**116a**:**116b**[b]	
4	4-Nitrophenol		trace	-	
5	2,4,6-trichloro-phenol		46	75:25	>95:5 for both

Table 1. Screening of activating agents. [a] Combined isolated yield.
[b] **a**:**b** ratio and dr determined by ^{1}H NMR analysis of the crude mixture.

2.3.2.2 Isothiourea screening

Having determined the optimal activation mode, the chiral isothioureas (*S*)-tetramisole hydrochloride **22**, (*R*)-benzotetramisole **23** and (2*S*,3*R*)-HyperBTM **25** (Table 2) were evaluated as Lewis base catalysts. The only chiral isothiourea to give any conversion into lactones **116a**/**116b** was HyperBTM **25** (entry 4), with the other isothioureas returning unreacted starting material (entries 2-3). Using (2*S*,3*R*)-HyperBTM **25**, excellent enantioselectivities were obtained giving major product **116a** in 98:2 er and >99:1 er for minor product **116b** with an **a**:**b** ratio of 75:25. Importantly, in absence of the catalyst no reaction was observed (entry 1).



115
TCP = 2,4,6-$Cl_3C_6H_2$

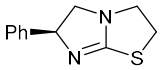
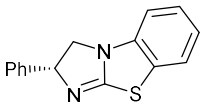
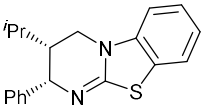
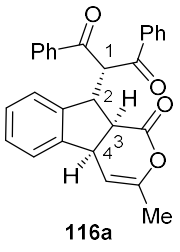
Entry	Isothiourea cat.		Yield (%)[a]	**116a**:**116b**	er[b]
1	-	-	-	-	-
2	(*S*)-TM·HCl **22**		trace	-	-
3	(*R*)-BTM **23**		trace	-	-
4	(2*S*,3*R*)-HyperBTM **25**		46	75:25	98:2 (>99:1[c])

Table 2. Screening of chiral isothioureas. [a] Combined isolated yield.
[b] Determined by HPLC analysis for major product **116a**. [c] er of minor product **116b**.

2.3.2.3 Absolute and relative configuration

The absolute and relative configuration of lactone **116a** (the major product) was determined by X-ray crystallographic analysis and is illustrated in Figure 10. The protons on the stereocentres 2, 3 and 4 have a relative *trans,cis* configuration respectively, which also corresponds to the spectroscopic data reported by Studer.[26] Interestingly, in his work using NHC catalysts, the product with the same relative configuration was obtained as the minor diastereoisomer.



116a

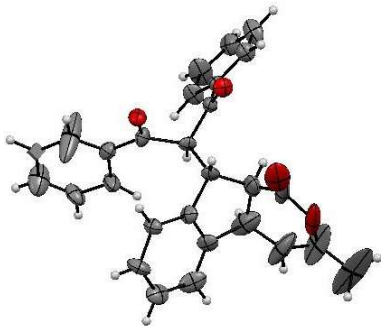


Figure 10: X-Ray crystal structure confirming the relative and absolute stereochemistry of indane **116a**.

The relative configuration of minor product **116b** was determined by nOe analysis of an inseparable mixture of **116a** and **116b** (Figure 11). The regioisomers are identified in the ^{1}H NMR were by characteristic shifts of the doublets between protons 1 and 2. Selective irradiation of proton 1 in **116b** showed a response on both protons 2 and 3, with a slightly higher intensity at the neighbouring proton 2. The same results with positive nOes were observed by selectively irradiating protons 2 and 3, which indicates the *syn*-configuration of all three protons.

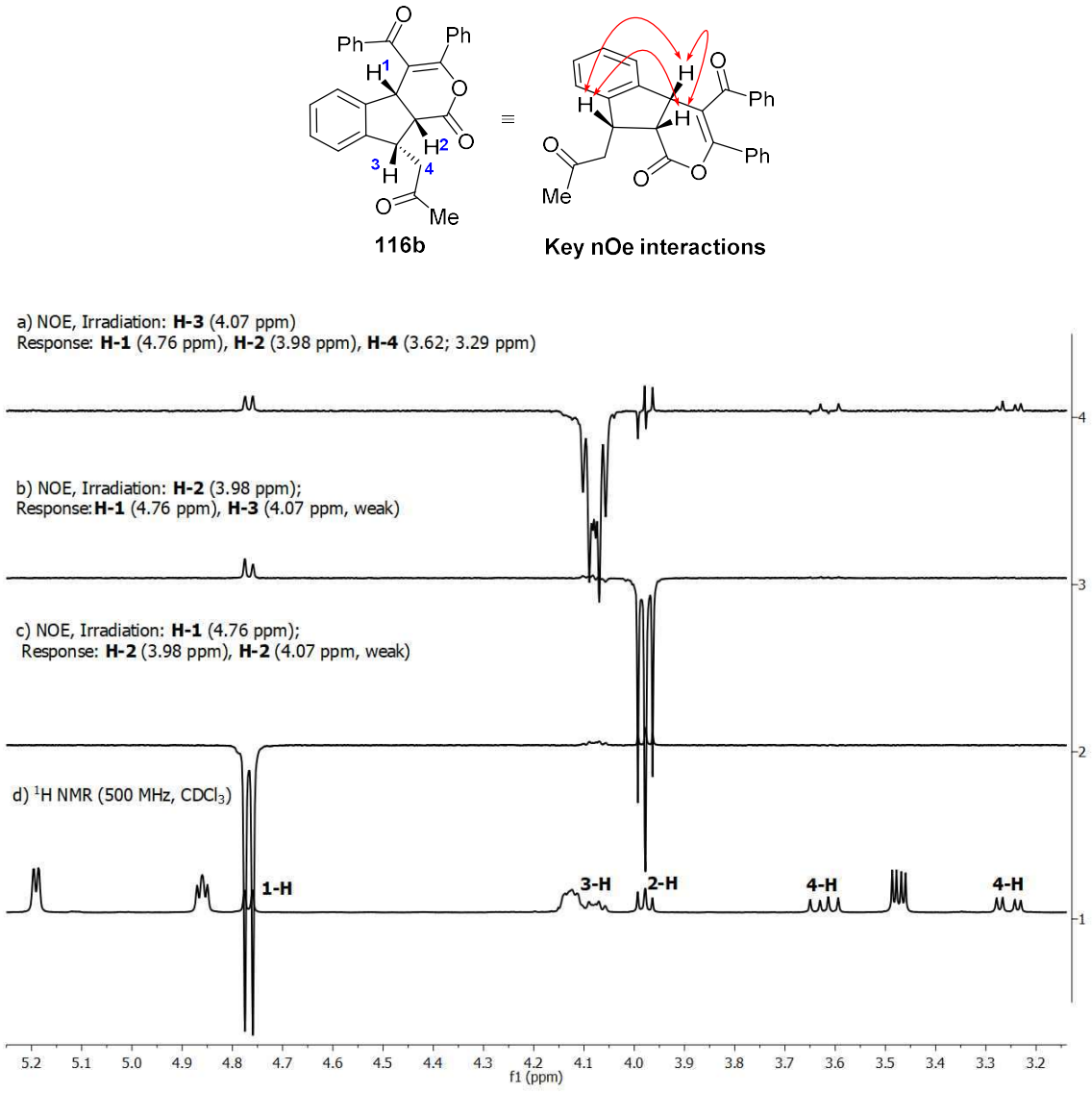
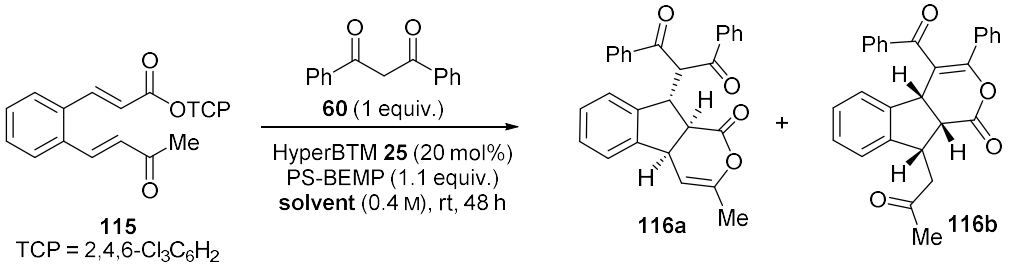


Figure 11: Summary of nOe analysis to confirm the relative configuration of indane **116b.**

2.3.2.4 Solvent screening

To study the effect of the reaction solvents, different polar and non-polar aprotic solvents were tested in the model reaction. A large solvent effect was observed on both yields and selectivities (Table 3). Using chlorinated solvents (entries 1, 4, 6), the isolated yields were higher than with coordinating solvents like THF (entry 2) and 1,4-dioxane (entry 3), although the latter did give high enantioselectivity. Slightly lower enantiocontrol was observed conducting the reaction in acetonitrile (97:3 er) (entry 7). However, significant yield enhancement (62%) and much better product ratio (86:14 **a**:**b**) were obtained, so acetonitrile was chosen for further study.



Entry	Solvent	Yield (%)[a]	**116a**:**116b**	er[b]
1	CH_2Cl_2	46	75:25	98:2
2	THF	21	75:25	>99:1
3	1,4-Dioxane	20	71:29	>99:1
4	$C_2H_4Cl_2$	35	80:20	98:2
5	PhMe	15	83:17	99:1
6	$CHCl_3$	47	78:22	99:1
7	**MeCN**	**62**	**86:14**	**97:3**

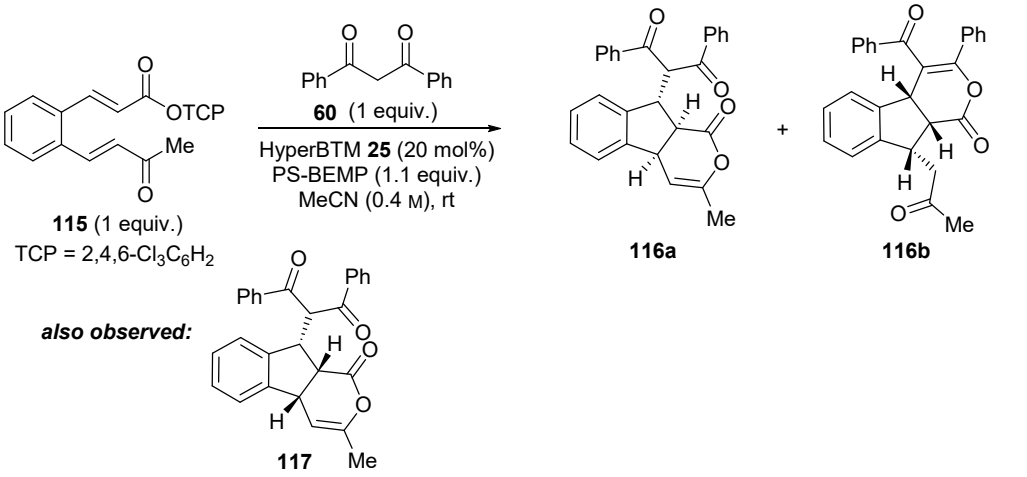
Table 3. Screening of solvents. [a] Combined isolated yield of inseparable products. [b] Determined by HPLC analysis for major product **116a**.

2.3.2.5 NMR observation

To gain a better understanding of the process, the reaction was monitored by ^{1}H NMR spectroscopy over 72 hours, and aliquots were removed, evaporated and analysed by ^{1}H NMR spectroscopy ($CDCl_3$). The concentration of the reaction components was determined using 1,4-dinitrobenzene as an internal standard (Figure 12). After 6 hours, 50% conversion of activated ester **115** along with formation of three different compounds were observed: major product **116a**, minor product **116b** and product **117**, which could be potentially a diastereomer of major lactone **116a**.

Over the whole reaction the concentration of starting material **115** gradually decreased, although the rate was slow and after 72 hours ester **115** was still present with a concentration of 0.1 M.

Smooth formation of major product **116a** was observed during the reaction. The maximum concentration of 0.23 M was achieved at the end of the experiment. After 5 h the concentration of minor product **116b** remained constant (0.06 M) throughout the remainder of the experiment. After 24 hours compound **117**, detected at the beginning of the reaction, completely disappeared. This product was assigned as a diastereoisomer of **116a** by comparing ^{1}H NMR of previously reported lactone **61a**.[26] Whether this compound is degrading, or the reaction proceeds in equilibrium and the products are interconvertible will be discussed later in further mechanistic studies of this domino process.



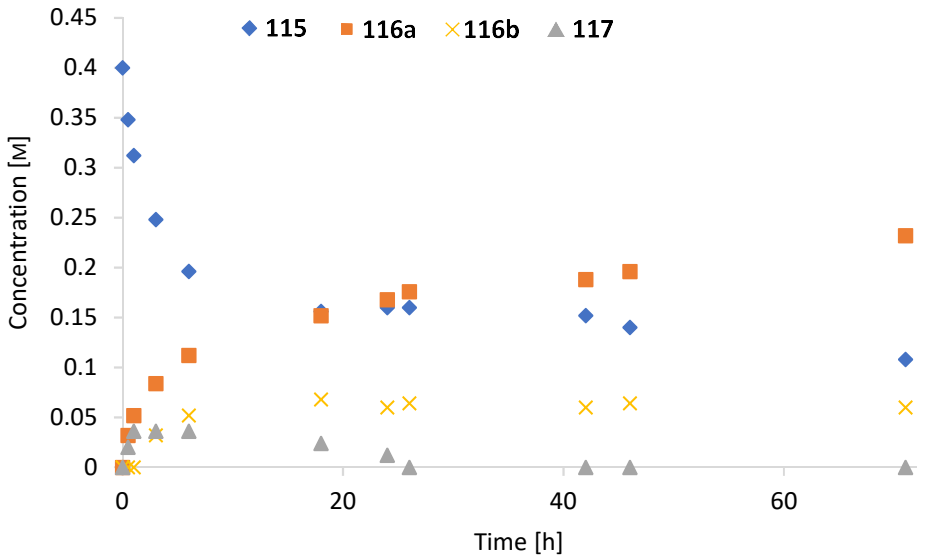
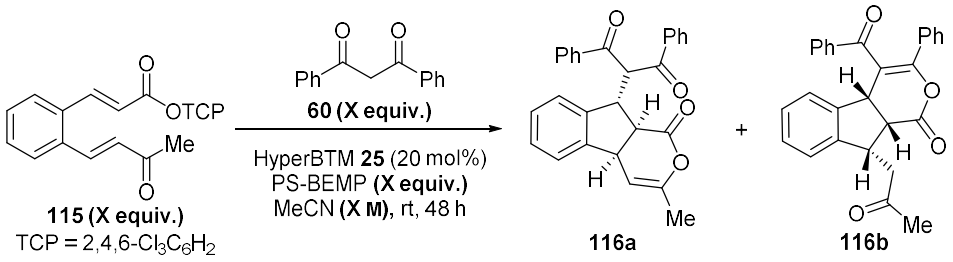


Figure 12. Monitoring the reaction by ^{1}H NMR spectrocopy. Reaction conditions: **115** (400 mM) in MeCN (0.25 mL), 1,4-dinitrobenzene (400 mM), rt; Key: = ◆ **115**; ■ = **116a**; × = **116b**; ▲ = **117**.

2.3.2.6 Reaction stoichiometry and concentration

To further increase conversion into lactones **116a** and **116b**, as well as improve the product ratio, the effect of changing the stoichiometry of the reaction partners was investigated. A series of reactions in acetonitrile was conducted varying equivalents of **115** or **60** (Table 4). An enhanced yield of 70% was obtained using an excess of the nucleophile and base (2 equiv.) along with improved **a**:**b** ratio of 91:9 for major product **116a** and roughly the same er (96:4) (entry 2). Further increasing the equivalents of diketone **60** resulted in the same yield (71%) but slightly lower selectivity (89:11 **a**:**b**) (entry 3). Interestingly, using an excess of Michael acceptor **115** (2 equiv.) decreased the reactivity dramatically with only traces of the desired product observed (entry 4). A lower conversion was also observed upon diluting the reaction concentration from initial 0.4 M to 0.2 M (entry 5). Higher concentration (0.8 M) caused poor solubility and mobility of the reactants, decreasing the reaction efficiency (entry 6).

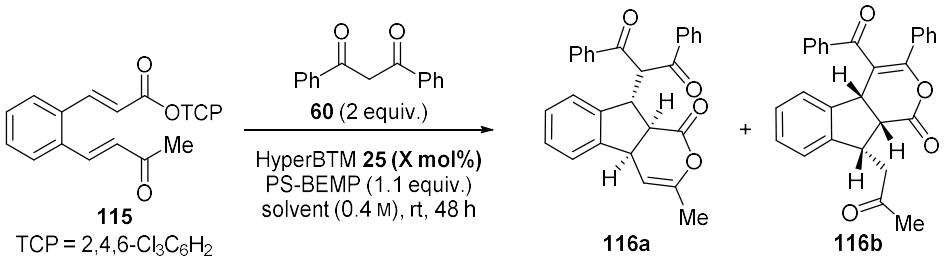


Entry	**115**:**60**:base (equiv.)	Concentration (M)	Yield (%)[a]	**116a**:**116b**	er[b]
1	1:1:1	0.4	62	86:14	97:3
2	**1:2:2**	**0.4**	**70**	**91:9**	**96:4**
3	1:3:3	0.4	71	89:11	96:4
4	2:1:1	0.4	trace	-	-
5	1:2:2	0.2	51	90:10	97:3
6	1:2:2	0.8	57	91:9	96:4

Table 4. Varying the reaction stoichiometry. Reaction held on 0.1 mmol scale.
[a] Combined isolated yield. [b] Determined by HPLC analysis for the major product **116a**.

2.3.2.7 Catalyst loading

The series of optimisation experiments was continued by varying the catalyst loading (Table 5). Surprisingly, changing the amount of catalyst (10 and 30 mol%) did not affect either the yield or er using acetonitrile as solvent. A modest decrease in product distribution was obtained in both cases (83:17 **a**:**b**). The catalyst loading was also varied in CH_2Cl_2, which resulted in an improved yield (88%) and enantioselectivity (99:1 er) in presence of 30 mol% of HyperBTM **25**, however a poor **a**:**b** ratio was still an issue.

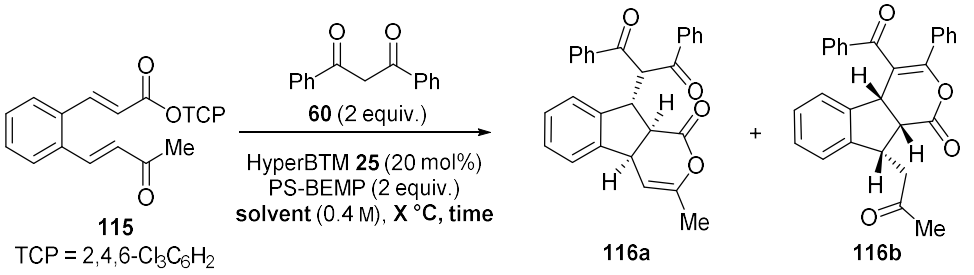


Entry	Solvent	HyperBTM (mol%)	Yield (%)[a]	**116a**:**116b**	er[b]
1	MeCN	10	69	83:17	96:4
2	**MeCN**	**20**	**70**	**91:9**	**96:4**
3	MeCN	30	70	83:17	96:4
4	CH_2Cl_2	10	56	80:20	98:2
5	CH_2Cl_2	30	88	71:29	99:1

Table 5. Catalyst loading optimisation. [a] Combined isolated yield. [b] Determined by HPLC analysis for the major product **116a**.

2.3.2.8 Effects of temperature and solvent

The effect of temperature in several reaction solvents was next investigated (Table 6). Lowering the temperature to 0 °C in acetonitrile afforded better enantiocontrol. However, the reaction rate was decreased dramatically, which resulted in prolonged reaction times, poor yields and selectivities (entry 1). Heating the reaction mixture to 50 °C afforded increased selectivity (93:7 **a**:**b**) and a shorter reaction time (16 h), but a drop in er to 94:6 was observed (entry 2). Using THF resulted in slightly higher er but a lower yield (entry 3). Interestingly, leaving the reaction in THF to reach a full conversion of ester **115** (24 h at rt) and subsequently heating the reaction mixture to 50 °C for 16 h gave lactone **116a** in 58%, >99:1 er and >95:5 **a**:**b** ratio (entry 4). Similar results were obtained by conducting the reaction at rt with an extended reaction time of 48 h (entry 5). Consequently, THF was chosen as the optimum reaction solvent because it afforded the major product in good yield without compromising on the **a**:**b** ratio or enantioselectivity. Decreasing the catalyst loading to 10 mol% did not affect the product ratio or enantioselectivity, however led to slower product formation and lower yield (48%) with ~15% of **115** returned unreacted (entry 6).

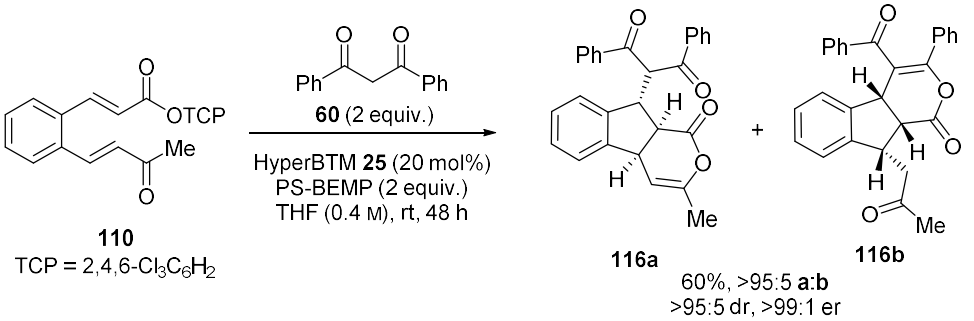


Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)[a]	**116a**:**116b**	er[b]
1	MeCN	>48	0	26	50:50	99:1
2	MeCN	16	50	64	93:7	94:6
3	THF	16	50	49	91:9	97:3
4	**THF**	**24/16[c]**	**rt→50**	**58**	**>95:5**	**>99:1**
5	**THF**	**48**	**rt**	**60**	**>95:5**	**>99:1**
6[d]	THF	64	rt	48	>95:5	>99:1

Table 6. Effects of temperature and solvent [a] Combined isolated yield. [b] Determined by HPLC analysis for the major product **116a**. [c] 24 h at rt, then 16 h at 50 °C. [d] 10 mol% cat. was used.

2.3.2.9 Optimised reaction conditions

The optimised reaction conditions are summarised in Scheme 32. The use of 2,4,6-trichlorophenol-activated ester was the only suitable activation mode of carboxylic acid **104**, affording two isomeric lactones in moderate yields but with high enantioselectivities. As a base, PS-BEMP was required to achieve a full conversion of the starting material, while using an excess of the nucleophile was crucial for increasing both yields and selectivity. A concentration of 0.4 M for the activated ester was optimal and afforded a full conversion of the ester starting material. Selective formation of lactone **116a** was achieved using either acetonitrile or THF as a solvent, however THF was chosen due to the higher enantioselectivity. Further studies into this domino process were conducted with the finalised reaction conditions.



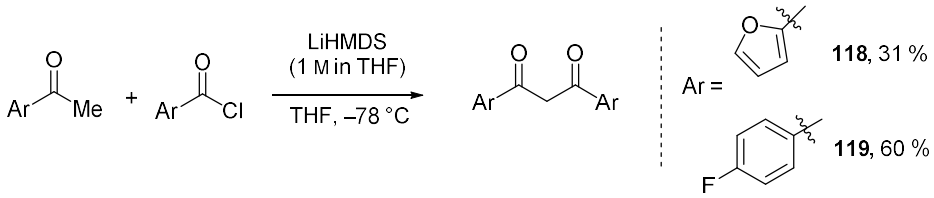
Scheme 32. Optimised reaction conditions for domino Michael-Michael-lactonisation reaction.

2.3.3 Reaction scope

2.3.3.1 Variation of the nucleophile

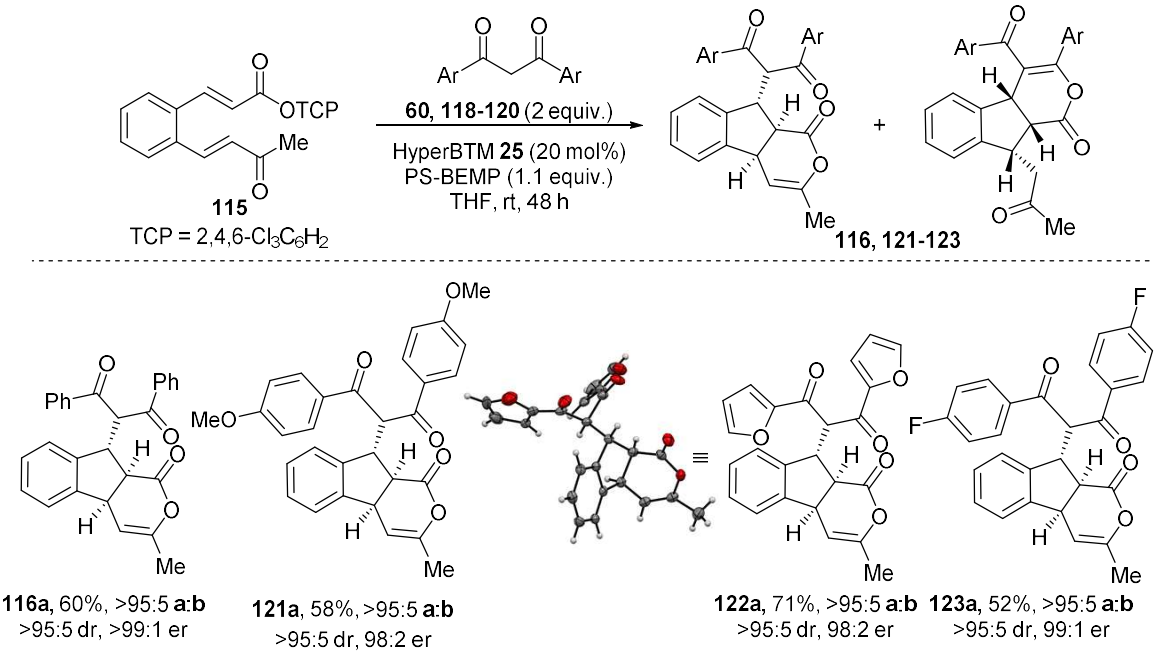
Having determined the optimum reaction conditions for the Michael-Michael-lactonisation reaction the scope of this domino process was surveyed. The incorporation of electron-rich and electron-poor alkyl and aryl substituents within both the dicarbonyl and Michael acceptor components was investigated.

A range of symmetrical dicarbonyl nucleophiles was probed first, employing aryl diketones. Dicarbonyls **118** and **119** were synthesised using the procedure reported by Matsubara[40] LiHMDS deprotonation of aryl ketones and addition to aryl acid chlorides afforded symmetrical diketones **118** and **119** with moderate to good yields (Scheme 33).



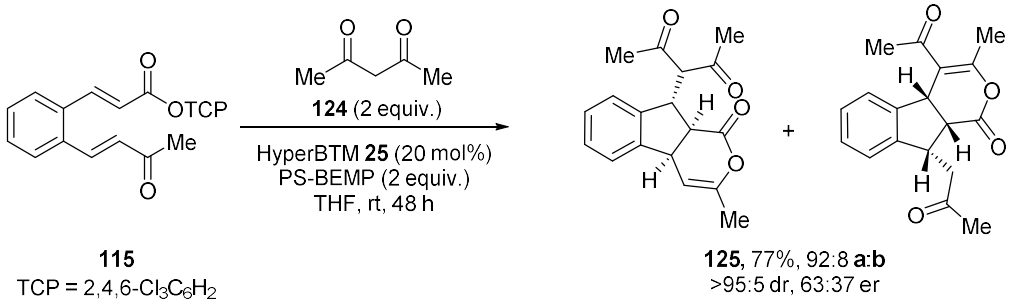
Scheme 33. Synthesis of symmetrical aryl diketones.

These aryl diketones along with commercially available 1,3-bis(4-methoxyphenyl)propanedione **115** were subjected to the MML reaction (Scheme 33). Diketone **120** gave similar results as 1,3-diphenylpropane-1,3-dione **60**, forming lactone **121** as a single enantiomer (>99:1 er) in 58% yield and high selectivity (>95:5 **a**:**b**). Electron-rich bisfuranoyl-substituted diketone **118** afforded lactone **122** with an improved yield (71%) compared with model nucleophile **60** (60%) without compromising the selectivity (>95:5 **a**:**b**, 98:2 er). The absolute and relative configuration of **122a** was confirmed by X-ray crystallographic analysis (Scheme 34). Slightly lower yield (**123**, 52 %) was obtained using electron-poor dicarbonyl **119**, however excellent **a**:**b** selectivity and enantiocontrol (>95:5 **a**:**b**, 98.5:1.5 er) was observed.



Scheme 34. Symmetrical aryl diketones as nucleophiles.

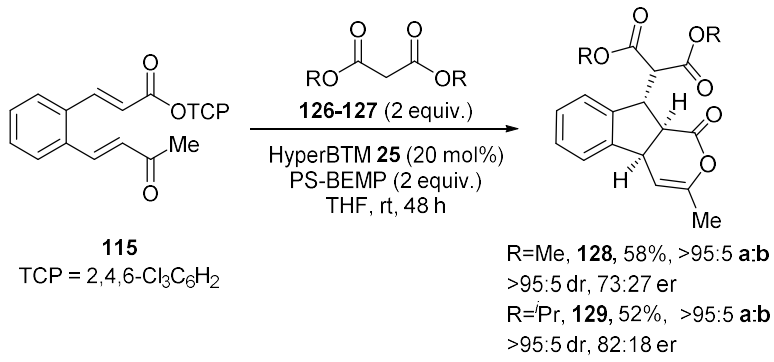
While the aryl nucleophiles afforded excellent enatioselectivities, the reaction with alkyl-substituted diketones such as acetylacetone **124** led to a slight drop in product selectivity and a significant reduction in enantioselectivity for **125a** (63:37 er), although the diastereoselectivity remained high. (Scheme 35). Similarly, low enantiocontrol was observed in the previous work of the Smith group with 69:31 er of the corresponding product with acetylacetone in the annulation of cinnamic anhydride **59** catalysed by HyperBTM **25**. A control experiment in the absence of HyperBTM did not lead to product formation, demonstrating that a racemic base-promoted background reaction is not responsible for the observed drop in enantioselectivity. The low er may be explained due to the reduced steric bulk of dimethyl substitution leading to poor facial discrimination in the transition state.[7]



Scheme 35. Michael-Michael-lactonisation reaction with alkyl-substituted diketone.

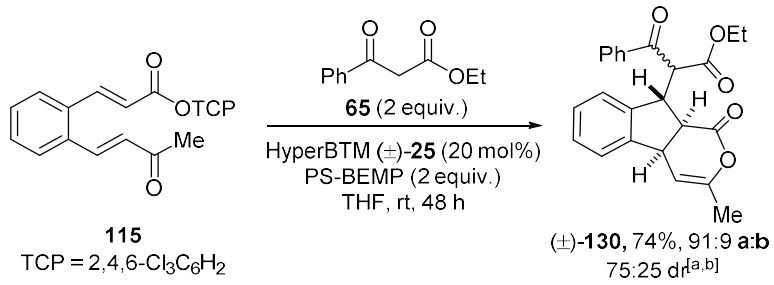
To test the scope of the isothiourea-catalysed reaction further, symmetrical diesters were employed instead of diketones (Scheme 36). Malonates **126** and **127** are competent nucleophiles

in this process, selectively forming fused products **128a** and **129a** with high diastereoselectivity, but with slightly reduced enantioselectivity. The low enantiocontrol is attributed to a base-promoted background reaction, which was observed upon carrying out a control reaction without HyperBTM **25** (38%, >95:5 dr, 90:10 **a:b)**. The presence of a background reaction in this case is attributed to the decreased pK_a of the α-protons within the diester nucleophile compared with diketones. Slightly higher enantioselectivity of diisopropyl malonate-derived product **129a** might be attributed to a steric effect of the isopropyl group in the transition state.



Scheme 36. Symmetrical diesters as nucleophiles.

To further investigate the scope, non-symmetrical dicarbonyl **65** was also examined. Reaction of **115** with ethyl benzoylacetate **65** gave indane (±)-**130** in 74% yield, although the additional stereogenic centre was only modestly controlled leading to a 75:25 mixture of diastereoisomers. The lactones were difficult to separate by flash silica chromatography and it proved impossible to separate the diastereomers of the racemic sample by chiral HPLC (Scheme 37). Similarly, modest diastereoselectivities with non-symmetrical dicarbonyls were reported by Studer in his work with NHC catalysts.[26]

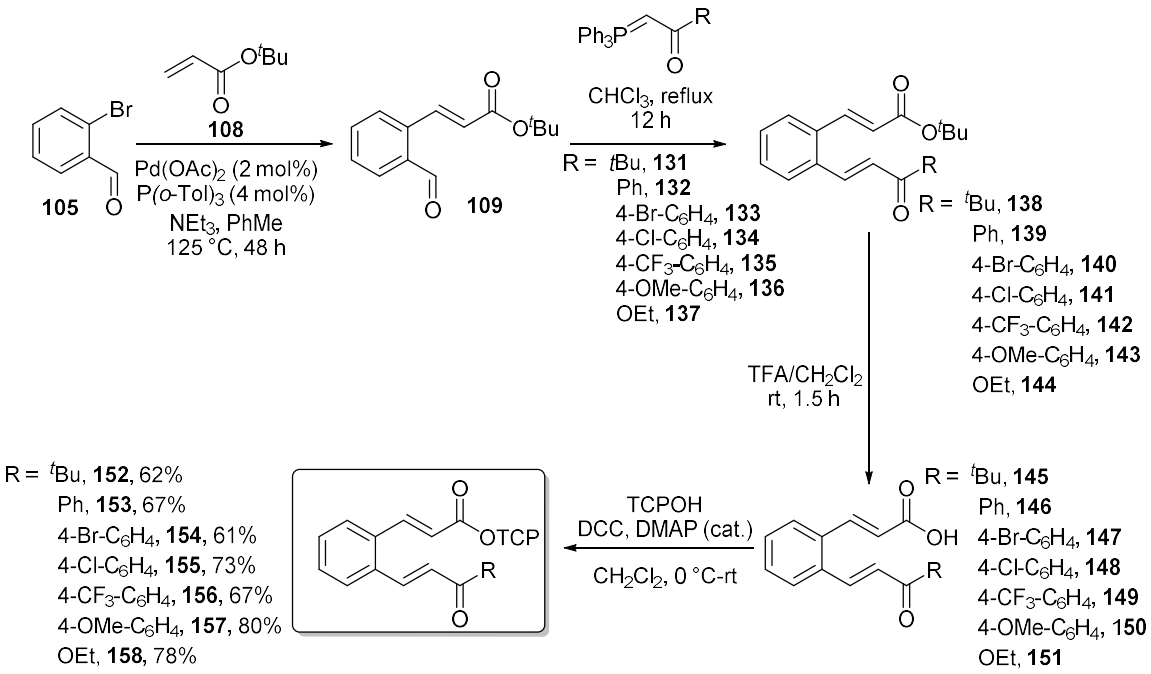


Scheme 37. β-Ketoester as a non-symmetrical dicarbonyl nucleophile.
[a] Reaction performed using (±)-HyperBTM **25**. [b] dr at additional stereocentre.

2.3.3.2 Variation of the electrophile: enone substituent

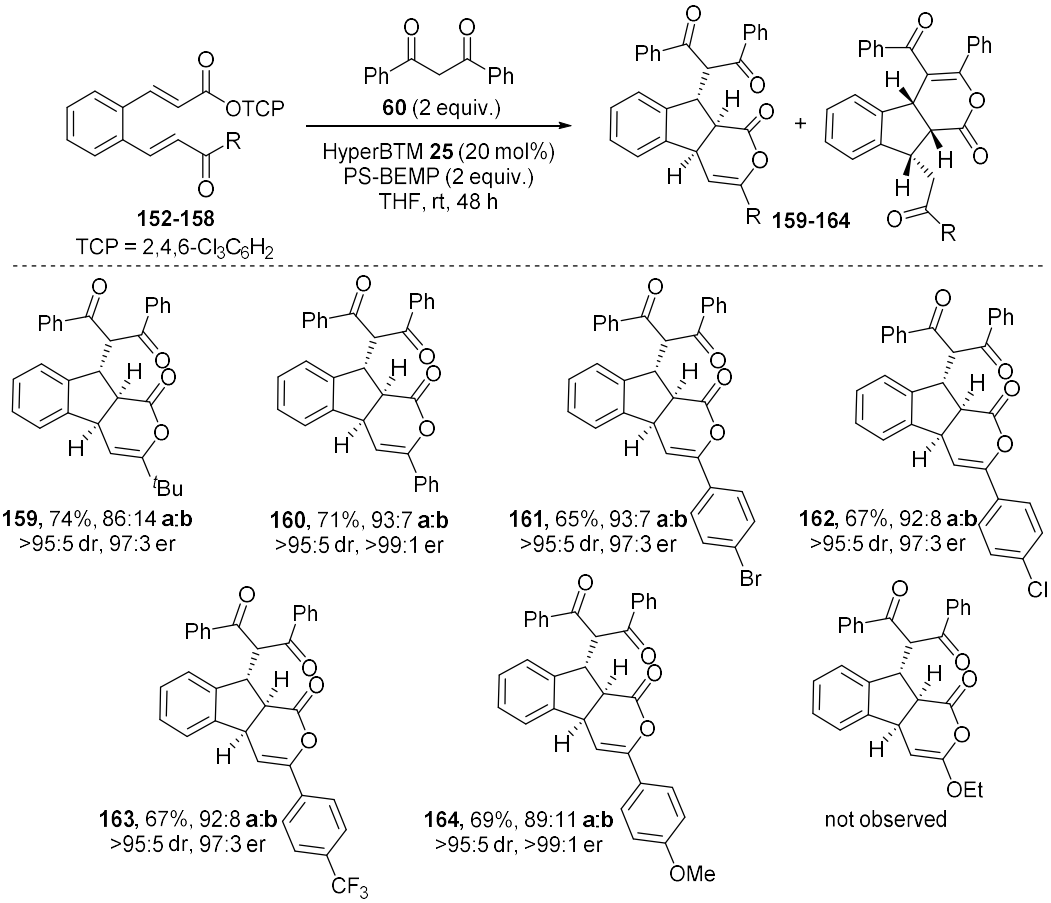
The reaction scope was further expanded through variation of the electrophilic substrate. First, the enone functionality was varied with diverse alkyl and aryl substituents on the keto-group. The

corresponding substrates were prepared *via* the same procedure described in Section 2.3.1 with the overall yields for substrates **152**–**158** shown in Scheme 38.



Scheme 38. Synthesis of activated esters varying the enone substituent.

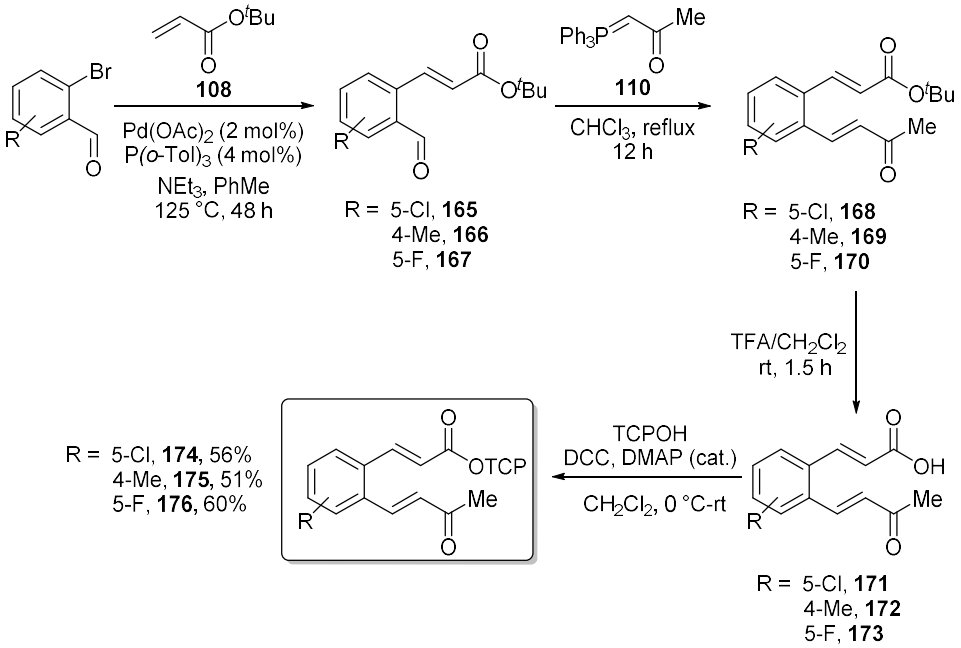
Symmetrical diketone 1,3-diphenylpropanedione **60** was employed with the standard nucleophile in this reaction series (Scheme 39). All substrates with alkyl and aryl enone substituents were well tolerated, affording good yields (up to 74%) and excellent stereoselectivity in all cases (>95:5 dr, up to >99:1 er). However, changing the keto-function to the ester in substrate **158** did not show any reactivity under the previously optimised conditions. *tert*-Butyl substitution resulted in lower selectivity (86:14 **a**:**b**), presumably due to the increased steric bulk reducing lactonisation through the enone oxygen atom in **159**. Improved selectivity was observed with aryl substitution, with phenyl (**160**) and electron-donating (**164**) groups giving slightly higher er (>99:1) than halogen (**161**, 96:4 er; **162**, 96:4 er) and electron-withdrawing substituents (**163**, 97:3 er). Replacing a methyl group with a phenyl substituent in the work of Studer with NHC catalysis resulted in decreased reactivity and a lower yield of the corresponding lactone.[26]



Scheme 39. Variation of the enone substituent in the MML reaction.

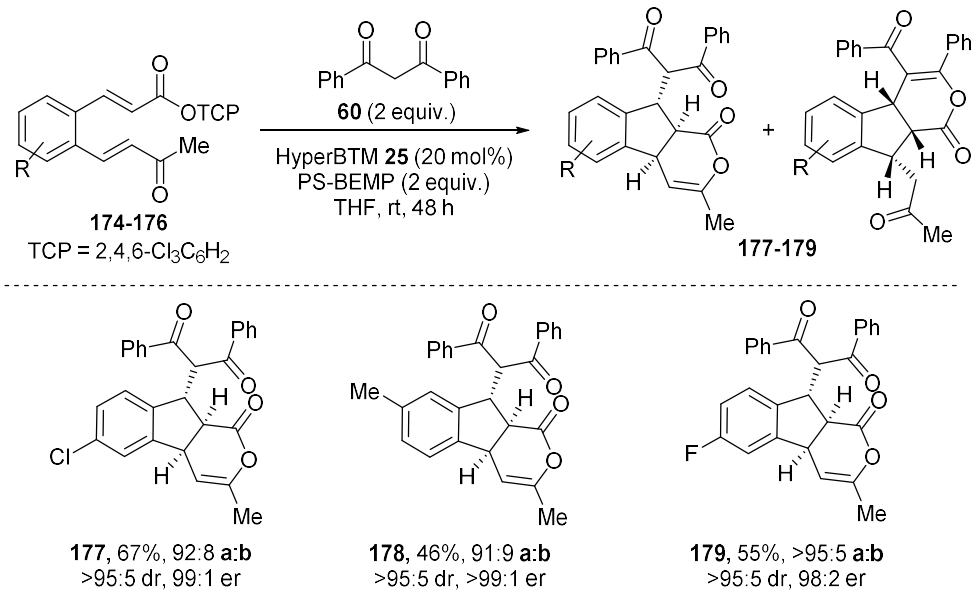
2.3.3.3 Variation of the electrophile: arene moiety

We then continued variation of the electrophile by substituting the aryl ring with both electron-rich (4-Me) and electron-poor (5-Cl, 5-F) substituents. Synthesis of the corresponding substrates **174**–**176** is shown in Scheme 40.



Scheme 40. Synthesis of activated esters varying the arene moiety.

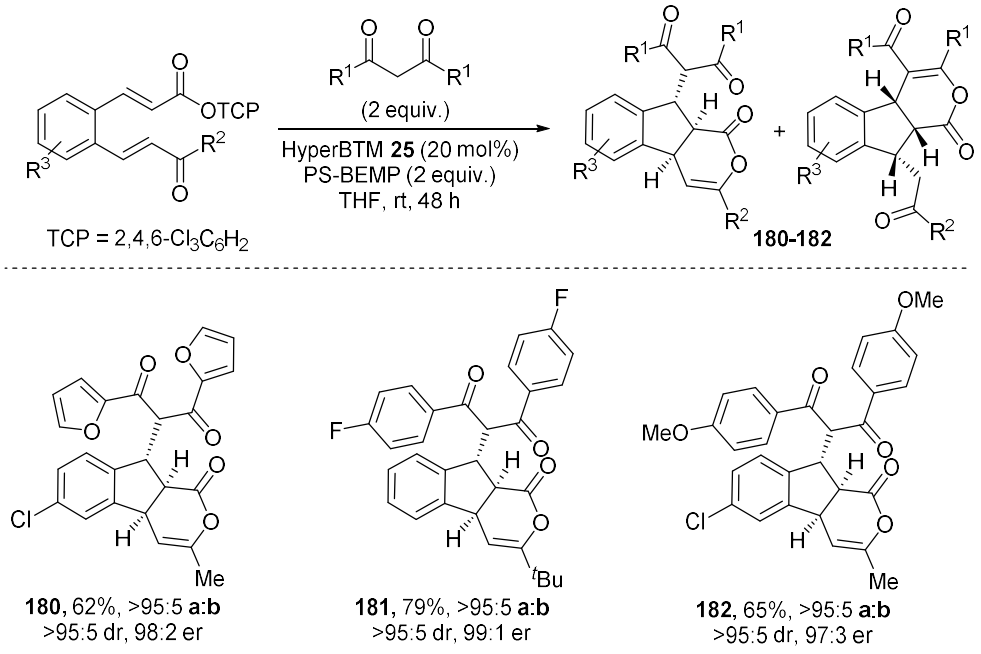
In the reaction with diketone **60**, the corresponding lactones were isolated with moderate to good yields and high stereoselectivity (Scheme 41). With β-arylenone esters bearing a halogen atom within the arene moiety, the domino process delivered products **177** and **179** with slightly higher yields (67% and 55%) than substrate **175** bearing a methyl group (**178**, 46%). However, the major lactone product was formed with excellent enantioselectivity in all cases (Scheme 41).



Scheme 41. Variation of the arene moiety in the MML reaction.

2.3.3.4 Mixed combinations

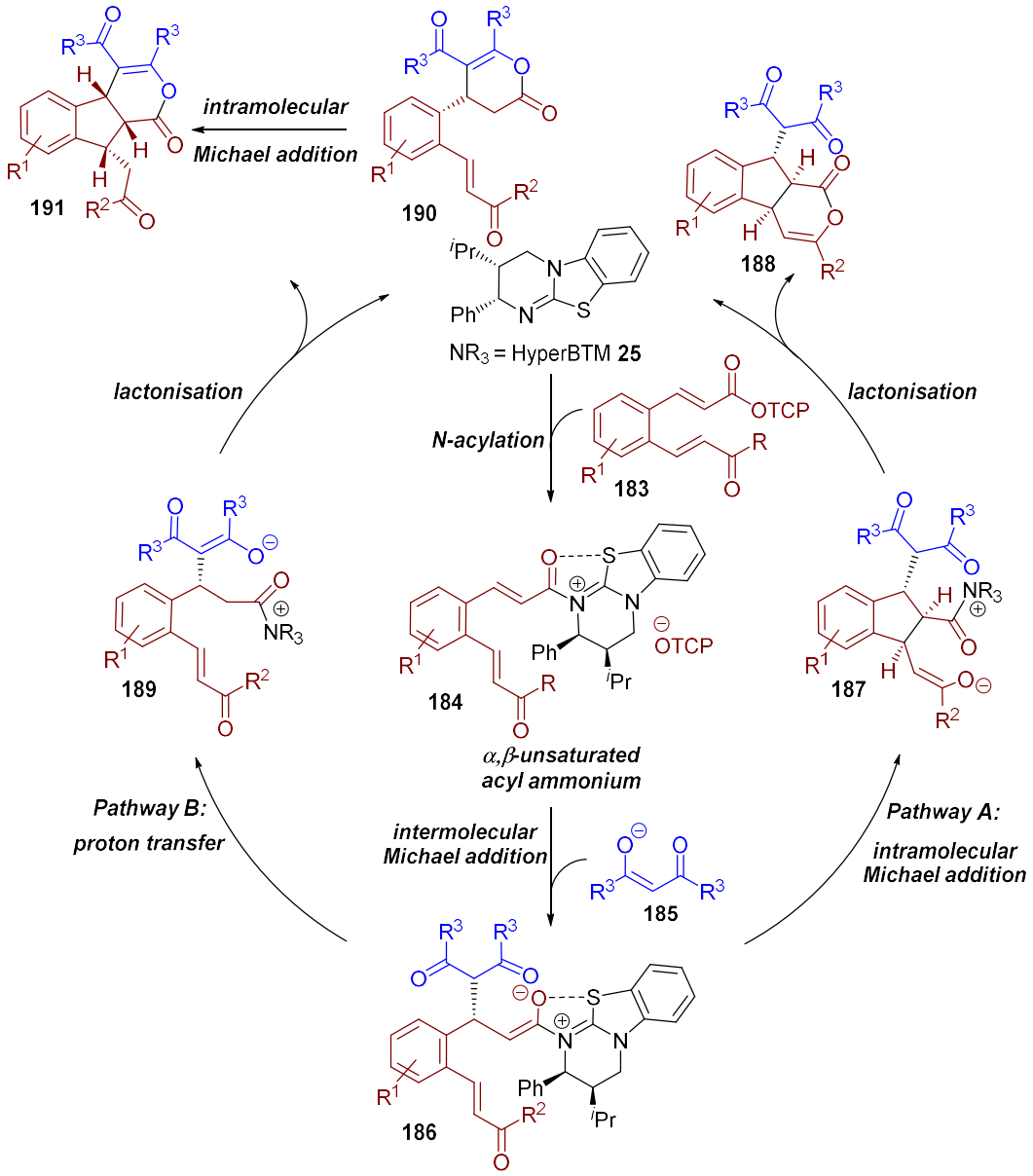
To complete the scope with symmetrical diketones, several examples were obtained by varying both the electrophilic and nucleophilic components (Scheme 42). Halogen containing arenes showed good reactivity with electron-rich diketones, delivering lactones **180** and **182** in good yields and excellent stereoselectivity. However, the best example in the scope of this domino process with symmetrical diketones was achieved employing *tert*-butyl substituted Michael acceptor **152** and 1,3-bis(4-fluorophenyl)propane-1,3-dione **119**, which gave product **181** in 79% isolated yield as a single enantiomer and excellent selectivity (>95:5 **a**:**b**). Interestingly, related lactone **159** bearing a *tert*-butyl enone substituent was formed with significantly lower **a**:**b** ratio (86:14) (Scheme 39). The reason for the enhanced selectivity in **181** was not identified.



Scheme 42. Combinations of substituted α,β-unsaturated TCP esters with different aryl 1,3-diketones.

2.3.4 Reaction mechanism

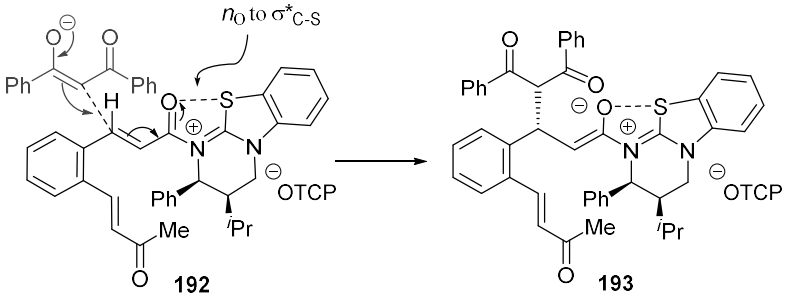
The proposed catalytic cycle (Scheme 43) for the general reaction with dicarbonyl compounds as nucleophiles is related to the previous work of Smith with α,β-unsaturated acyl ammonium intermediates,[7] as well as the NHC-catalysed MML process reported by Studer.[26] The reaction is proposed to start with nucleophilic attack of the isothiourea catalyst into TCP-activated ester **183** to give α,β-unsaturated acyl ammonium intermediate **184**. Next, intermolecular Michael addition of nucleophile **185** into the α,β-unsaturated intermediate delivers enolate **186**, which can undergo two possible mechanistic pathways. In pathway (A), the enolate undergoes intramolecular 1,4-addition to generate intermediate **187**. Intramolecular acylation of **187** affords lactone **188** and releases catalyst **25**. Alternatively, in pathway (B), proton transfer gives enolate **189** followed by lactonisation to give intermediate **190** along with HyperBTM. Subsequent intramolecular 1,4-addition proceeds under substrate control to form minor product **191**. To check the reversibility of formation for both major and minor isomers products **116a** and **116b** were subjected to basic and/or catalytic conditions. However, the lactones were not interconvertible, with major isomer **116a** remaining stable and minor product **116b** degrading in the reaction mixture. Further investigations into the origin of observed major and minor products are underway.



Scheme 43. Proposed catalytic cycle for the domino MML reaction with dicarbonyls as nucleophiles.

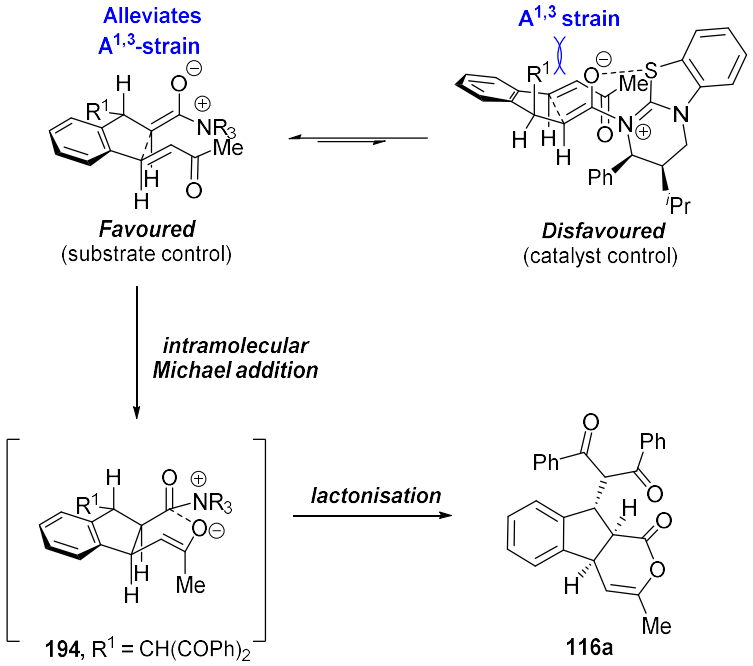
2.3.5 Stereochemical model

The structural features of the isothiourea catalyst described before (Figure 5) are likely to be responsible for the high enantioselectivity observed in the MML reaction. The *s-cis* conformation of isothiouronium intermediate **192** is presumably favoured, with the carbonyl oxygen adopting a *syn*-conformation with respect to the isothiourea sulfur atom due to a stabilising non-bonding O···S interaction (n_O to σ^*_{C-S}).[10] The *Si*-face of isothiouronium **192**, with the phenyl ring pseudoaxial and ^{i}Pr-substituent pseudoequatorial, is effectively blocked for the nucleophilic attack. Michael addition of the diketone enolate must proceed to the *Re*-face of the olefin of α,β-unsaturated isothiouronium species **192** to generate enolate intermediate **193** (Scheme 44).



Scheme 44. Stereochemical rationale of the nucleophilic addition.

The high diastereoselectivity observed during the second Michael addition step for the formation of the major lactone isomer can be rationalised building upon the stereochemical model suggested by Romo (Scheme 20).[12] Selective formation of a *cis*-fused 5-membered cycle must proceed under substrate control with the 1,3-dicarbonyl, ammonium enolate and enone all adopting pseudo-equatorial positions in the five-membered pre-transition state assembly as illustrated in Scheme 45. Subsequent lactonisation of **194** affords major product **116a** with three contiguous stereocentres and the *trans*,*cis* relative configuration. Cyclisation under catalyst control is presumably disfavoured due to the presence of $A^{1,3}$ strain between the 1,3-dicarbonyl substituent and the ammonium enolate.



Scheme 45. The origin of diastereoselectivity in the MML reaction.

2.4 Conclusions and outlook

The first use of α,β-unsaturated acyl ammonium intermediates generated in a Michael addition-lactonisation reaction with 1,3-dicarbonyls[7] was successfully extended to a more complicated Michael-Michael-lactonisation (MML) domino process using bench-stable α,β-unsaturated TCP esters as α,β-unsaturated acyl ammonium precursors bearing pendent Michael acceptors. This method gives a quick and simple approach to a wide range of highly functionalised lactones bearing three contiguous stereocentres in moderate to good yields and excellent enantioselectivities. Moreover, the resulting products contain a stereodefined indane unit that can be found in a large number of biologically and pharmaceutically relevant molecules.

Compared with the existing syntheses of chiral indane motifs, e.g. using NHCs by the Studer group,[26] advantages of the isothiourea-catalysed system include the use of bench-stable, easily accessible starting materials. Comparable yields and enantioselectivities were obtained in this work. Importantly, this new method gives selective access to a single diastereomer with a different absolute and relative configuration from those previously reported. Both methods are complementary depending on the desired diastereoisomer.

Variation of the Michael acceptor and Michael donor components afforded a wide reaction scope. Michael acceptors with aryl and alkyle enone substituents were very well tolerated as well as substrates bearing a halogen atom at the arene moiety. A variety of aryl diketones were successful in the reaction with both electron-rich and electron-poor substituents. Also, some limitations were observed during exploring the scope. Diesters can be employed as nucleophiles giving a single product in good yields but poor enantioselectivities. Non-symmetrical β-ketoesters were also tolerated in the reaction but the additional stereogenic centre at the α-position to the keto-function was not controlled providing modest diastereoselectivity. Due to the additional possibility of *O*-cyclisation in the Michael acceptor a more complex reaction mechanism was postulated for the domino MML reaction with 1,3-dicarbonyls in comparison with the Michael-lactonisation reaction. The absolute and relative configurations for the lactone products resulted from both catalyst and substrate control and were explained in the corresponding stereochemical model.

Given the importance of indane motifs in several natural products of biological relevance, the lactone products obtained in this work could be potentially evaluated for their biological and pharmaceutical activities. Having observed the synthetic power of this strategy to generate complex structural architectures bearing multiple stereocentres in high diastereo- and enantioselectivity, this method could be extended to the use of alternative nucleophiles.

2.5 References

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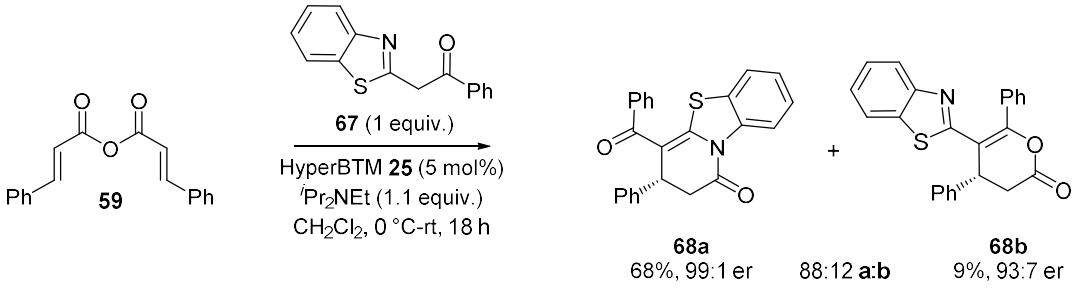
3 Benzazoles in enantioselective domino reactions

3.1 Background of application of benzazoles

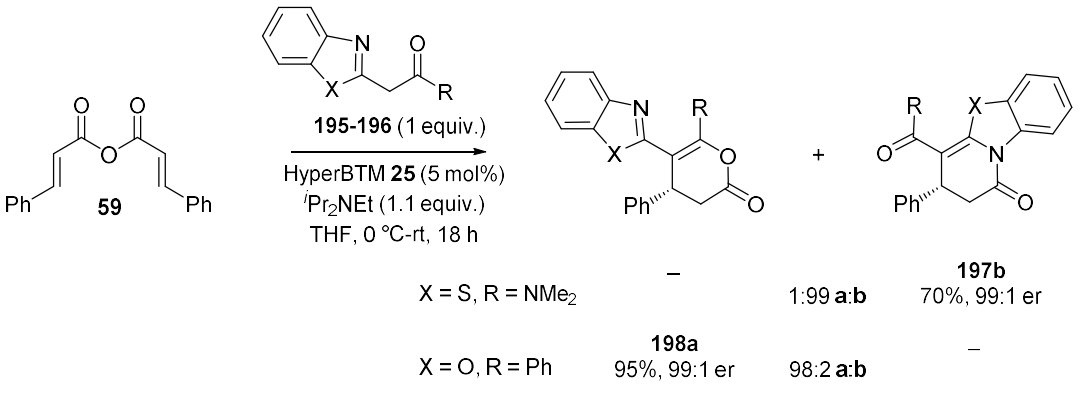
In the previous report of the Smith group,[1] the scope of the isothiourea-catalysed Michael addition-cyclisation methodology was expanded beyond the use of 1,3-dicarbonyl nucleophiles. Being inspired from rare but promising reports using acyl benzazoles as nucleophiles,[2-4] the nucleophilic addition of acyl benzazoles to α,β-unsaturated acyl ammonium intermediates was investigated.

To test benzazoles on the Michael-lactonisation reaction, the Smith group employed 2-phenacylbenzothiazole **67** in a model reaction with homoanhydride **59** as described in Section 2.1.1 (Scheme 16).[1] Two regioisomers, lactam **68a** and lactone **68b**, were obtained with **a**:**b** ratio of 88:12 (Scheme 46).



Scheme 46. Michael addition-annulation reaction with benzothiazoles as nucleophiles.

This interesting nature of selective lactamisation over lactonisation was studied extensively employing other benzazoles to investigate the relationship between nucleophile structure and selectivity. The Smith group has shown that varying the benzazoles or changing the electronics of the acyl group allows selective access to either *N*- or *O*-cyclised products. For example, while azaarylamide **195** allowed for selective formation of lactam **197b**, use of 2-phenacylbenzoxazole **196** afforded *O*-cyclisation (**198a**) in excellent selectivity, with only a small amount of the *N*-cyclised product (Scheme 47).[1b]



Scheme 47. *N*- or *O*-Selective cyclisation with azaaryl amides and benzoxazoles.

This methodology provides an interesting way of installing benzazole moieties that are found within structures possessing biological activity including antibacterial, antimicrobial, antiviral, or antifungal activities.[5-8] Benzoxazole **199**, benzothiazole **200** and benzimidazole **201** containing compounds (Figure 13) can be found in several natural products and are often incorporated in drug design.

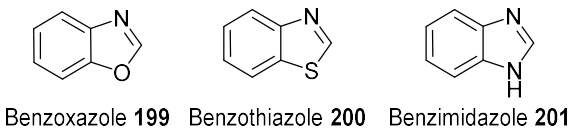


Figure 13. Structure of benzazoles.

3.2 Project aims

Having observed the interesting selectivity of the Michael addition-annulation reaction using benzazoles, we aimed to expand the scope for the domino Michael-Michael-lactonisation reaction and investigate the activity of heterocyclic nucleophiles in a complex domino process. A potential complication of this reaction is the presence of three different possibilities for cyclisation onto the acyl ammonium intermediate (Figure 14). We aimed to study a range of benzazole nucleophiles to determine the effects of the nucleophile on the selectivity of the process.

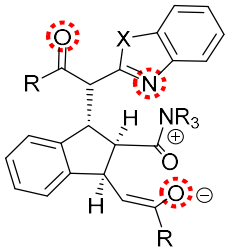
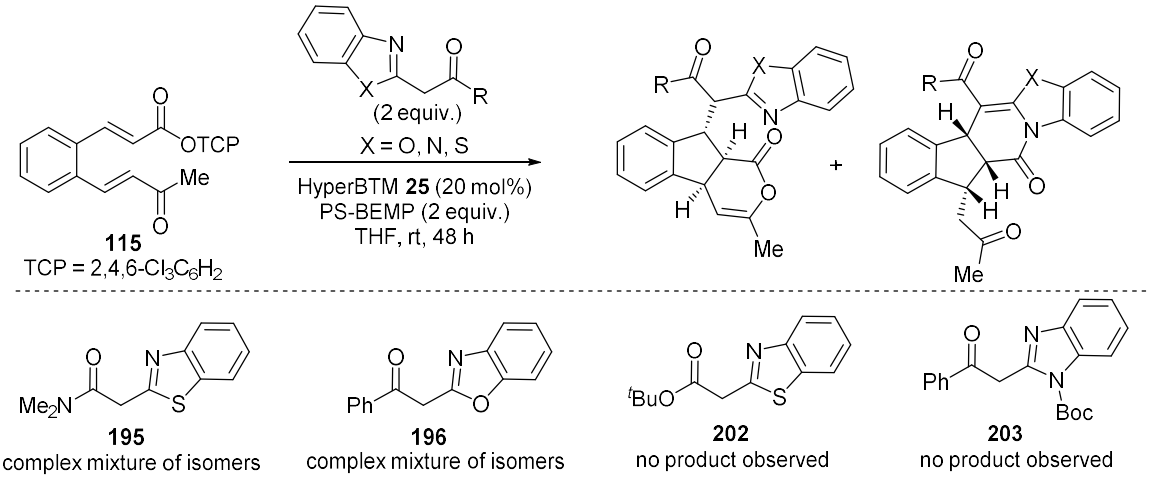


Figure 14. Cyclisation possibilities in the domino Michael-Michael-annulation reaction.

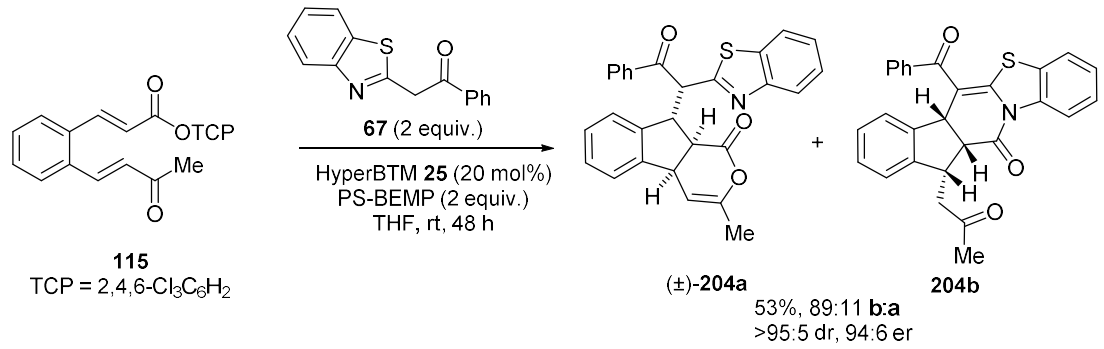
3.3 Screening of benzazoles

Various benzazoles were employed in the MML reaction under the conditions optimised for 1,3-dicarbonyl nucleophiles using TCP-ester **115** (Section 2.3). As expected, more complex cyclisation processes were observed compared with the Michael-lactonisation reaction. With azaaryl amide **195** and benzoxazole **196** a complex mixture of isomers was obtained. No product was observed using ester **202** or *N*-Boc-protected benzimidazole **203** (Scheme 48). Notably, an attempt to use protected benzimidazoles in Michael-lactonisation reaction also proved unsuccessful.[1b]



Scheme 48. Screening of benzazoles for MML reaction.

Combination of α,β-unsaturated TCP ester **115** with 2-phenacyl benzothiazole **67** under the previously optimised conditions using HyperBTM **25** (20 mol%) as the catalyst gave a separable mixture of two products **204a** and **204b**, in 53% yield with the lactam **204b** formed as a major product (89:11 **b**:**a**). in good er (94:6) (Scheme 49), resulting from preferential cyclisation through the benzothiazole nitrogen, as previously observed using this class of nucleophile.[1]



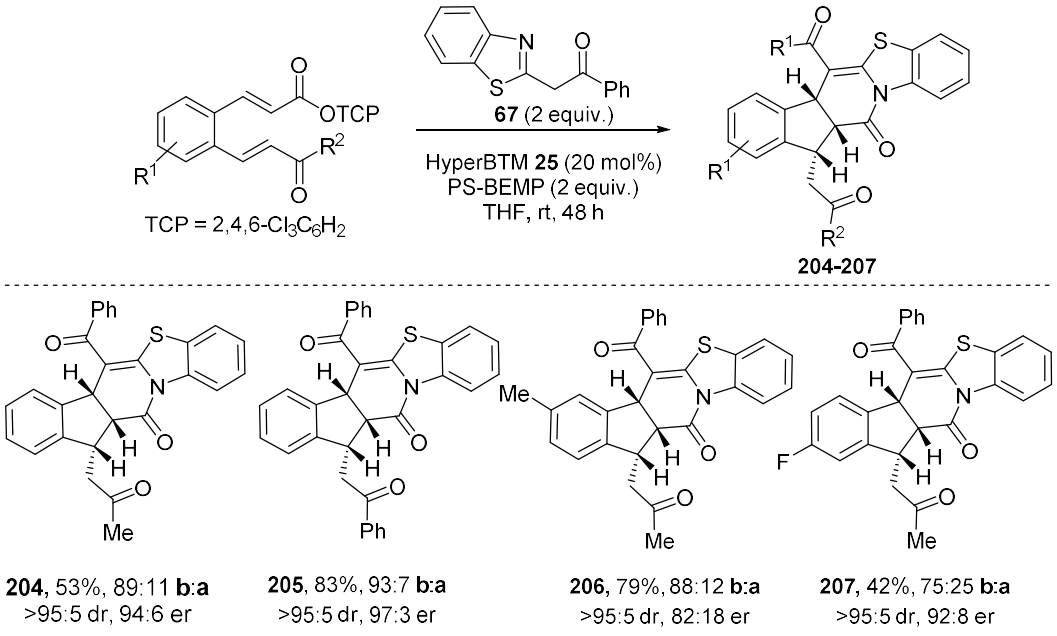
Scheme 49. Reaction with 2-phenacyl benzothiazole **67**.

Interestingly, while the diastereo- and enantioselectivity of this process remained high (>95:5 dr, 94:6 er), the relative configuration around the fused indane **204b** is identical to that observed within the minor product from the reaction using 1,3-dicarbonyls. The relative configuration of the minor product **204a** could not be determined, although it is formed as a racemate suggesting that it may arise from a base-mediated background process. A control experiment in the absence of HyperBTM **25** confirmed the presence of a base-promoted reaction in this case giving a complex mixture that contained both products **204a** and **204b**.

3.4 Domino Michael-lactamisation-Michael reaction using acyl benzothiazoles

3.4.1 Reaction scope with benzothiazoles: variation of the Michael acceptor

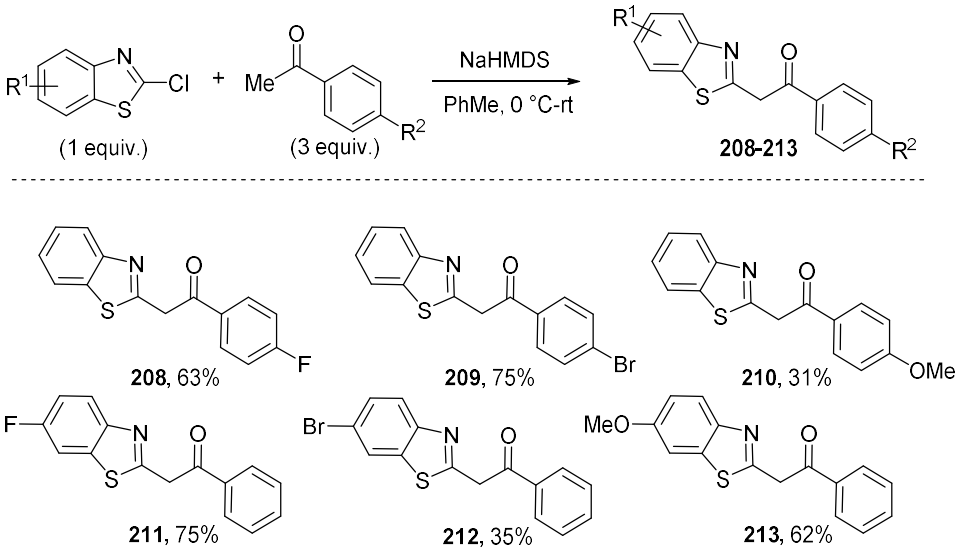
Intrigued by the change in constitution and configuration within the major product, the scope of the domino process with a variety of acyl benzothiazoles was investigated. First, 2-phenacyl benzothiazole **67** was used as a model nucleophile to react with a range of Michael acceptors (Scheme 50). Aryl enone containing substrate **153** worked particularly well, forming indane **205** in 83% yield with high **b**:**a** selectivity (93:7 **b**:**a**) and excellent stereocontrol (>95:5 dr, 97:3 er). Substitution within the benzenoid ring of the α,β-unsaturated ester was also tolerated, although the presence of a methyl group resulted in lower enantioselectivity (84:16 er for **206**). Arene **176** bearing an electron-withdrawing fluorine atom gave a slightly lower yield (42%) of **207**, however showed improved enantiocontrol (92:8 er). In all cases **b** and **a** were isolated as inseparable mixture of two products.



Scheme 50. Variation of Michael acceptors with 2-phenacylbenzothiazole.
[a] Reactions performed on 0.1 mmol scale. [b] Combined yield. [c] **a**:**b** ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [d] dr determined by ^{1}H NMR spectroscopic analysis. [e] er determined by HPLC analysis.

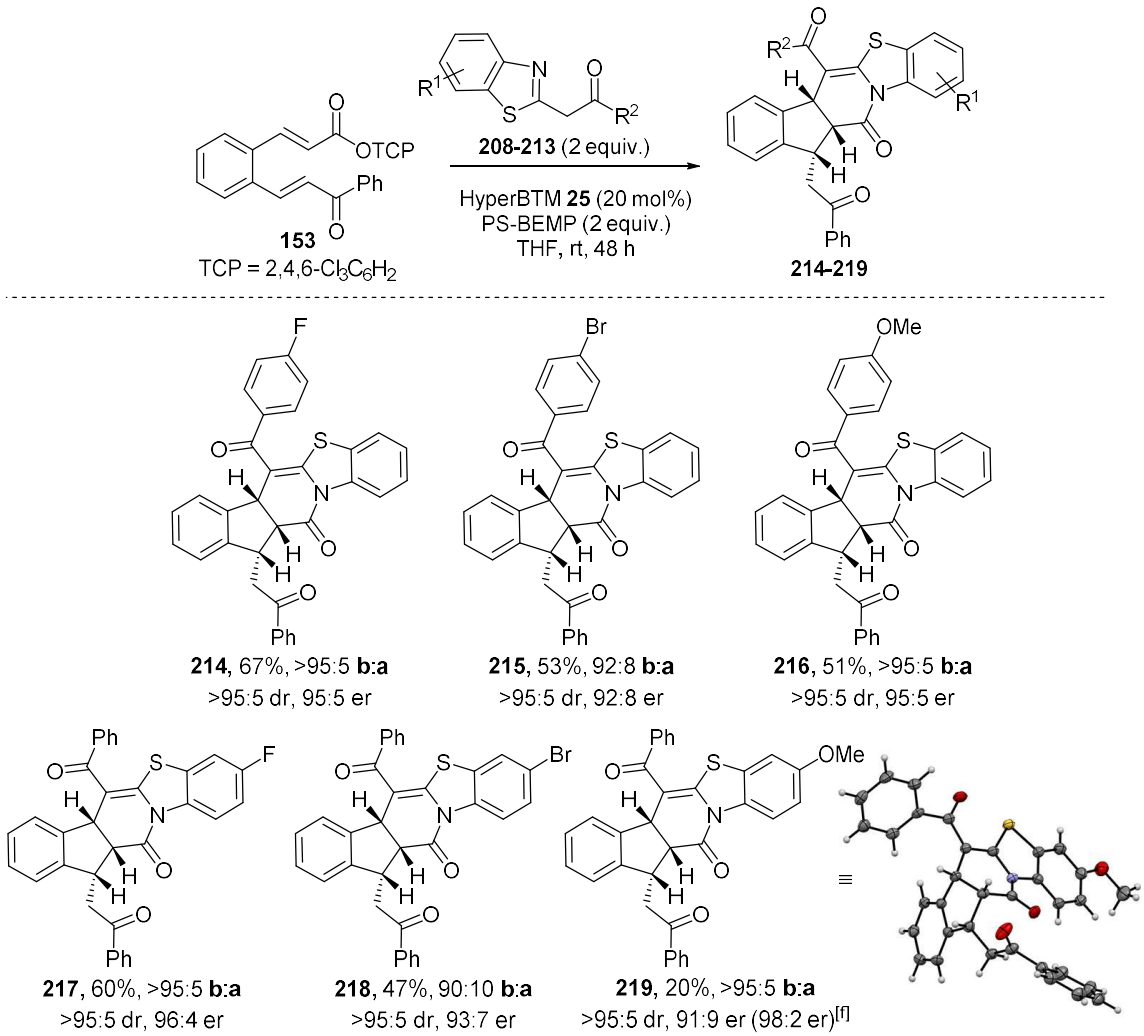
3.4.2 Nucleophile effects on selectivity

Next, a range of alternative benzothiazoles was synthesised *via* NaHMDS-mediated coupling of acetophenones with chloro-benzothiazoles (Scheme 51).[9] The electronic properties of either the acyl group or the benzothiazole aryl ring were varied to investigate the relationship between nucleophile structure and selectivity of the lactam formation.



Scheme 51. Synthesis of benzothiazoles *via* an NaHMDS coupling strategy.

Substrate **153** bearing a phenyl enone substituent was chosen as a model Michael acceptor due to easier chromatographic separation and analysis of the products. The results of this reaction series are shown in Scheme 52. Various 2-arylacyl benzothiazole substituents were well tolerated, forming fused polycyclic products **214**-**216** with high product selectivity and with good diastereo- and enantiocontrol. Halogen substitution around the benzenoid ring afforded products **217** and **218** in moderated to good yields (47-60%) and high stereoselectivity. A lower yield was obtained for **219** bearing an electron-donating methoxy substituent (20%), although the stereocontrol remained high (>95:5 dr, 91:9 er). The relative and absolute configuration of **219b** was confirmed by X-ray crystallographic analysis, with all other products assigned by analogy.

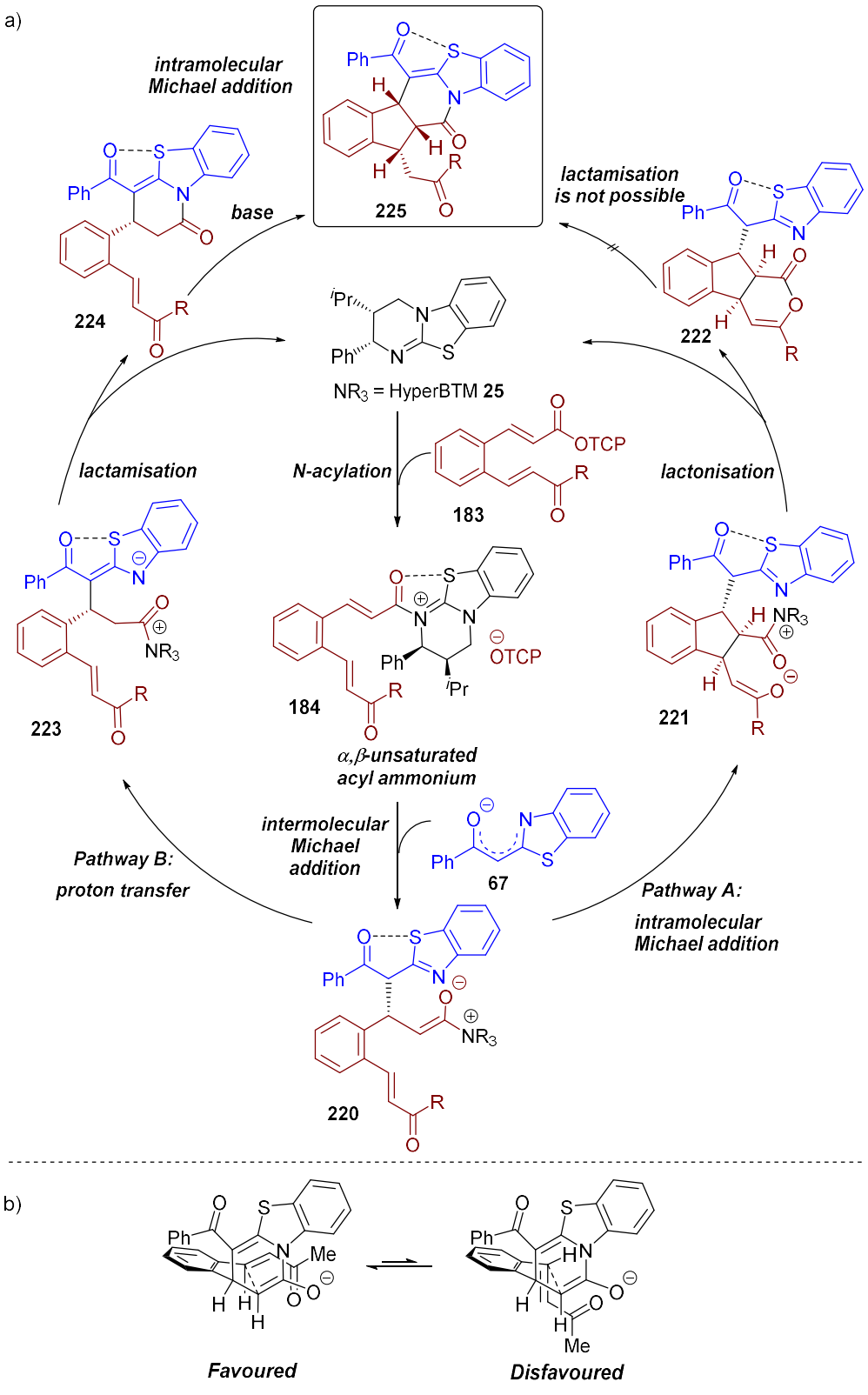


Scheme 52. Effects of the benzothiazoles on annulation regioselectivity.
[a] Reactions performed on 0.1 mmol scale. [b] Combined yield. [c] **a**:**b** ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [d] dr determined by ^{1}H NMR spectroscopic analysis. [e] er determined by HPLC analysis. [f] er obtained upon single recrystallisation.

3.4.3 Proposed mechanism and stereochemical rationale

The stereochemical outcome using acyl benzothiazoles compared with 1,3-diketones can be rationalised through the operation of an alternative domino Michael-lactamisation-Michael (MLM) pathway. After initial Michael addition of heterocyclic nucleophile **67** onto α,β-unsaturated acyl ammonium **184** resulting ammonium enolate **220** can react further *via* two different catalytic pathways. In pathway (A), intramolecular Michael addition followed by proton transfer generates acyl ammonium intermediate **221**. Subsequent lactonisation gives lactone **222** and releases catalyst **25**. *N*-cyclisation could convert **222** to lactam, however this would give a different relative configuration of the product compared with the observed stereochemistry in lactam **225**. Alternatively, in pathway (B) ammonium enolate **220** undergoes proton transfer to give acyl ammonium **223**. Lactamisation of the benzothiazole nitrogen onto the acyl ammonium generates dihydropyridone **224** and releases the catalyst. Subsequent base-mediated cyclisation

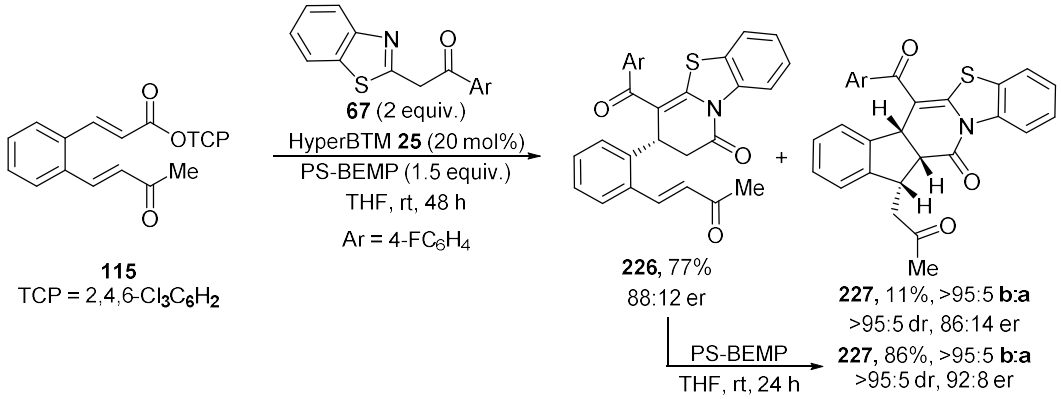
of **224** generates the observed polycyclic indane **225** (Scheme 53a). In this case, the intramolecular Michael-addition occurs through the conformationally restricted enolate of dihydropyridone **224**, with the enone adopting a pseudo-equatorial position in the forming indane ring (Scheme 53b).



Scheme 53. a) Proposed domino Michael-lactamisation-Michael using acyl benzothiazoles. b) Stereochemical rationale.

Consistent with the proposed mechanism (Pathway B), reaction of TCP ester **115** with acyl benzothiazole **67** using only 1.5 equiv. PS-BEMP afforded dihydropyridone **226** as the major

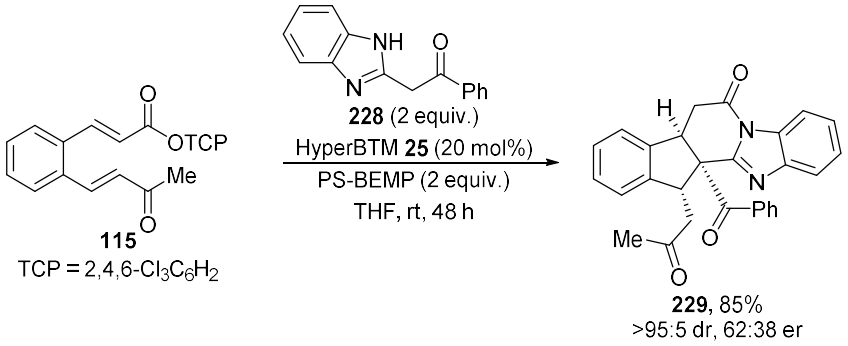
product (77% yield, 88:12 er), with only 11% of cyclised product **227** isolated with comparable levels of stereocontrol (Scheme 54). Subjecting isolated dihydropyridone **226** to basic conditions in the absence of catalyst led to further cyclisation into **227**, which was isolated in 86% yield as a single diastereoisomer in 92:8 er. This is consistent with **226** being a viable precursor to lactam product **227** and the stereochemical outcome of the stepwise cyclisation is consistent with that observed in the domino processes.



Scheme 54. Formation of pre-cyclised dihydropyridone **226**.

3.5 Domino Michael-lactamisation-Michael reaction using acyl benzimidazoles

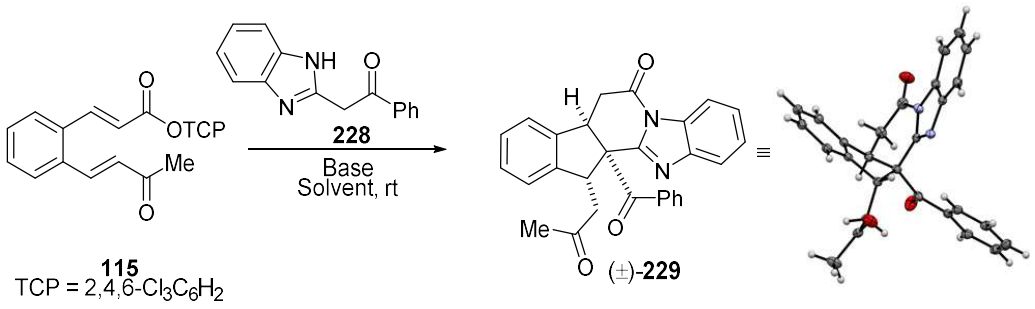
Having observed a new domino reaction pathway using acyl benzothiazoles the reactivity of alternative acyl benzazoles was explored. While combination of 2-phenacyl benzoxazole **196** with α,β-unsaturated TCP ester **115** under the previously optimised conditions led to a complex isomeric mixture, reaction with 2-phenacyl benzimidazole **228** gave a single major product isolated in 83% yield (Scheme 55). Further characterisation using 2D-NMR experiments (COSY, HSQC and HMBC) revealed its structure to be fused polycycle **229** containing three contiguous stereocentres, including one all-carbon quaternary stereocentre. Notably, **229** was formed as a single diastereoisomer, however the enantioselectivity was low (62:38 er). Related imidiazoquinolinone structures are known in the literature as potentially useful therapeutic agents for treating autoimmune diseases.[10]



Scheme 55. Reaction outcome with 2-phenacyl benzimidazole.

3.5.1 Optimisation of racemic reaction

Given the possibility of accessing another distinct domino pathway with high levels of chemo- and diastereoselectivity, reaction with 2-phenacyl benzimidazole **228** was further explored with a series of optimisation experiments (Table 7). A significant base-promoted background reaction in the absence of HyperBTM **25** also led to product **229** in 79% yield and >95:5 dr (entry 1), which accounts for the observed low enantioselectivity, with X-ray crystallographic analysis confirming the structural assignment and relative configuration. Consequently, the racemic base-promoted domino process of **115** with **228** was first investigated. Weaker organic bases such as $^{i}Pr_2NEt$ did not give the desired product, however addition of DMAP (20 mol%) afforded **229** in 31% yield (entries 2 and 3). The use of the amidine base DBU resulted in a complex mixture (entry 4), therefore PS-BEMP was chosen for further study. The domino process was most efficient in CH_2Cl_2 (90% NMR yield) compared with either THF (79%) or MeCN (90%). Further yield enhancement was achieved by changing the reaction stoichiometry with both **228** and PS-BEMP reduced to 1.5 equiv., giving **229** in 90% isolated yield as a single diastereoisomer (entries 5-7). The reaction was also performed on a bigger scale (3.5 mmol), leading to the isolation of 1.3 g of fused polycycle **229** in 84% yield (entry 8).

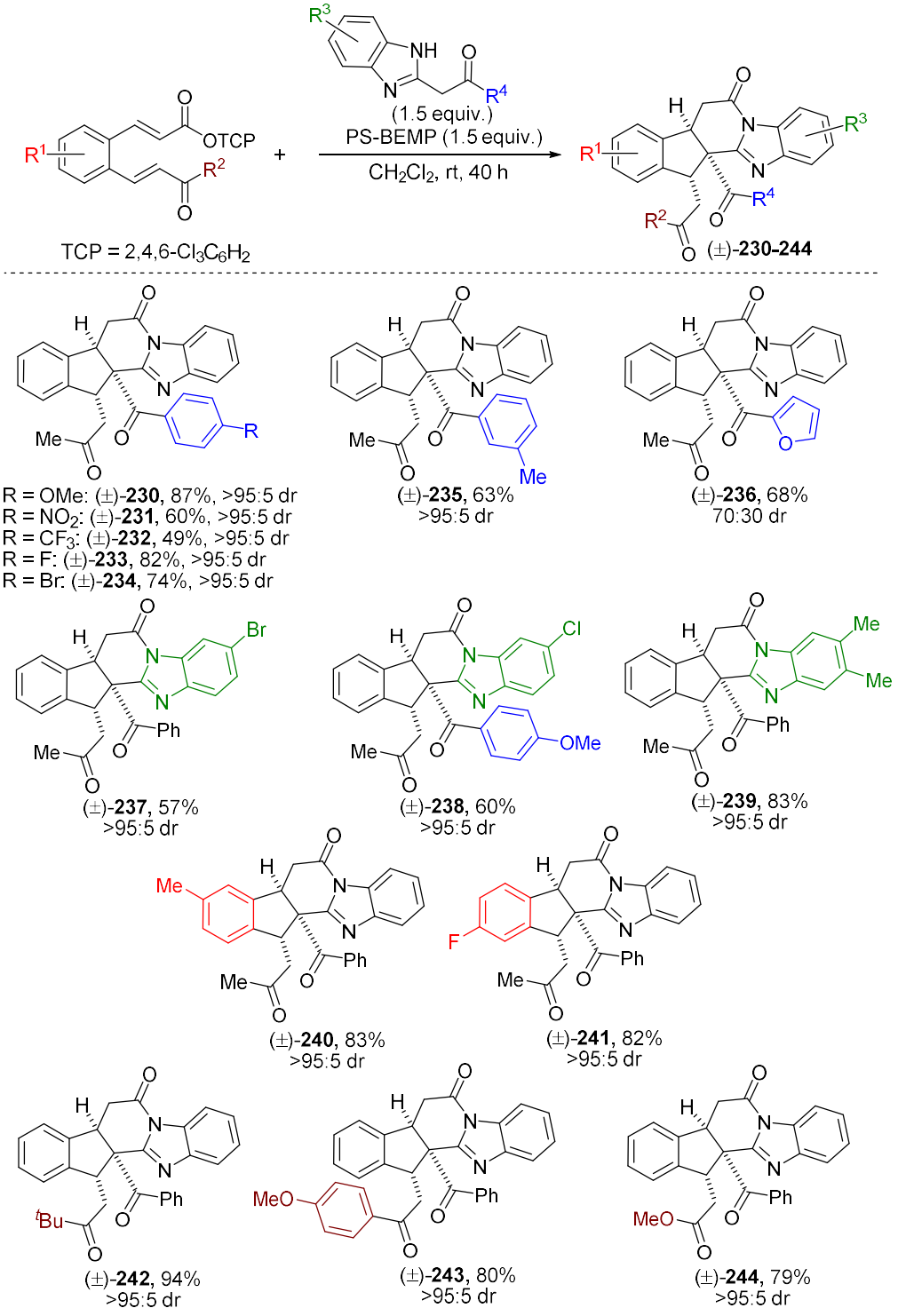


Entry	Base	Solvent	**115**:**228**:base	t (h)	Yield (%)[b]	dr[c]
1	PS-BEMP	THF	1:2:2	16	79	>95:5
2	$^{i}Pr_2NEt$	THF	1:2:2	16	Trace	–
3[d]	$^{i}Pr_2NEt$	THF	1:2:2	16	31	>95:5
4	DBU	THF	1:2:2	16	–	–
5	PS-BEMP	MeCN	1:2:2	16	56	>95:5
6	PS-BEMP	CH_2Cl_2	1:2:2	24	90	>95:5
7	PS-BEMP	CH_2Cl_2	1:1.5:1.5	40	97 (90)[e]	>95:5
8[f]	PS-BEMP	CH_2Cl_2	1:1.5:1.5	40	(84)[e]	>95:5

Table 7. Optimisation of racemic reaction with 2-phenacyl benzimidazole.
[a] Reactions performed on 0.1 mmol scale. [b] NMR yield using 1,4-dinitrobenzene as an internal standard. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Reaction using 20 mol% DMAP. [e] Isolated yield in parentheses. [f] Reaction performed on a 3.5 mmol scale.

3.5.2 Reaction scope with acyl benzimidazoles

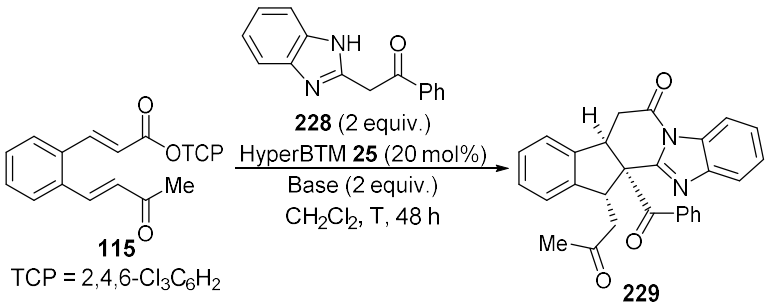
To explore the scope and limitations of this process a variety of the acyl benzimidazoles and the α,β-unsaturated TCP esters were tested (Scheme 56). Substituted benzimidazoles with either halogens, electron-rich or electron-poor groups were well tolerated, forming fused indanes **230**-**235** in generally good yield and excellent diastereoselectivity. Slightly decreased diastereoselectivity was observed in the reaction with 2-furyl-containing benzimidazole which gave product **236** in 68% yield and 70:30 dr. Substitution around the benzimidazole ring was also well tolerated affording indanes **237**-**239** as single diastereoisomers in good to high yields (57-83%). The introduction of substituents within the benzenoid ring of the α,β-unsaturated TCP ester gave selective access to products **240** and **241** in excellent yield and diastereocontrol. By changing the alkyl enone from a methyl to a *tert*-butyl substituent the corresponding polycycle **242** was formed in further improved 94% yield. Notably, only an electron-rich aryl enone substituent could be incorporated, forming product **243** in 80% yield. The presence of either electron-withdrawing or halogen substituted aromatic rings on the enone led to mixtures of products and low yields. In contrast with the reactions using acyl benzothiazoles, the pendent enone could be replaced with an α,β-unsaturated methyl ester, giving indane **244** in 79% yield with excellent selectivity.



Scheme 56. Substrate scope using acyl benzimidazoles as nucleophiles.
[a] Reactions performed on 0.1 mmol scale. [b] dr determined by ^{1}H NMR spectroscopic analysis.

3.5.3 Optimisation of enantioselective reaction

To further demonstrate the utility of the new highly diastereoselective domino process using benzimidazoles as nucleophiles, the possibility of an isothiourea-catalysed enantioselective variant was revisited (Table 8). Using TCP ester **115** and benzimidazole **228** in presence of HyperBTM **25** (20 mol%) under the previously optimised reaction conditions for the racemic process gave product **229** with low enantioselectivity, however with excellent diastereocontrol (entry 1). Enhanced er was obtained by lowering the temperature to 0 °C with **229** formed in 71:29 er (entry 2). Changing the base used also had an impact on enantioselectivity. A strong amidine base DBU led to a complex mixture, while the use of a weaker organic base 2,6-lutidine gave product **229** in a further improved 83:17 er (entries 3-4). Finally, using $^{i}Pr_2NEt$ allowed **229** to be isolated in slightly lower 60% yield but as a single diastereoisomer in 88:12 er (entry 5). This reaction was warmed up to 10 °C to achieve a full conversion of the starting ester within a reasonable amount of time.



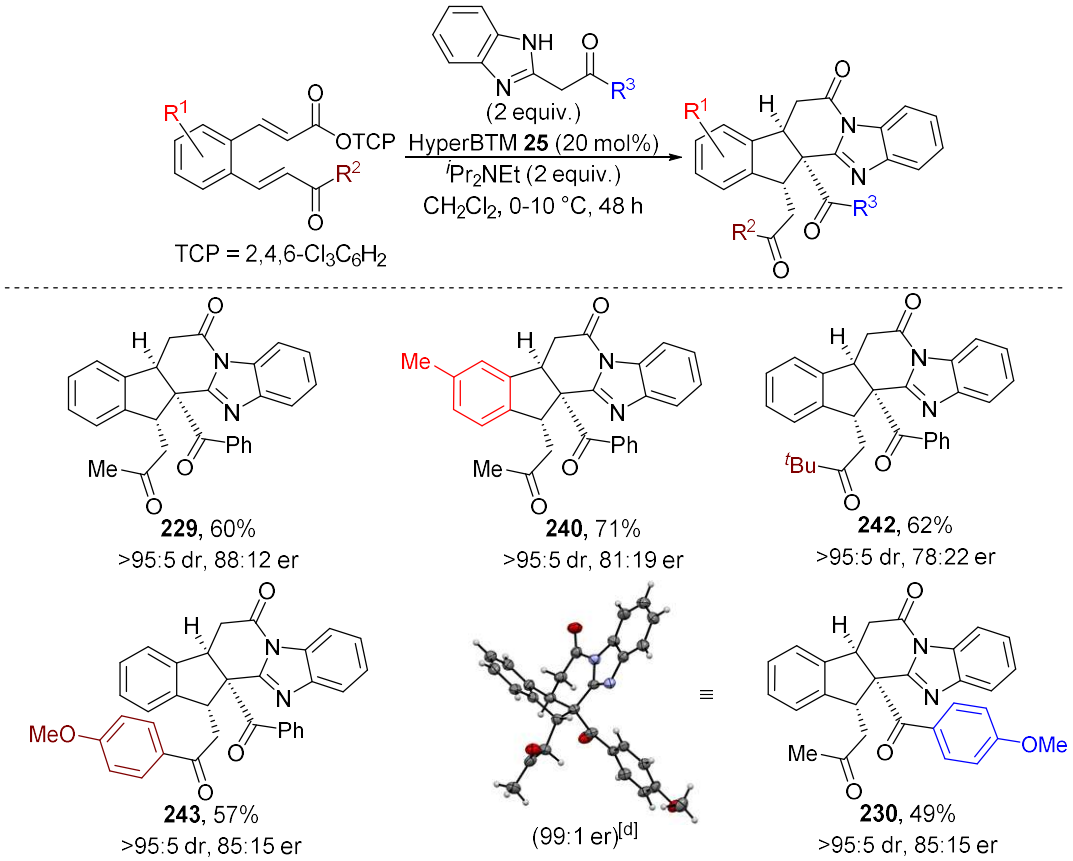
Entry	Base	T (°C)	Yield (%)[b]	dr[c]	er[d]
1	PS-BEMP	rt	97	>95:5	57:43
2	PS-BEMP	0	65	>95:5	71:29
3	DBU	0-10	–	–	–
4	2,6-lutidine	0-10	70	>95:5	83:17
5	**$^{i}Pr_2NEt$**	**0-10**	**68 (60)[e]**	**>95:5**	**88:12**

Table 8. Optimisation of enantioselective reaction with 2-phenacyl benzimidazole. [a] Reactions performed on 0.1 mmol scale. [b] NMR yield using 1,4-dinitrobenzene as an internal standard. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by HPLC analysis. [e] Isolated yield in parentheses.

3.5.4 Scope of the enantioselective process

To extend the scope of the HyperBTM **25**-promoted reaction using benzimidazoles, the newly optimised conditions were applied to the enantioselective synthesis of a group of the fused polycycles made previously in racemic fashion (Scheme 57). First, structural variation within the α,β-unsaturated TCP ester was probed, with the substrates containing a substituted benzenoid ring, both the alkyl and aryl enone substituents giving the corresponding polycycles **240**-**243** in

synthetically useful yields (57-71%) and good enantioselectivity. Modified benzimidazole structure was also tolerated, forming fused indane **230** in comparable levels of diastereo- and enantioselectivity. The absolute and relative configuration of this polycycle was confirmed through X-ray crystallographic analysis of a recrystallised sample (99:1 er), with all other products in this reaction series assigned by analogy.

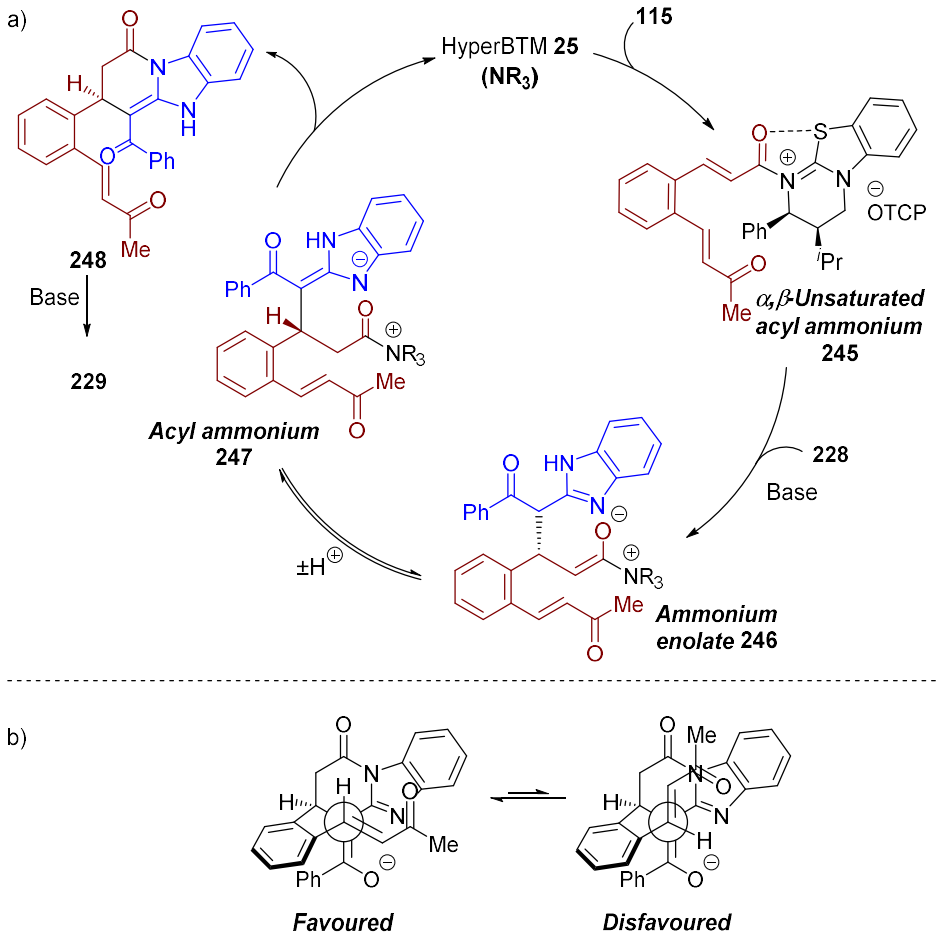


Scheme 57. Scope of the enantioselective process.
[a] Reactions performed on 0.1 mmol scale. [b] dr determined by ^{1}H NMR spectroscopic analysis. [c] er determined by HPLC analysis. [d] er obtained upon single recrystallisation.

3.5.5 Proposed mechanism and stereochemical rationale

To rationalise the reactivity and stereoselectivity observed for the domino process using benzimidazoles the Michael-lactamisation-Michael pathway can be proposed as depicted in Scheme 58a. The catalytic cycle starts with formation of key reactive α,β-unsaturated acyl ammonium intermediate **245**. Michael addition of acyl benzimidazole **228** occurs on the *Re*-face of α,β-unsaturated acyl ammonium **245** to generate ammonium enolate **246** with subsequent proton transfer and lactamisation of the resulting acyl ammonium **247** to give fused dihydropyridone **248** and release the catalyst. Deprotonation of the benzimidazole, followed by intramolecular Michael addition of the enolate formed onto the pendent α,β-unsaturated ketone, gives observed product **229** containing three contiguous stereocentres, including one all-carbon

quaternary stereocentre. The diastereoselectivity can tentatively be rationalised by the enone adopting a sterically less hindered pseudo-equatorial position in the forming indane ring during the intramolecular Michael addition, since in the axial position the bulky enone group is in close proximity to the benzimidazole moiety (Scheme 56b). An alternative pathway in which the intramolecular Michael addition occurs from acyl ammonium **247** prior to lactamisation cannot be ruled out, however the Michael-lactamisation-Michael pathway is currently favoured by drawing analogy with the reactions using acyl benzothiazoles.



Scheme 58. a) Proposed domino Michael-lactamisation-Michael using acyl benzimidazoles. b) Stereochemical rationale.

3.6 Conclusions and outlook

α,β-Unsaturated acyl ammonium intermediates generated from an isothiourea catalyst and bench-stable α,β-unsaturated TCP esters bearing pendent Michael acceptors undergo various enantioselective nucleophile-dependent domino reactions. Three divergent processes are observed using either 1,3-dicarbonyls, acyl benzothiazoles, or acyl benzimidazoles as pro-nucleophiles, demonstrating synthetic power of an α,β-unsaturated acyl ammonium intermediate in isothiourea catalysis.

Having evaluated the reactivity of α,β-unsaturated acyl ammonium intermediates using 1,3-dicarbonyls, the scope of the reaction has also been extended employing heterocyclic nucleophiles. Acyl benzothiazoles proved excellent nucleophiles in the study of selectivity of this domino process. Previously explored selective *N*-cyclisation using benzothiazoles[58,61] was also observed in this work. Changing the electronic properties of benzothiazoles influenced the formation of lactams dramatically from good yields with electron-withdrawing substituents to low yields with electron-donating groups. Interestingly a different diastereomer was obtained for the products with benzothiazoles which is due to substrate-controlled Michael addition after the *N*-cyclisation step.

Use of benzimidazole in the Michael-Michael-annulation reaction showed unexpected but interesting reactivity furnishing a complex imidazoisoquinolinone derivative as a single product, however the enantiocontrol was notably lower than previously observed with 1,3-dicarbonyls and benzothiazoles. Regarding the possibility of accessing another distinct domino pathway, the reaction was studied in both racemic and enantioselective fashion giving a wide range of complex polycycles. The absolute and relative configurations of the products in this series were also confirmed by crystallographic analysis. The product formation and its configuration were rationalised by the proposed mechanism and stereochemical model respectively. Given the importance of related imidazoisoquinolinone structures as therapeutic agents, this reactivity might be a source for future investigations.

3.7 References

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4 Aryloxide-facilitated catalyst turnover in α,β-unsaturated acyl ammonium catalysis

4.1 Alternative catalyst turnover in α,β-unsaturated acyl ammonium catalysis

As demonstrated in the previous Chapter, Lewis Base catalysis is a powerful tool for the rapid generation of molecular complexity with high levels of chemoselectivity and stereocontrol. In particular, the area of α,β-unsaturated acyl ammonium catalysis has gained rising attention given the feasibility to form multiple bonds and stereocentres in a single operation.[1] Complex substituted carbo- and heterocycles have been constructed with high levels of stereoselectivity, with a range of examples from Fu,[2] Romo,[3] Birman,[4] Matsubara[5] and Smith[6] groups (Figure 15a). Although versatile, current methodologies require the reactive partner to contain two distinct nucleophilic functionalities to 1) undergo conjugate addition to the α,β-unsaturated acyl ammonium intermediate, and 2) enable turnover of the Lewis base catalyst (Figure 15a). This requirement inherently limits the scope within α,β-unsaturated acyl ammonium catalysis and must be overcome to allow more diverse processes. To broaden the current concept, turnover of the catalyst could be achieved by *intermolecular* attack of a second nucleophile. One possible solution would be the use of an aryloxide counterion generated *in situ* during the reaction from an α,β-unsaturated aryl ester as the α,β-unsaturated acyl ammonium precursor. Upon conjugate addition of a simple nucleophile and concomitant protonation of the ammonium enolate intermediate, an aryloxide acts as a second nucleophile to release the Lewis base catalyst and afford enantioenriched functionalised aryl esters (Figure 15b).

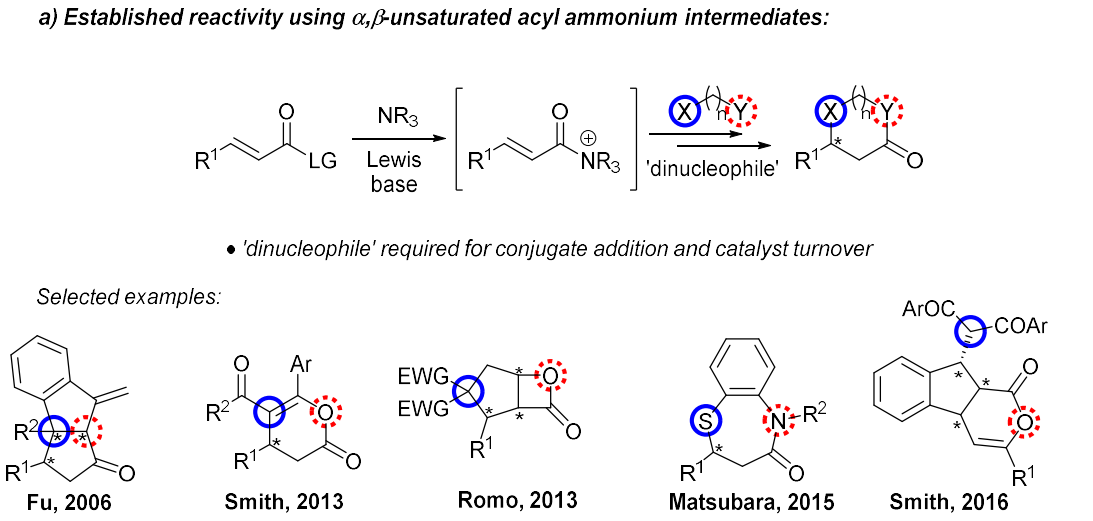


Figure 15. a) Established reactivity of α,β-unsaturated acyl ammonium intermediates in catalysis. b) Alternative aryloxide-facilitated catalyst turnover strategy.

4.2 Aryloxide-facilitated catalyst turnover

The feasibility of Lewis base mediated approaches to achieve catalyst turnover using aryloxide has been demonstrated within both ammonium and azolium enolate catalysis.[7] α-Aryloxyaldehydes have been used as azolium enolate precursors in NHC catalysis, whilst aryl esters have been utilised as ammonium enolate precursors in tertiary amine catalysis. In NHC catalysis, the addition of a carbene initiates the elimination of an aryloxide to give a nucleophilic enol, which can trap a suitable electrophile. The aryloxide can then attack onto carbonyl to regenerate the catalyst and create enantioenriched aryl ester in the process (Figure 16).

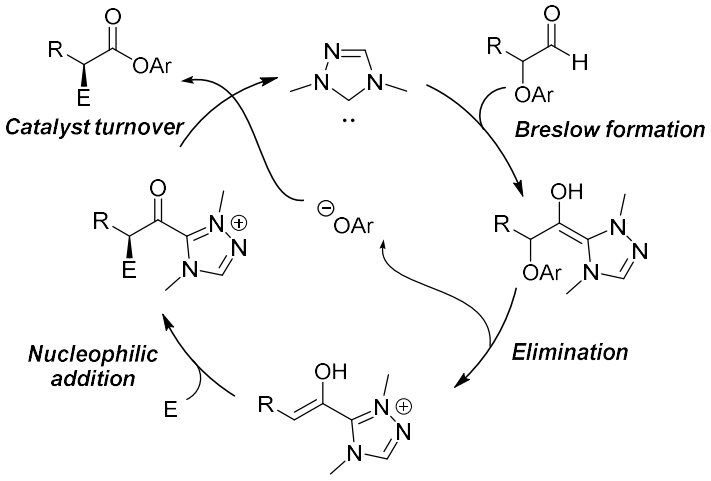


Figure 16. Aryloxide-facilitated catalyst turnover in NHC catalysis.

Alternatively, in tertiary amine catalysis, *N*-acylation of a tertiary amine initiates the elimination of an aryloxide with concomitant deprotonation of the generated acyl ammonium. Upon reaction with an electrophile, the aryloxide can add to the resultant acyl ammonium to facilitate turnover of the amine catalyst (Figure 17).[7]

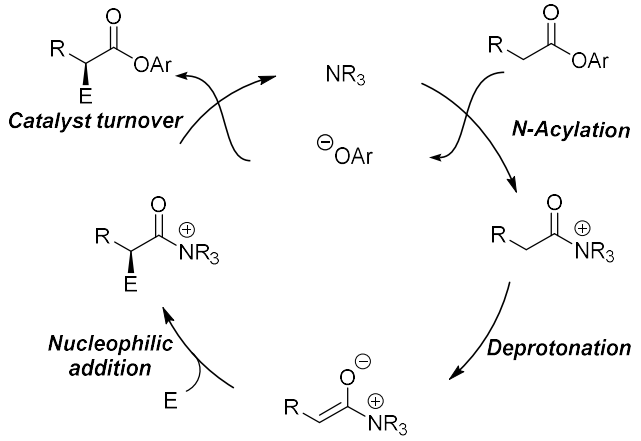
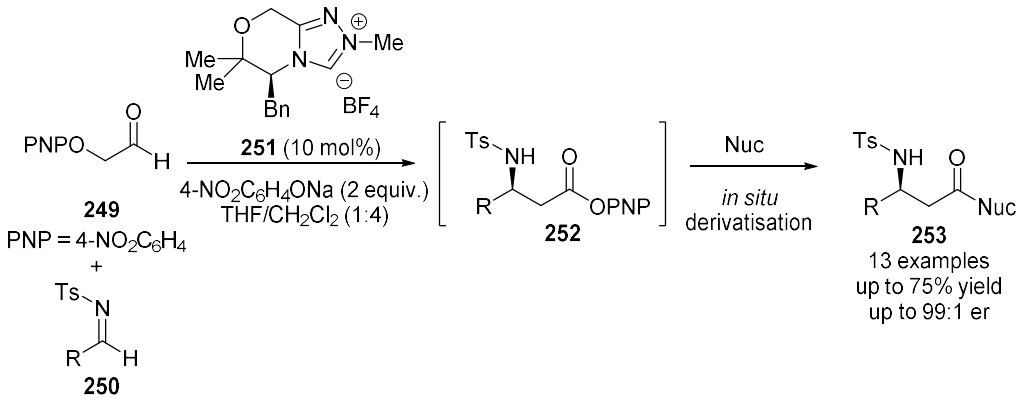


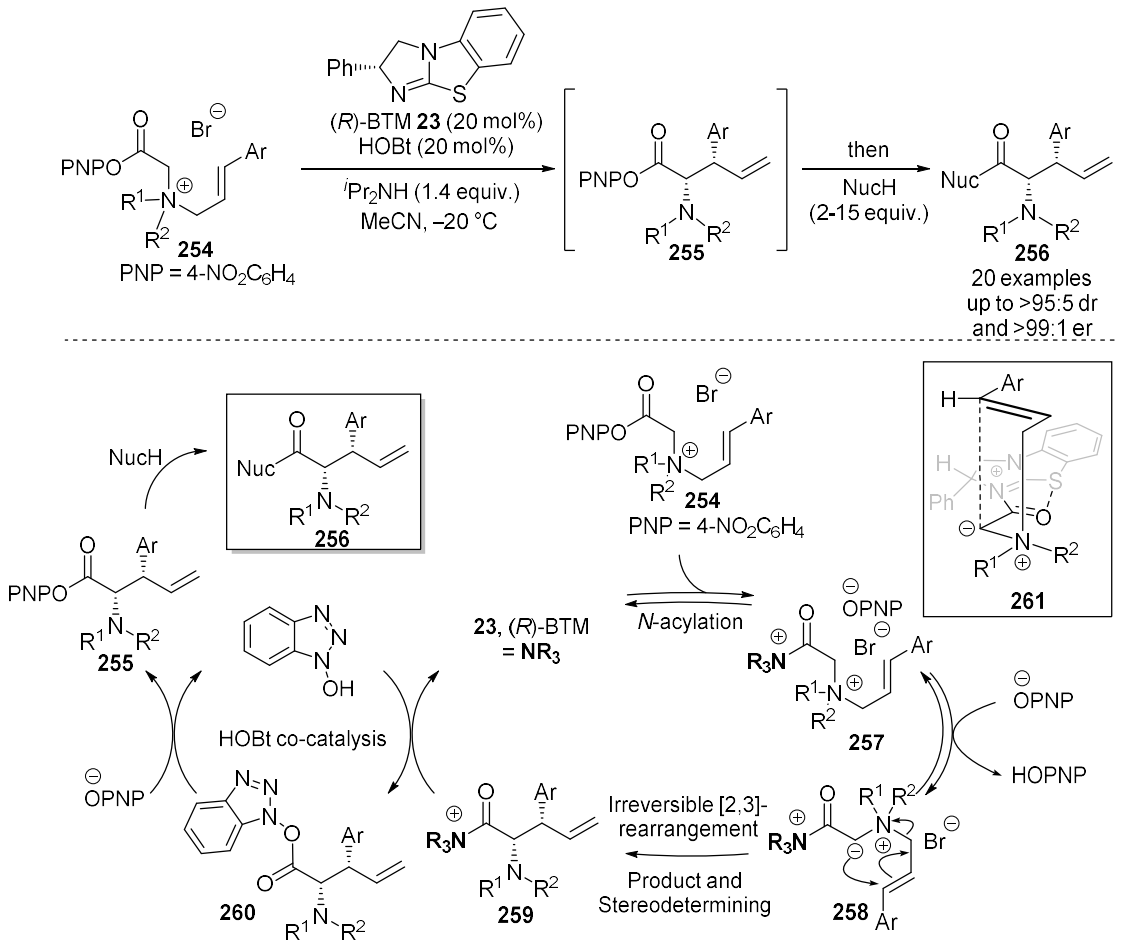
Figure 17. Aryloxide-facilitated catalyst turnover in tertiary amine catalysis.

In 2009 Scheidt reported the first application of the aryloxide strategy in NHC-catalysed enantioselective Mannich reactions with α-aryloxyacetaldehyde **249**.[8] In the presence of NHC precatalyst **251** and base this substrate reacts with activated imines **250** to generate β-amino ester **252**, which can be intercepted *in situ* to afford valuable nitrogen-containing compounds of the type **253**. Notably, the presence of 2 equiv. of 4-nitrophenoxide was crucial to provide the desired reactivity, with alternative bases, such as NEt_3 or NaH giving ~30% lower yield and decreased product enantioselectivity (Scheme 59).



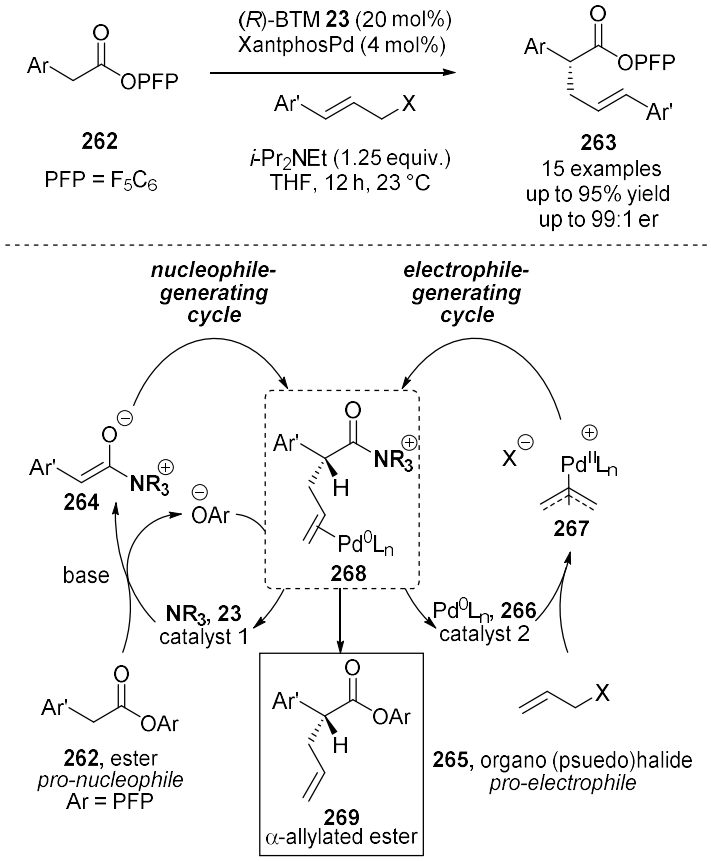
Scheme 59. Aryloxide strategy in NHC-catalysed enantioselective Mannich reaction.

In the first analogous process implicating acyl ammonium intermediates, Smith and co-workers applied 4-nitrophenoxide as a catalyst turnover agent in an enantioselective [2,3]-sigmatropic rearrangement of allylic ammonium ylides using the isothiourea catalyst benzotetramisole (BTM, **23**) and HOBt as a co-catalyst (Scheme 60).[9] In this process initial acylation of aryl ester-derived ammonium salt **254** gives dicationic species **257** with release of 4-nitrophenoxide, that acts as a base to deprotonate at the α-position of intermediate **257**. Subsequent [2,3]-rearrangement of ylide **258** to generate **259**, followed by esterification of this species with HOBt gives intermediate ester **260** that facilitated catalyst turnover. While this process can be performed in the absence of HOBt, its addition provides a subtle enhancement in both diastereo- and enantioselectivity. Transesterification of **260** with the aryloxide generates desired product **255**. Enantioenriched aryl ester **255** can be either isolated or derivatised *in situ* with a suitable nucleophile to generate a range of functionalised α-amino acid derivatives **256**. The origin of the high stereoselectivity was rationalised by the transition state model **261**, in which the carbonyl oxygen preferentially lies *syn* to the S atom within the isothiouronium ion, allowing a stabilising electrostatic or n_o to σ^*_{C-S} interaction,[10] to provide transition state rigidity and high enantiocontrol. A π-cation interaction between the allylic *C*(3)-aryl or styryl substituent and the acyl isothiouronium ion, previously suggested in other asymmetric isothiourea-catalysed processes,[10f] is proposed as a necessary requirement for high *syn*-diastereocontrol.



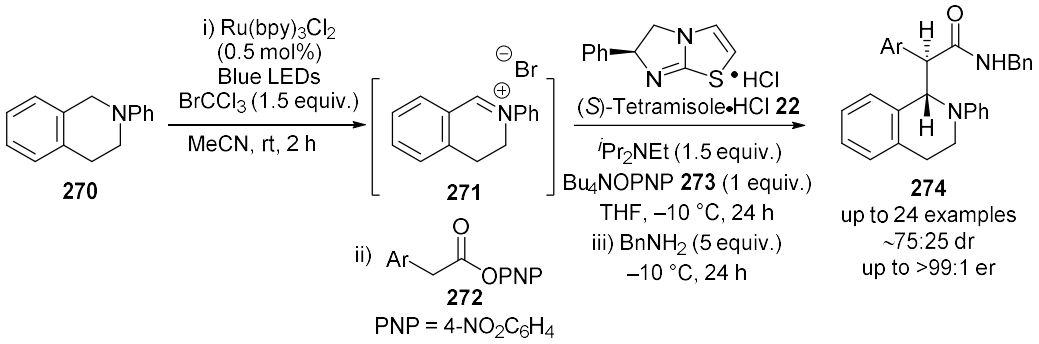
Scheme 60. Enantioselective [2,3]-rearrangement of allylic ammonium ylides and the proposed mechanism.

A similar strategy for catalyst turnover was successfully employed by Snaddon and co-workers in a co-operative transition metal-organocatalytic enantioselective allylation of pentafluorophenyl esters (Scheme 61).[11] This system relies on two co-operative cycles for the catalytic generation of a nucleophile and an electrophile respectively. In the nucleophile-generating cycle, pentafluorophenyl ester **262** reacts with Lewis base isothiourea **23** to release the aryloxide, with subsequent deprotonation to give ammonium enolate **264**. In the electrophile-generating cycle, the allylic species **265** coordinates to palladium(0) catalyst **266**, which following oxidative addition generates the electrophilic π-allyl complex **267**. At this stage, two catalytic cycles converge, with the chiral ammonium enolate intercepted by allylic species **267** to give intermediate **268**. Finally, turnover of the Lewis base catalyst is facilitated by nucleophilic attack of the released aryloxide into acyl ammonium **268**, generating asymmetric α-allylated ester **269**. Notably, in this protocol, the presence of additional equivalent of aryloxide was not required for achieving high yields and levels of stereocontrol. Following this work, analogous co-operative catalytic processes were recently developed by Hartwig[12a] and Smith[12b] groups.



Scheme 61. Snaddon's α-allylation of aryl esters and postulated mechanism.

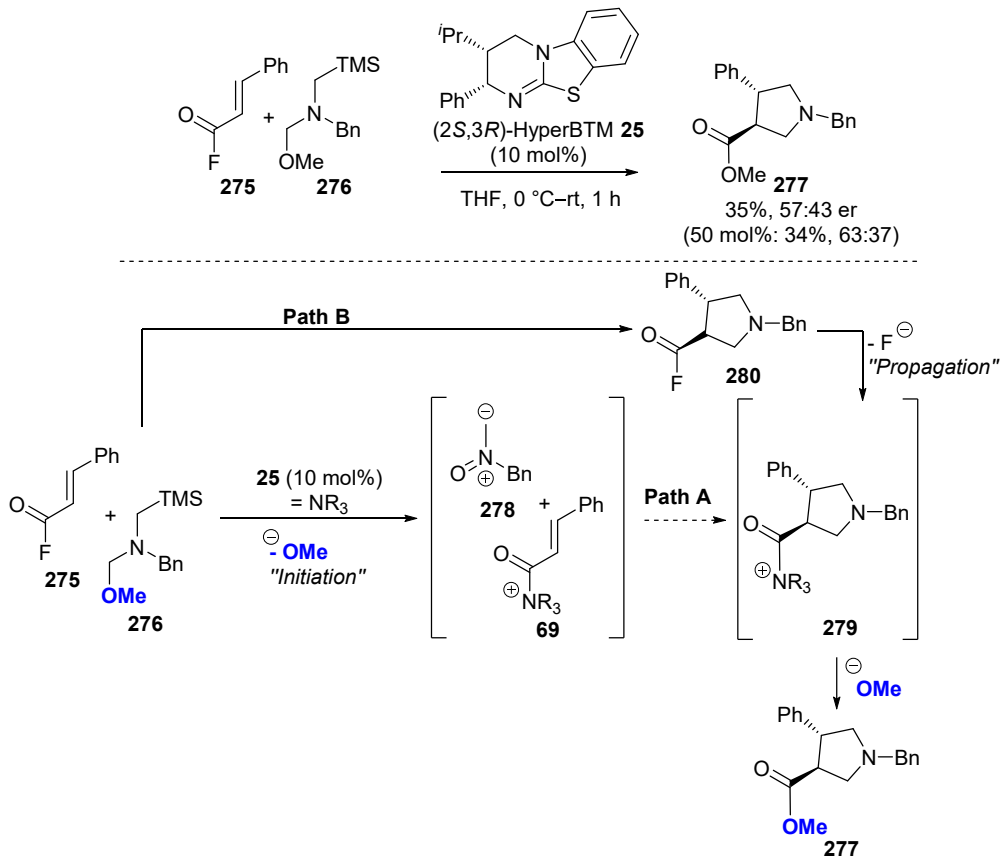
A further recent example of exploiting the aryloxide strategy was reported by Smith[13] who applied this concept for the photoredox/isothiourea-catalysed enantioselective addition of 4-nitrophenyl esters to tetrahydroisoquinoline-derived iminium ions (Scheme 62). In the presence of $Ru(bpy)_3Cl_2$ and $BrCCl_3$ with blue LED light, oxidation of *N*-phenyl tetrahydroisoquinoline **270** was achieved to give iminium intermediate **271**. This can be intercepted by a nucleophilic ammonium enolate, generated *in situ* from an arylacetic acid ester **272** and Lewis base **22** leading to the formation of substituted tetrahydroisoquinolines **274** in high yield and excellent er. Similarly to Scheidt's observation, the presence of additional aryloxide (tetrabutylammonium 4-nitrophenoxide, Bu_4NOPNP, **273**) was crucial for achieving high yield and enantioselectivity. This effect was rationalised due to a combination of increased polarity of the reaction mixture and the influence of 4-nitrophenoxide in facilitating catalyst turnover.



Scheme 62. Smith's sequential photoredox/isothiourea catalysis.

4.3 Aims and objectives

Notably, prior to this work the application of aryloxide-facilitated catalyst turnover strategy has not been described for enantioselective α,β-unsaturated acyl ammonium catalysis. A recent attempt to address this limitation using an alkoxide-facilitated turnover approach was reported by Lupton and co-workers in the Lewis base-catalysed 1,3-dipolar cycloaddition of unstabilised azomethine ylides (Scheme 63).[14] In their reaction design, an α,β-unsaturated acid fluoride **275** and HyperBTM **25** as a chiral Lewis base were used to generate α,β-unsaturated acyl ammonium **69**. Formation of azomethine ylide **278** *via* fluoride-mediated desilylation of the azomethine precursor **276** would also result in the release of methoxide (Scheme 63, Path A). Azomethine ylide **278** can undergo a 1,3-dipolar cycloaddition with α,β-unsaturated acyl ammonium **69** to form pyrrolidine intermediate **279**. Nucleophilic attack of methoxide into acyl ammonium **279** gives pyrrolidine **277** and regenerates the Lewis base catalyst. However, only low enantioselectivity in this process was observed, possibly due to the highly competitive background reaction. It was found that cycloaddition occurs preferentially between the α,β-unsaturated acyl fluoride and azomethine ylide *via* acid fluoride **280** (Scheme 63, Path B), evidenced by competition studies and supported by ^{19}F NMR monitoring.



Scheme 63. Isothiourea-catalysed 1,3-dipolar cycloaddition.

The limitation of formal cycloaddition chemistry within more complex α,β-unsaturated acyl ammonium catalysis remains challenging. Current methodologies still require the reactive partner to contain two distinct nucleophilic functionalities. To allow for more diverse processes, it is important to develop a new general concept of alternative catalyst turnover for α,β-unsaturated acyl ammonium catalysis, and is the main purpose of this Chapter. The principal objectives of the project are to apply the strategy of aryloxide-facilitated turnover and determine the nature of aryloxide counterion required for catalyst turnover by testing various α,β-unsaturated aryl esters as the α,β-unsaturated acyl ammonium precursors (Figure 18). A range of simple nucleophiles as Michael donor components will be screened for their applicability to selectively undergo the desired catalytic pathway. In addition, the utility of the resulting aryl esters has to be explored with potential application in the synthesis of biologically relevant molecules. Finally, preliminary experimental mechanistic work within this area will be reported.[15]

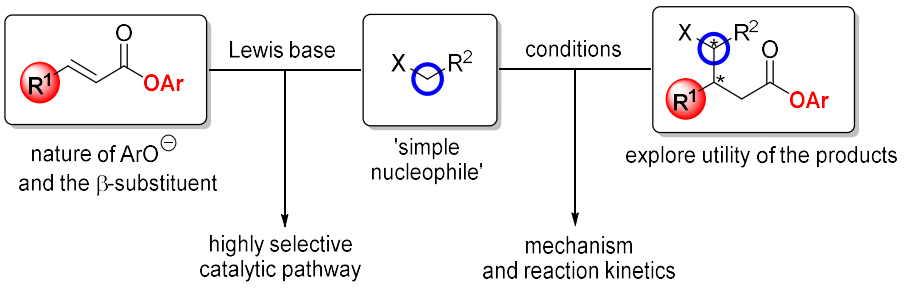
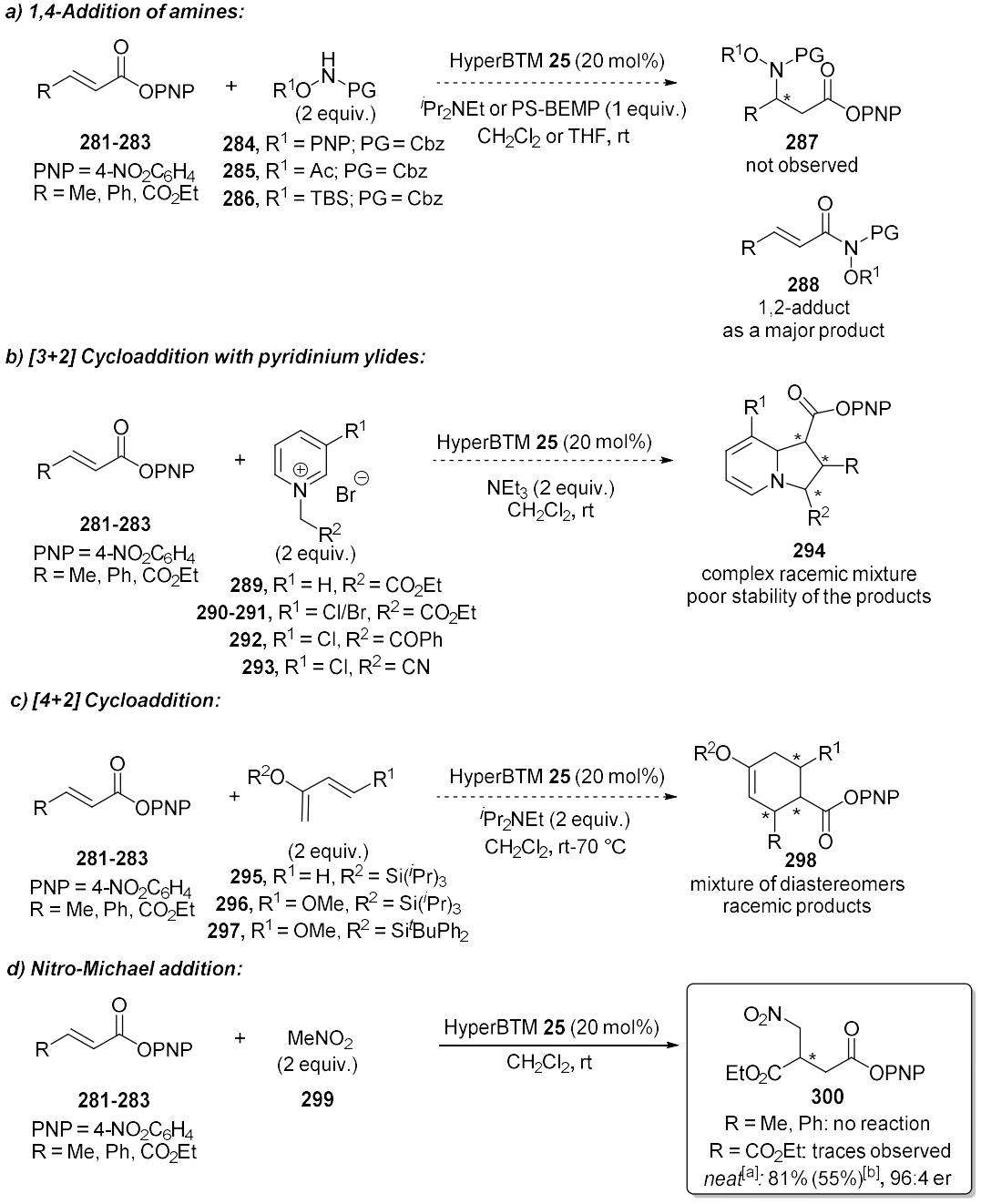


Figure 18. Exploring the concept of external turnover in α,β-unsaturated ammonium catalysis.

4.4 Screening of nucleophiles

Proof-of-principle investigations began by screening different nucleophiles with 4-nitrophenol esters **281-283**, bearing either phenyl, methyl or ester substituents in the β-position in the presence of HyperBTM **25** as a Lewis base catalyst (Scheme 64). *N*-centred nucleophiles have previously been reported as useful nucleophiles for enantioselective organocatalytic amine conjugate addition to α,β-unsaturated aldehydes using iminium catalysis.[16] However, screening protected secondary amines **284-286** with each aryl ester **281-283** did not afford desired Michael addition product **287**. Notably, substrate **283** with the β-ester substituent was slightly more reactive, however, an α,β-unsaturated amide **288** resulting from 1,2-addition was isolated as a major product. Mayr[17] and Dowden[18] pioneered the use of pyridinium ylides in racemic 1,3-dipolar cycloadditions with α,β-unsaturated ketones and oxindoles respectively. Application of pyridinium ylides **289-293** in isothiourea catalysis was also tested. Unsubstituted pyridinium ylide **289** (R^1 = H) was not a competent substrate due to its poor stability. 3-Halo-substituted ylides **290-293** (R^1 = Cl or Br) proved more stable under the reaction conditions giving indolizine products **294** as a complex mixture of diastereoisomers, however no enantiocontrol was obtained. This was attributed to a competitive background reaction between the pyridinium ylide and the aryl ester in the absence of Lewis base catalyst **25**. Further studies of this reaction proved complicated due to poor stability of the dearomatised heterocycles. The use of Danishefsky-type dienes **295-297** was also investigated, affording corresponding Diels-Alder products **298**, however, again no enantioselectivity was observed indicating formation of the products *via* reaction of the PNP esters with the dienes rather than under the influence of the Lewis base catalyst. The reaction of PNP esters with nitromethane **299** was next tested. Using 2 equiv. of nitromethane in CH_2Cl_2 with aryl esters **281-282** bearing methyl and phenyl groups in the β-position provided no product, while the β-ester substituted substrate **283** gave traces of corresponding nitro-Michael adduct **300**. Gratifyingly, performing the reaction in neat nitromethane resulted in drastically increased 81% yield of **300** by ^{1}H-NMR using an internal standard and 55% isolated yield. More importantly, the corresponding aryl ester was obtained in

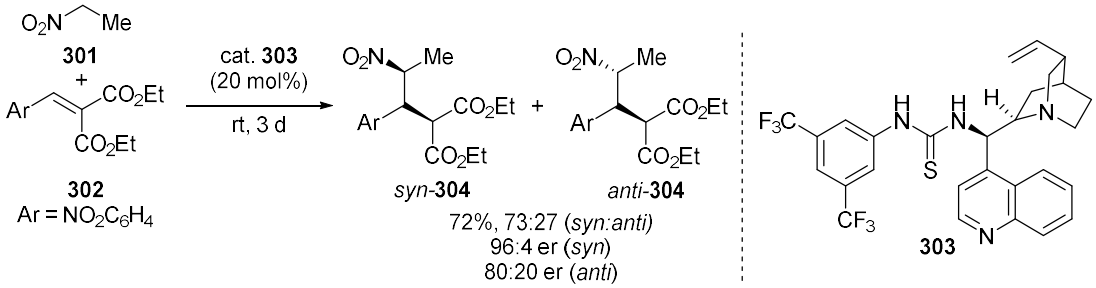
high enantioselectivity (96:4 er), which was a promising proof-of-concept to continue the reaction investigation.



Scheme 64. Screening of nucleophiles with aryl esters **281-283**. [a] 0.2 M $MeNO_2$. [b] Determined by ^1H NMR spectroscopic analysis using 1,4-dinitrobenzene as internal standard (isolated yields given in parentheses).

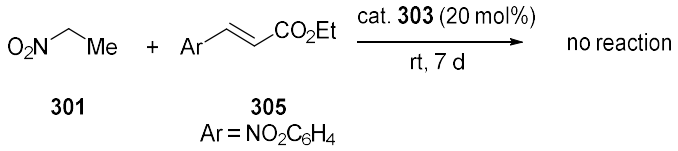
4.5 Enantioselective Michael addition of nitroalkanes

Conjugate additions of nitroalkanes to enones and enals promoted by chiral organocatalysts have been known since at least the mid-1970s,[19] but only in the past decade has their development provided important results in terms of efficiency and enantiomeric excess. Proline derivatives,[20] imidazolidines[21] cinchona alkaloids[22] and phase-transfer catalysts[23] are useful promoters of conjugate additions of nitroalkanes to enones. Much more challenging and rare however is an asymmetric conjugate addition of nitroalkanes at the carboxylic acid oxidation level. Notably, γ-nitro carboxylic acid derivatives are useful intermediates for the preparation of γ-amino acids especially due to the versatility of the nitro group.[24] Maruoka and co-workers reported the first example of enantioselective conjugated addition of nitroalkanes to alkylidenemalonates, mediated by a chiral phase-transfer catalysts,[25] followed by Quintavalla and their application of thiourea-based bifunctional organocatalysts (Scheme 65).[26] In the latter work, addition of nitroethane **301** to diethyl 2-(4-nitrobenzylidene)malonate **302** in the presence of *cinchona*-thiourea **303** provided product **304** in good yield and moderate diastereoselectivity with the major *syn* isomer obtained in higher enantioselectivity. Although the reaction proceeds with a wide range of substrates, extended reaction times up to 11 days were required for less activated alkenes bearing no electron-withdrawing substituent in the aryl group. This observation is in accordance with the Mayr reactivity scale, which predicts that the reaction can occur on the basis of a nucleophilicity value (*N*) of nitroethane (in DMSO) = 21.54 and an electrophilicity index (*E*) = –17.67 for **302** (Ar = $NO_2C_6H_4$). Sluggish reactivity is expected between nitroethane and unsubstituted benzylidenemalonate (Ar = Ph, (*E*) = –20.55).[27]



Scheme 65. Enantioselective conjugate addition of nitroalkanes to alkylidenemalonates.

In addition, the catalytic system was tested also on simpler α,β-unsaturated ester **305** (Scheme 66), however no traces of product were isolated even after 7 days. From these findings, it became apparent that the malonate group enhanced the electrophilicity of the substrate to the level that makes the coupling with the nitronate ion possible.

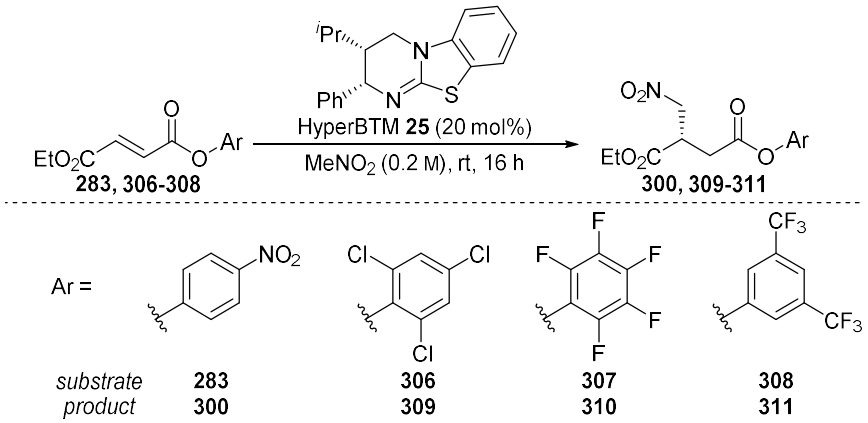


Scheme 66. Attempted conjugate addition of nitroethane to α,β-unsaturated ester **305**.

The intermolecular asymmetric Michael addition of nitroalkanes to unsaturated esters is an unresolved challenge in organocatalysis.[26] The limitations shown by α,β-enoates triggered several authors to find alternative and more active synthetic equivalents, such as α,β-unsaturated imides,[28] *N*-acylpyrroles,[29] and acyl phosphonates,[30] but in most cases the donor is limited to nitromethane only. These processes are promoted by thiourea hydrogen-bonding catalysts, however Lewis base catalysis of nitro-Michael addition has not been demonstrated at the carboxylic acid oxidation level.

4.6 Initial studies and optimisation

Having observed promising reactivity of α,β-unsaturated aryl ester **283** with excess nitromethane in the presence of HyperBTM catalyst **25** (Scheme 64d) further studies screened α,β-unsaturated aryl esters **306-308**, bearing different electron-deficient aryl groups (Table 9). Pleasingly, the reaction proved general for all the esters, with Michael addition products **300**, **309-311** formed in moderate to excellent yield (48-81%) and with high enantioselectivity (up to 96:4 er) and complete regioselectivity in each case. The isolated yields were 13-33% lower than the yields determined by ^{1}H NMR spectroscopy using an internal standard, which was attributed to hydrolysis of the aryl esters upon purification by flash silica column chromatography. The highest yield was obtained using 4-nitrophenyl (PNP) and 3,5-bis(trifluoromethyl)phenyl esters **283** and **308**, with PNP ester **283** chosen for further reaction optimisation due to the higher yield and enantioselectivity obtained.



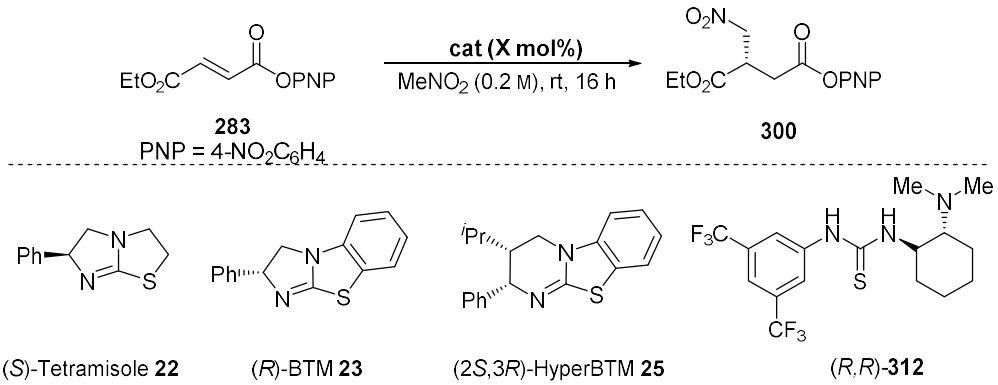
Entry	Substrate	Yield (%)[a]	er[b]
1	**283**	81 (55)	96:4
2	**306**	54 (41)	94:6
3	**307**	48 (33)	95:5
4	**308**	78 (45)	93:7

Table 9. Screening of activated aryl esters.

[a] Determined by ^{1}H NMR spectroscopic analysis using 1,4-dinitrobenzene as internal standard (isolated yields given in parentheses). [b] Determined by chiral HPLC analysis.

4.6.1 Catalyst screening and loading

Further optimisation experiments screened alternative Lewis basic and hydrogen-bonding catalysts (Table 10). Both tetramisole **22** and BTM **23** were competent catalysts to promote the enantioselective Michael addition with comparable reactivity and selectivity but gave either slightly lower yield or enantioselectivity in comparison with HyperBTM **25** (entries 1-3). A hydrogen-bonding catalyst, Takemoto's bifunctional chiral thiourea derivative **312**, has been previously reported to effectively promote Michael additions of nitroalkanes to enones due to the effective activation of the nitro group through hydrogen bonding with the thiourea moiety.[31] However, applying this strategy by using a combination of Takemoto's catalyst **312** and HyperBTM **25** resulted in decreased 46% yield, but with consistently high enantiocontrol (96:4, entry 4). The use of a mild Lewis acid $Sc(OTf)_3$ as catalytic additive for the alternative activation of the nitro-group proved inefficient and no desired product was formed with concomitant decomposition of α,β-unsaturated PNP ester **283** (entry 5). A control experiment in the absence of catalyst showed no product formation (entry 6) which explains high levels of enantioselectivity observed in this process under catalytic reaction conditions. Lower catalyst loadings (10 or 5 mol%, entries 7-8) did not affect the enantiomeric ratio, but resulted in incomplete conversion, which complicated product purification by flash silica column chromatography due to its co-elution with remaining α,β-unsaturated PNP ester **283**.



Entry	Catalyst	mol%	Yield (%)[a]	er[b]
1	(*S*)-Tetramisole **22**	20	77	4:96
2	(*R*)-BTM **23**	20	75	95:5
3	(2*S*,3*R*)-HyperBTM **25**	20	81	96:4
4	(2*S*,3*R*)-HyperBTM **25** /(*R*,*R*)-TUC **312**	10/10	46	96:4
5	(2*S*,3*R*)-HyperBTM **25**/ $Sc(OTf)_3$	20/10	-	-
6	no catalyst	-	no reaction	-
7	(2*S*,3*R*)-HyperBTM **25**	10	76 (20%)[c]	96:4
8	(2*S*,3*R*)-HyperBTM **25**	5	68 (27%)[c]	96:4

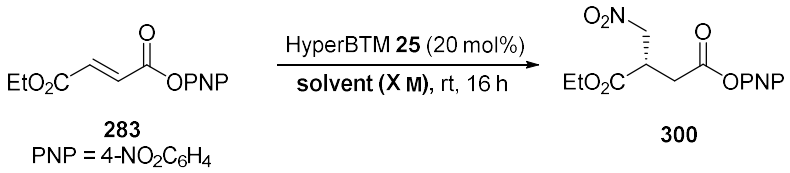
Table 10. Catalyst screening and loading.

[a] Determined by ^{1}H NMR spectroscopic analysis using 1,4-dinitrobenzene as internal standard.
[b] Determined by chiral HPLC analysis. [c] Yields of unreacted ester **283** given in parentheses.

4.6.2 Variation of solvent and concentration

Further studies screened alternative solvents and the effect of reaction concentration (Table 11). Using nitromethane **299** as a reagent (5 equiv.) in THF resulted in drastically decreased yield of product **300** (23%, entry 2). Mixed solvent systems also proved ineffective, with lower yields obtained when using a 1:1 mixture of $MeNO_2$ and either THF or MeCN (entries 3-4). Interestingly, the reactivity was completely shut down in a polar solvent DMF (entry 5). These results indicated that the use of neat nitromethane was crucial for the observed reactivity. Changing the concentration of neat $MeNO_2$ from 0.2 M to 0.4 M and 0.1 M did not give improved yield of PNP ester **300** (67% and 79% respectively, entries 6-7). The use of anhydrous nitromethane (distilled over CaH_2) did not affect the reactivity or selectivity, so commercially available nitromethane was used for further studies. In an attempt to reduce the reaction times,

the reaction was heated at 70 °C, however, no product was formed, with gradual hydrolysis of the starting material as monitored by TLC and ^{1}H NMR (entry 9).



283
PNP = 4-$NO_2C_6H_4$

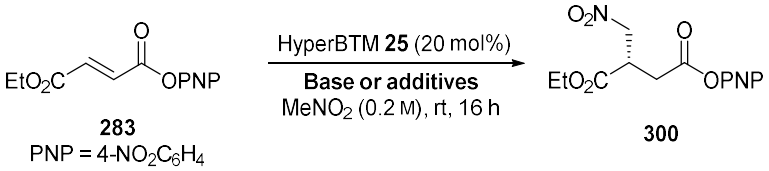
300

Entry	Solvent	Concentration (M)	Yield (%)[a]	er[b]
1	neat	0.2	81	96:4
2	THF[c]	0.4	23	ND
3	$MeNO_2$: THF (1:1)	0.2	50	ND
4	$MeNO_2$: MeCN (1:1)	0.2	43	ND
5	DMF[d]	1.0	-	-
6	neat	0.4	67	96:4
7	neat	0.1	79	96:4
8	neat[e]	0.2	78	96:4
9	neat[f]	0.2	-[g]	-

Table 11. Screening of sovents and reaction concentration.
[a] Determined by ^{1}H NMR spectroscopic analysis using 1,4-dinitrobenzene as internal standard. [b] Determined by chiral HPLC analysis. [c] 5 equiv. $MeNO_2$. [d] 10 equiv. $MeNO_2$. [e] $MeNO_2$ distilled over CaH_2. [f] Reaction mixture was heated to 70 ºC. [g] Starting material decomposition. ND = not determined.

4.6.3 Effect of base and additives

Next, the reaction was investigated in the presence of base and other additives, with both organic and inorganic bases demonstrating a crucial effect on reactivity (Table 12, entries 1-2). Using one equivalent of either ^{i}Pr$_2$NEt or Cs_2CO_3 led to a full conversion of ester **283** to give an alternative product that could not be isolated or unambiguously assigned by analysing the crude reaction mixture with 2D-NMR experiments. According to the previous literature reports, the addition of base could result in a Nef side-reaction, in which the nitroalkane product undergoes base-mediated reaction, leading to formation of aldehydes, ketones or anhydrides.[32] The addition of a hindered base (2,6-lutidine) did not give side-products (entry 3),[15] but afforded nitro-adduct **300** in a slightly lower 63% yield. Tetrabutylammonium-4-nitrophenoxide **273** (Bu_4NOPNP) was previously identified as an efficient promoter within aryloxide-facilitated turnover strategy in ammonium enolate chemistry (Scheme 62[13]), although in this case rapid hydrolysis of starting ester **283** was observed and no product could be isolated from the reaction mixture.



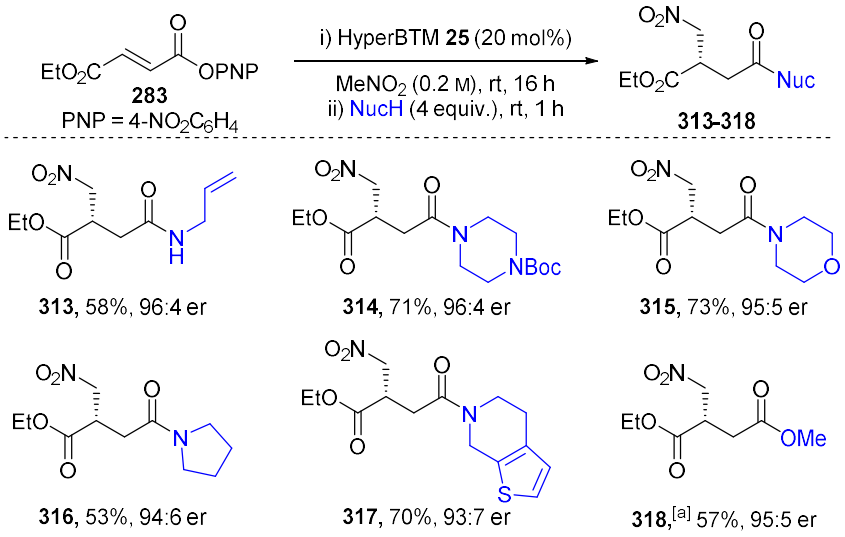
Entry	Base (equiv.)	Additive (equiv.)	Yield (%)[a]
1	$^{i}Pr_2NEt$ (1.0)	-	-[a]
2	Cs_2CO_3 (1.0)	-	-[a]
3	2,6-Lutidine (0.2)	-	63
4	-	Bu_4NOPNP (1.0)	-

Table 12. Effect of base and additives.
[a] Determined by ^{1}H NMR spectroscopic analysis using 1,4-dinitrobenzene as internal standard. [b] Different product formed, could not be isolated.

4.7 Reaction scope and limitations

4.7.1 Variation of nucleophilic quench

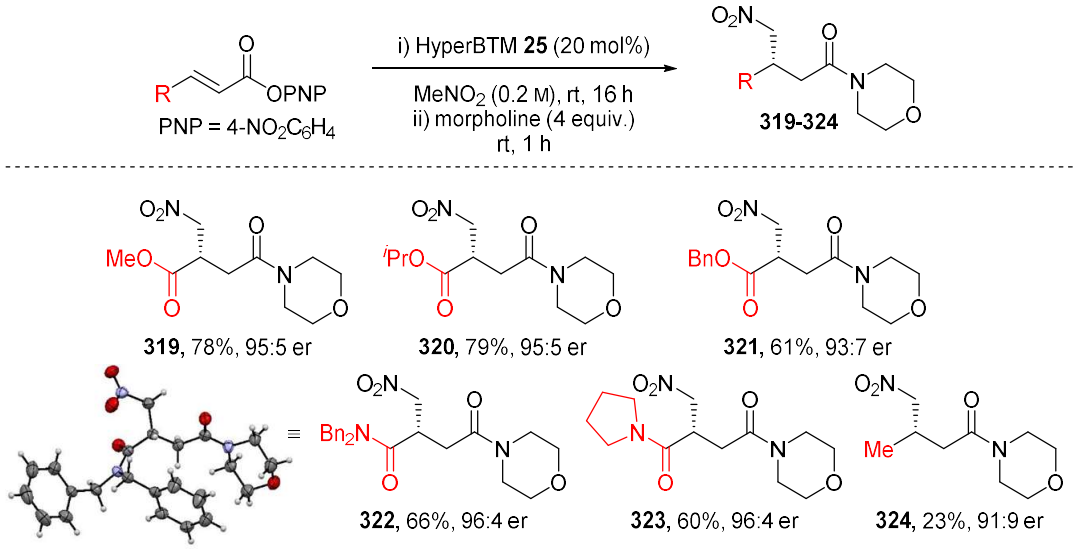
Due to partial hydrolysis of PNP ester products during purification, addition of a suitable nucleophile at the end of the reaction (consumption of starting material **283** monitored by TLC) was used to afford a range of readily isolable γ-nitro functionalised products (Scheme 67). Both primary and secondary amines gave corresponding secondary and tertiary amides **313-317** in good yield (58-73%), while addition of methanol led to formation of methyl ester **318**. Importantly, the resulting products were obtained in high er indicating no significant erosion of enantiopurity in the course of the derivatisation process. Given that the use of morpholine afforded product **315** in highest isolated yield and excellent enantioselectivity, this nucleophile was used to study the scope and limitations of the new methodology.



Scheme 67. Reaction scope: variation of nucleophilic quench.
[a] Excess MeOH and DMAP (20 mol%) used in step ii).

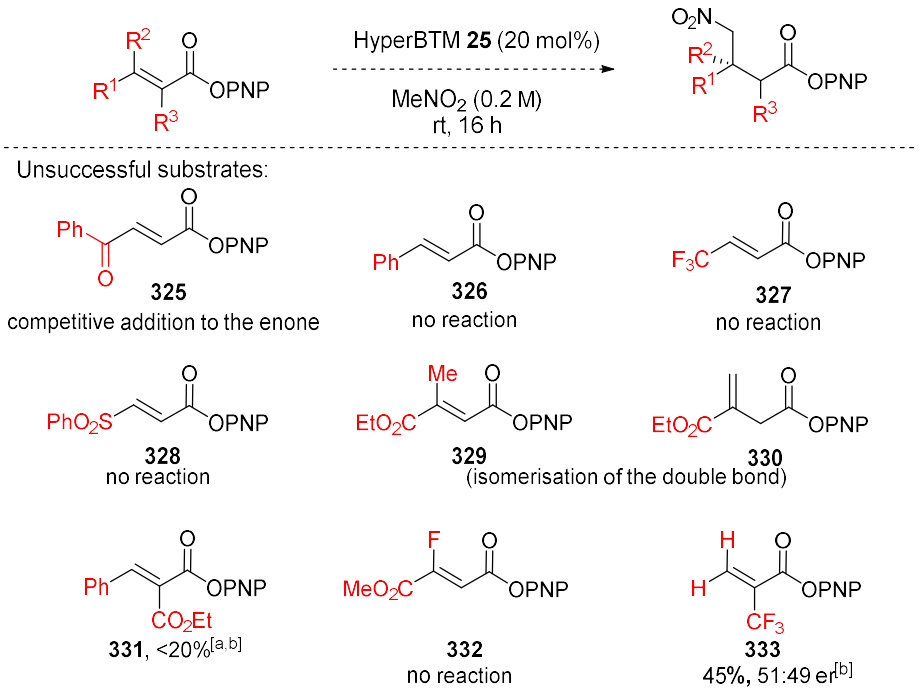
4.7.2 Variation of α,β-unsaturated 4-nitrophenyl ester

To further investigate the reaction scope, variation of the Michael acceptor through substitution at the β-position of the α,β-unsaturated PNP ester was tested (Scheme 68). Methyl and isopropyl esters gave Michael addition products **319**-**320** in high yield and enantioselectivity, whilst a benzyl ester led to formation of **321** in slightly reduced yield but comparable er. The incorporation of dibenzyl- and pyrrolidinyl-substituted amides was also tolerated, giving unsymmetrical succinamide derivatives **322** and **323** in similarly good yield and high levels of enantiocontrol. Pleasingly, a less activated derivative bearing β-alkyl substitution gave product **324** with excellent enantiocontrol, albeit in low yield. The absolute configuration of amide **322** was confirmed by single crystal X-ray analysis, with all other examples assigned by analogy.



Scheme 68. Reaction scope: variation of α,β-unsaturated PNP ester.

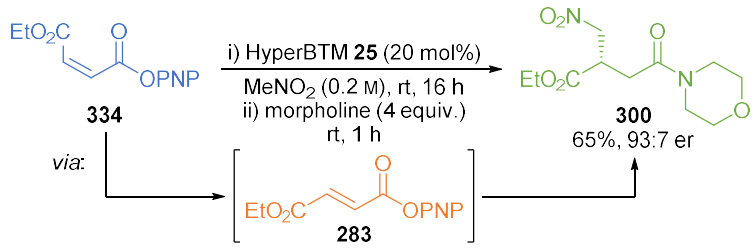
A number of limitations in the Michael acceptor scope were observed, including incompatibility of substrates such as γ-keto ester **325**, which gave a complex mixture of products, possibly resulting from conjugate addition at the α-position to the PNP ester due to the presence of the strongly activated enone moiety (Scheme 69). While β-phenyl, trifluoromethyl and sulfonyl substituents (**326**-**328**) did not show any reactivity, isomerisation of the double bond in PNP ester **329** and formation of ester **330** was observed possibly through deprotonation of the methyl group by the Lewis base catalyst. Malonate derivative **331** was also applied, although its reactivity was sluggish with <20% of the γ-nitro product observed by ^{1}H NMR. β,β-Disubstituted substrate **332** was next tested, however no Michael addition product was obtained with the starting material returned unreacted. α-CF_3-substituted acrylate **333** showed promising reactivity, giving corresponding nitro adduct in 45% yield, however the product was formed as a racemate, with no enantiocontrol observed in the formation of the stereogenic centre at the α-position.



Scheme 69. Reaction scope: unsuccessful substrates. [a] Inseparable *E*/*Z* (1:1) mixture of **330** was applied. [b] Yield and er of the corresponding Michael adduct.

4.7.3 Isomerisation of maleate to fumarate ester

To investigate the stereospecifity of the reaction, maleate PNP ester **334** was synthesised and applied under the standard reaction conditions. In the presence of HyperBTM **25** Michael addition product **300** was obtained in 65% yield but in the same enantiomeric form (93:7) as when fumarate PNP ester **283** (96:4 er) was used. The reason for the observed stereospecifity of the two reactions was further investigated by monitoring reaction progress by ^{1}H NMR spectroscopy. For the Michael addition of nitromethane to maleate **334** (200 mm), catalysed by HyperBTM **25** (40 mm), aliquots were removed, evaporated and analysed by ^{1}H NMR spectroscopy ($CDCl_3$). Rapid isomerisation of maleate **334** to fumarate PNP ester **283** on a faster timescale than formation of the product was observed, which explains formation of the same enantiomer using (*E*)- and (*Z*)-α,β-unsaturated 4-nitrophenyl esters (Scheme 70, Figure 19).



Scheme 70. Michael addition using maleate PNP ester **334**.

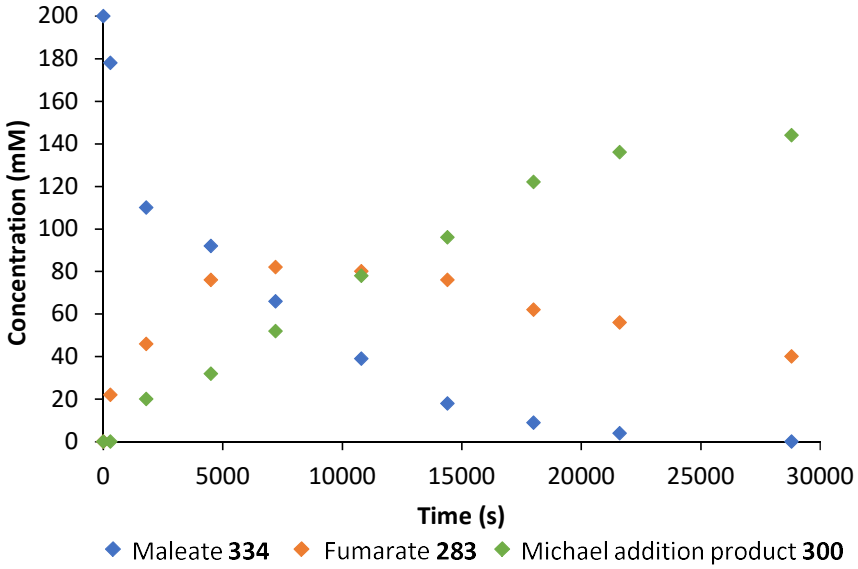


Figure 19. Reaction profile for the Michael addition of nitromethane to maleate ester **334**. Reaction conditions: **334** (200 mM), **25** (40 mM) in $MeNO_2$ (0.6 mL), 1,4-dinitrobenzene (200 mM), rt; Key: = ◆**334**; ◆= **283**; ◆= **300**.

It was hypothesised that this isomerisation process may take place *via* reversible conjugate addition of the aryloxide, HyperBTM **25** or nitromethane **299**. To investigate the origin of this stereochemical outcome, a number of control experiments were conducted in d_6-DMSO (similar polarity to $MeNO_2$) to monitor the appearance of fumarate (Figure 20). Notably, no isomerisation of maleate ester **334** (200 mM) was observed in d_6-DMSO in the absence of any other reagent. The addition of HyperBTM **25** (20 mM) resulted in isomerisation of the maleate to fumarate ester over time. This indicates that the isomerisation process is not caused by reversible addition of $MeNO_2$. To investigate if 4-nitrophenoxide, released following catalyst acylation, could facilitate this isomerisation,[35] the addition of tetrabutylammonium 4-nitrophenoxide (Bu_4NOPNP) **273** (200 mM) (in the absence of HyperBTM **25**) was tested. This also resulted in isomerisation, consistent with this hypothesis. The addition of a combination of Bu_4NOPNP **273** (200 mM) and HyperBTM **25** (20 mM) resulted in an increased rate of isomerisation relative to the use of either reagent in isolation. This could occur if an α,β-unsaturated acyl ammonium intermediate is formed under these conditions by addition of HyperBTM **25** to maleate ester **334**, and the rate of reversible Michael addition-β-elimination of 4-nitrophenoxide with the α,β-unsaturated acyl ammonium intermediate is faster than Michael addition-β-elimination of 4-nitrophenoxide with

maleate ester **334** alone. Based on these findings, it is safe to assume that 4-nitrophenoxide is responsible for the isomerisation, however the feasibility of HyperBTM **25** to also undergo reversible Michael addition-β-elimination cannot be ruled out.

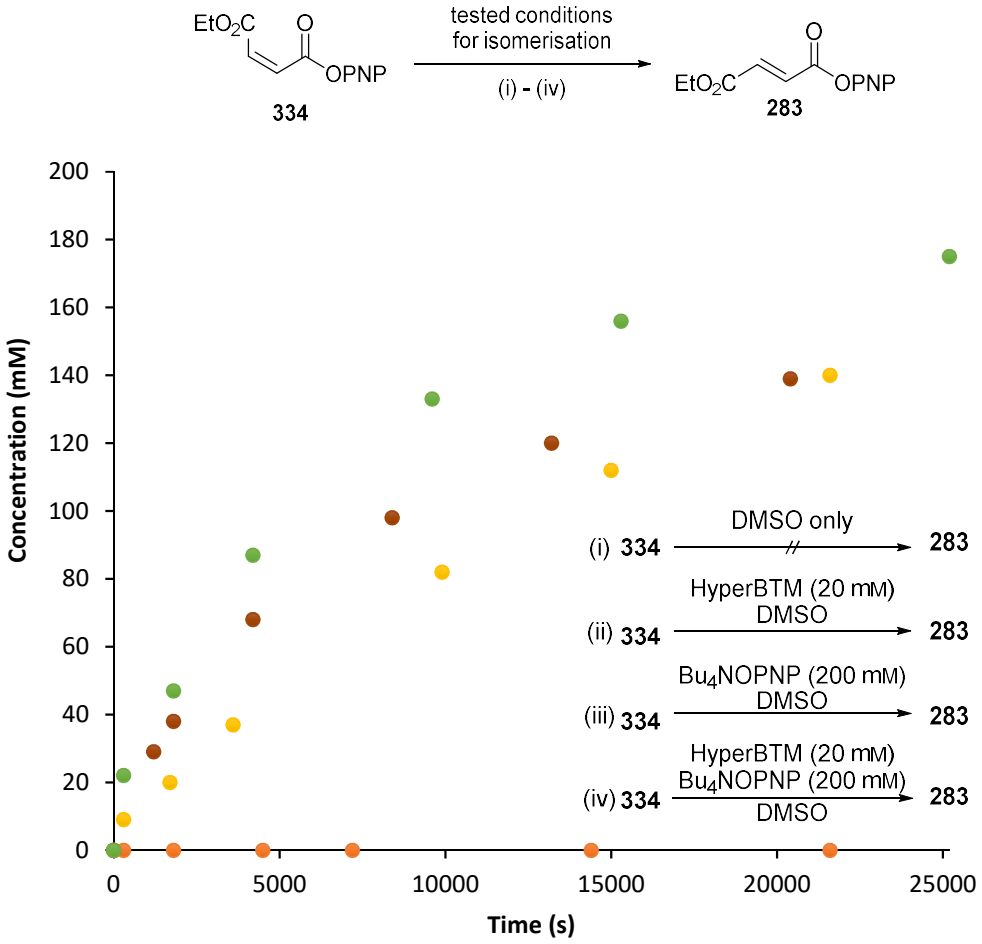
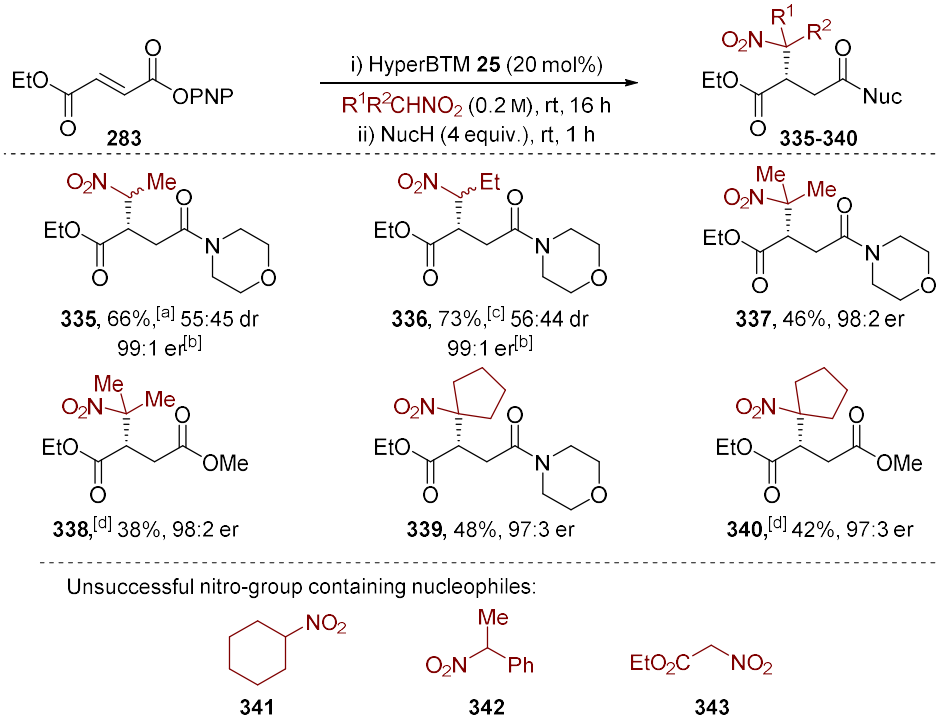


Figure 20. Reaction profiles for control reactions in d_6-DMSO. Key for the reactions: = • (i); • (ii); • (iii); • (iv).

4.7.4 Nitroalkane variation

Having explored the use of various Michael acceptors, attention was next turned to screening alternative nitroalkanes and subsequent derivatisation of the resulting PNP esters (Scheme 71). Commercially available nitroethane and 1-nitropropane proved suitable nucleophiles for this Michael addition process giving amide products **335**-**336** following reaction with morpholine. Although these products were obtained with low diastereocontrol, both stereoisomers were formed with excellent enantiocontrol (99:1 er). While nitroethane derivative **335** was isolated as an inseparable mixture of diastereoisomers, both stereoisomers of 1-nitropropane-derived addition product **336** were successfully separated and characterised. Although relative configuration of diastereoisomers was not identified unambiguously, it was assumed two diastereoisomers differ in configuration at $CHNO_2$ centre. Pleasingly, more sterically-demanding

disubstituted nitroalkanes 2-nitropropane and nitrocyclopentane were also tolerated giving corresponding products **337-340** as amides and methyl esters in moderate yield (38-48%) but excellent enantioselectivity (98:2-97:3 er). When nitrocyclohexane **341** was used, PNP ester **283** was returned unreacted. Nitroalkane-derived substrates **342-343** with adjacent aromatic or ester groups were also not competent nucleophiles under the neat reaction conditions, showing a complex mixture in the crude ^{1}H NMR spectrum. A current limitation of this methodology is that only simple nitroalkanes are tolerated under the reaction conditions.



Scheme 71. Reaction scope: nitroalkane variation.
[a] Isolated as a mixture of diastereoisomers. [b] er of both diastereoisomers. [c] Diastereoisomers separated by flash silica column chromatography [41% (major); 32% (minor)]. [d] Excess MeOH and DMAP (20 mol%) used in step ii).

4.8 Product derivatisation

Having explored the scope of the novel enantioselective Michael addition process, application of the resulting products through the synthesis of enantioenriched pyrrolidones was envisaged. The pyrrolidone (2-oxopyrrolidine) family of chemicals is a cyclic analogue of γ-aminobutyric acid (GABA), which plays a key role as a neurotransmitter in the mammalian central nervous system.[33a] GABA derivatives have therefore been of interest to chemists and pharmacologists, in particular structural analogues that show nootropic effects, which aid enhancement of learning and memory. Due to their similar psychopharmacological actions e.g., sedation, analgesia, or motor and behavioural changes, cyclic GABA analogues are commonly referred to as a separate

class of drugs called racetams (Figure 21). Despite recent advances in general synthetic methods, access to cyclic γ-amino acids in enantiomerically pure form remains challenging.[33b]

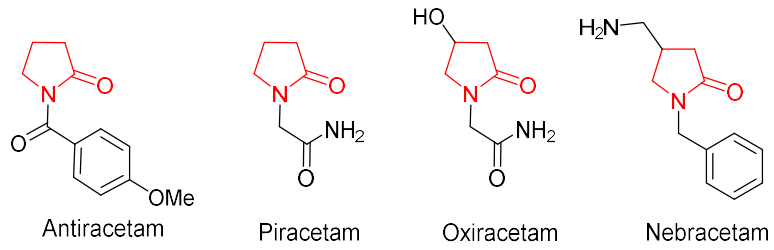
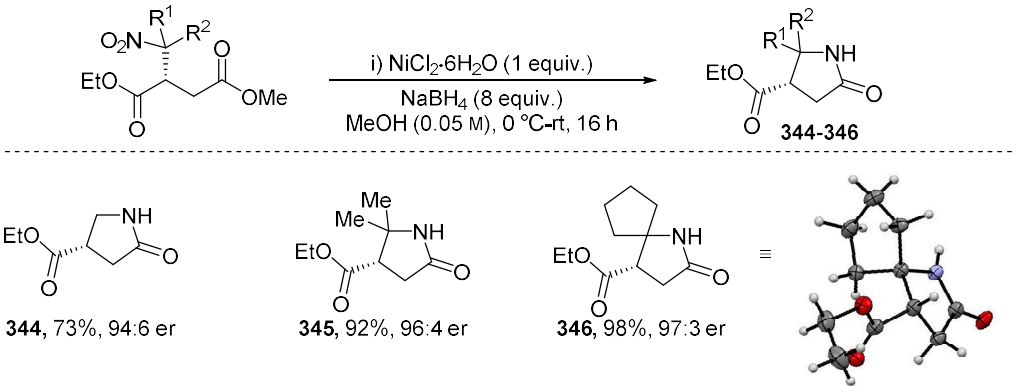


Figure 21. Structure of pyrrolidone-based drugs, or racetams.

Given the importance of cyclic γ-aminobutyric acid derivatives, their synthesis using the new methodology was envisaged. According to the literature, the nitro group can be reduced with nickel(II) chloride hexahydrate and sodium borohydride in the presence of an ester functionality with concomitant cyclisation to a cyclic amide.[34] Pleasingly, this reduction-cyclisation sequence of γ-nitro methyl esters **318**, **338** and **340** proceeded smoothly with no loss in enantiopurity to give pyrrolidinone derivatives **344-346** in excellent yield (73-98%) and er (Scheme 72). The structure of **346** was unambiguously confirmed by X-ray crystallographic analysis, with other cyclic pyrrolidones in this series assigned by analogy.



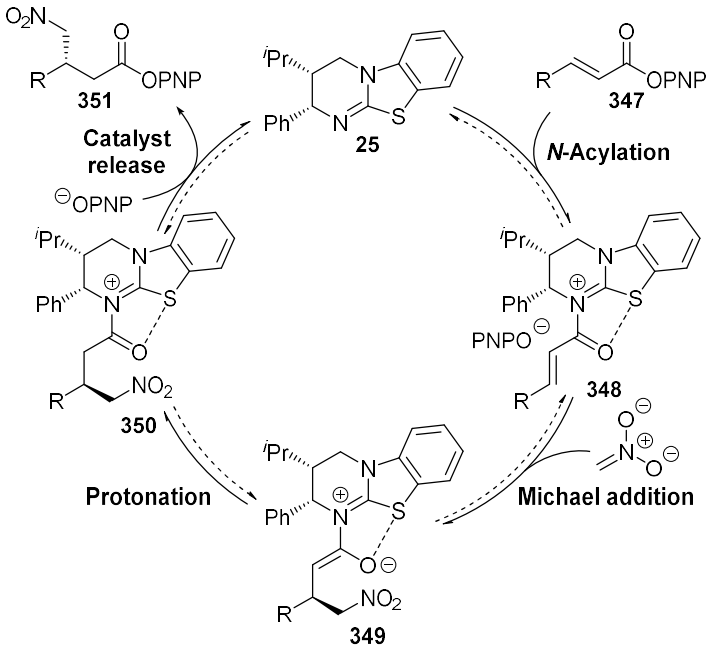
Scheme 72. Product derivatisation: synthesis of enantioenriched pyrrolidones.

4.9 Mechanistic investigations

4.9.1 Elucidation of the catalytic cycle

Having evaluated the scope and limitations of the new methodology, in-depth understanding of the first aryloxide-facilitated catalyst turnover mechanism within α,β-unsaturated acyl ammonium catalysis was desired. Based on the mechanisms of previously developed isothiourea-catalysed reactions,[35] a possible catalytic cycle is proposed (Scheme 73), which begins with *N*-acylation of HyperBTM **25** by α,β-unsaturated PNP ester **347** to form α,β-unsaturated isothiouronium **348**. Michael addition of nitronate to intermediate **349**, followed by protonation,

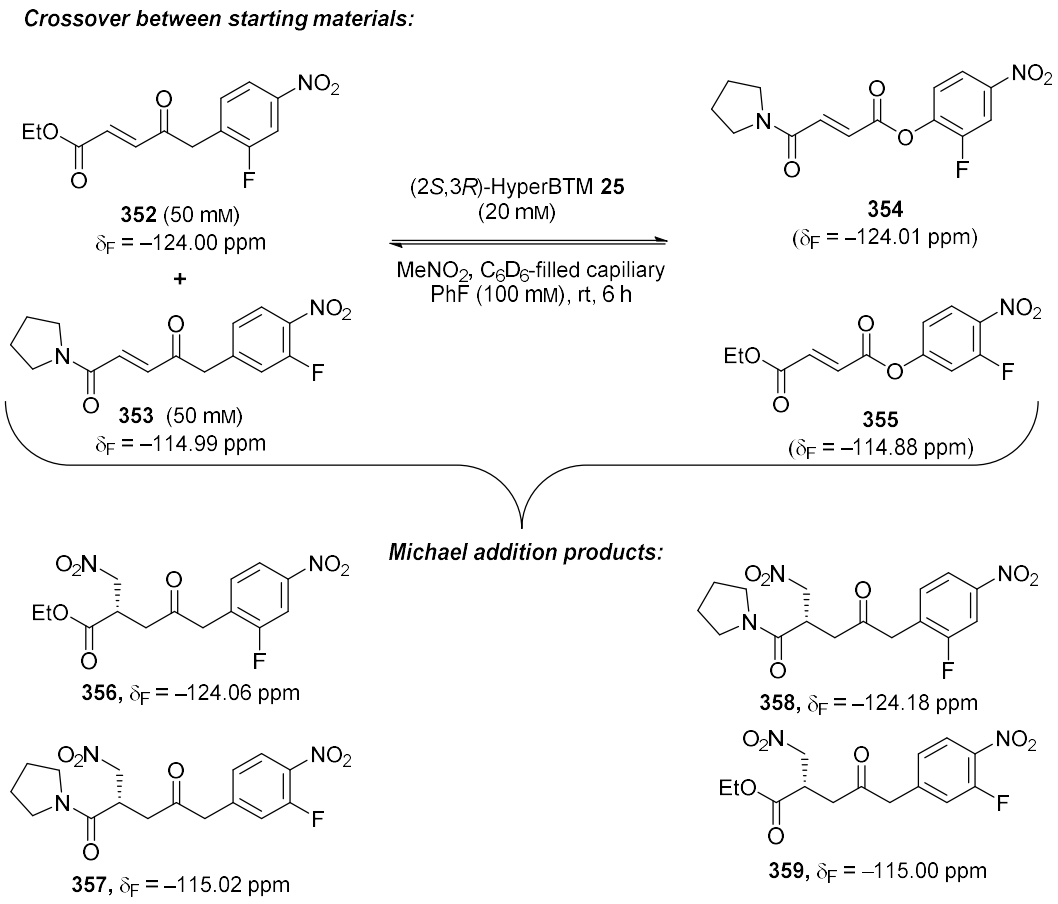
affords acyl ammonium **350**. Nucleophilic attack of the released 4-nitrophenoxide into acyl ammonium **350** facilitates catalyst turnover to afford Michael addition product **351** and regenerate HyperBTM **25**. We wished to investigate several critical aspects of the proposed catalytic cycle, including (i) the reversibility of each reaction step; (ii) the identification of the proposed reaction intermediates and assessment of their catalytic activity; (iii) the reaction orders of all the components.



Scheme 73. Proposed catalytic cycle.

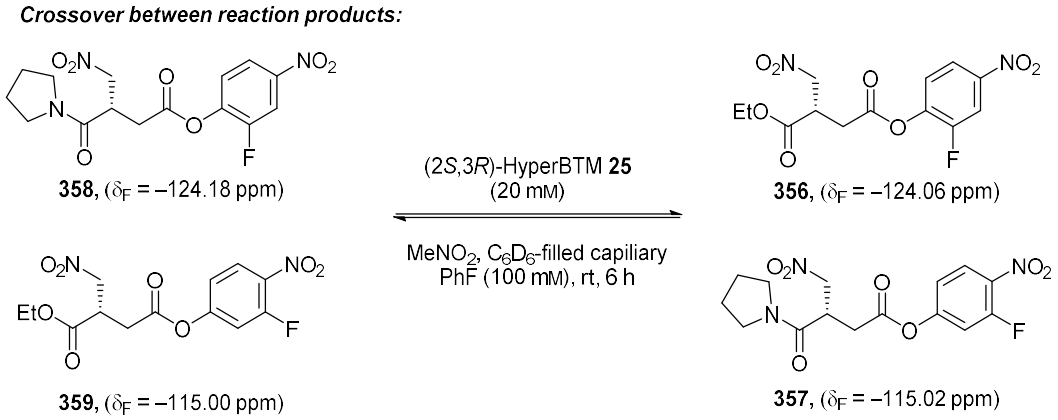
4.9.2 Crossover studies

A series of crossover experiments were performed to allow for a better understanding of the reaction mechanism, in particular by investigating the reversibility of the primary catalytic steps. For these reactions α,β-unsaturated esters **352** and **353** bearing two distinct PNP ester groups (2-fluoro and 3-fluoro) and two distinct β-substituents (amide and ester) were chosen in order to allow differentiation of the species based on their chemical shifts by ^{19}F NMR analysis. Treatment of the mixture of both esters (50:50 ratio) under catalytic conditions was monitored by *in situ* $^{19}F\{^{1}H\}$ NMR spectroscopy. By the time the first spectrum was collected (317 s), 18% conversion of the starting esters was obtained. All four possible α,β-unsaturated esters **352-355** (ratio: **352**:**353**:**354**:**355** = 21:28:29:22) and all four possible Michael addition products **356-359** (ratio: **356**:**357**:**358**:**359** = 44:6:6:44) were present (Scheme 74). In the absence of HyperBTM **25** no exchange was observed, which indicates very fast equilibration between the fluorinated 4-nitrophenyl esters, possibly due to reversible acylation of HyperBTM **25**. However, at this stage it was unclear, whether four Michael addition products form through reaction of each α,β-unsaturated ester with $MeNO_2$ or as a result of the crossover between the products.



Scheme 74. Crossover experiments using esters **352** and **353** monitored by *in situ* $^{19}F\{^{1}H\}$ NMR spectroscopy.

When the catalyst was added to a mixture of Michael addition products, a similarly fast equilibration was obtained, with equilibrium reached within 300 s (Scheme 75). This demonstrates that the catalyst can undergo reversible acylation with the products. Interestingly, no formation of starting materials was observed suggesting that the Michael addition step must be either irreversible or the reaction equilibrium strongly shifted to formation of post-Michael addition acyl ammonium **350**.

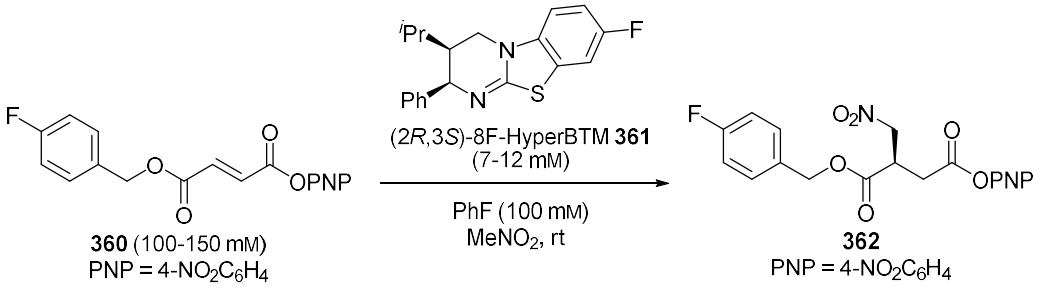


Scheme 75. Crossover reactions using products **358** and **359** monitored by *in situ* $^{19}F\{^{1}H\}$ NMR spectroscopy.

4.9.3 Kinetic studies

4.9.3.1 Model reaction

To identify possible reaction intermediates and side-products as well as study reaction kinetics of the process, the reaction was monitored by quantitative *in situ* $^{19}F\{^{1}H\}$ NMR spectroscopy. This analysis was achieved by using ^{19}F-labeled PNP ester **360** and (2*R*,3*S*)-8F-HyperBTM **361**[36] in $MeNO_2$ using PhF as internal standard and a C_6D_6-filled capillary reference (Scheme 76).



Scheme 76. Standard reaction components for the kinetic studies.

4.9.3.2 Starting material and product

The chemical shift of starting PNP-ester **360** (δ_F = −114.43) and Michael addition product **362** (δ_F = −114.39) were assigned according to the chemical shift of independently isolated compounds measured in $MeNO_2$ with C_6D_6-filled capillary and referenced to PhF (−114.05 ppm).

4.9.3.3 Initial observations and catalyst deactivation

Initial analysis of kinetic data revealed a substantial reduction in reaction rate over the course of the reaction. During the reaction, the ^{19}F chemical shift (δ_F) of the (2*R*,3*S*)-8F-HyperBTM catalyst **361** underwent a significant downfield drift (δ_F = −122.68 → ~−119.6 ppm), indicating a possible deactivation of the catalyst through protonation (Figure 22). Based on the chemical shift of the independently synthesised sample of **361**·HCl (δ_F = −116.62 ppm), it was proposed this drift arised from an equilibrating mixture of the protonated and free catalyst, with the downfield drift due to increasing concentration of the protonated form over the reaction course.

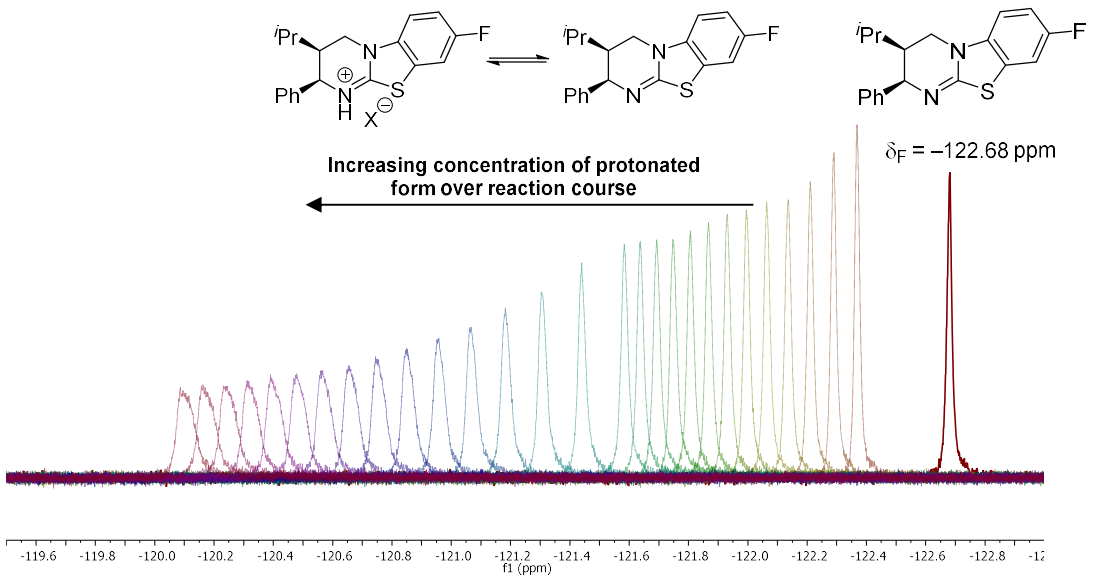


Figure 22. Typical superimposed reaction profile (−123.00-−119.50 ppm range); all identified species labelled.

The proportion of freebase isothiourea **361** in the reaction could in theory be calculated as a function of the observed chemical shift.[37] The ^{19}F chemical shift of **361**·HCl in $MeNO_2$ however was found to be concentration dependant. Upon incrementally increasing the concentration of **361**·HCl, an upfield shift was observed, which may be caused due to increasing ionic strength of the solvent.[38] The ^{19}F chemical shift ($\delta_{[\mathbf{361}\cdot HCl]}$) could be approximately described as a function of concentration of **361**·HCl by the equation 1 (Figure 23):

$$\delta_{\mathbf{361}\cdot HCl} = -0.073 \times \ln([\mathbf{361}\cdot HCl]) - 116.62 \qquad (1)$$

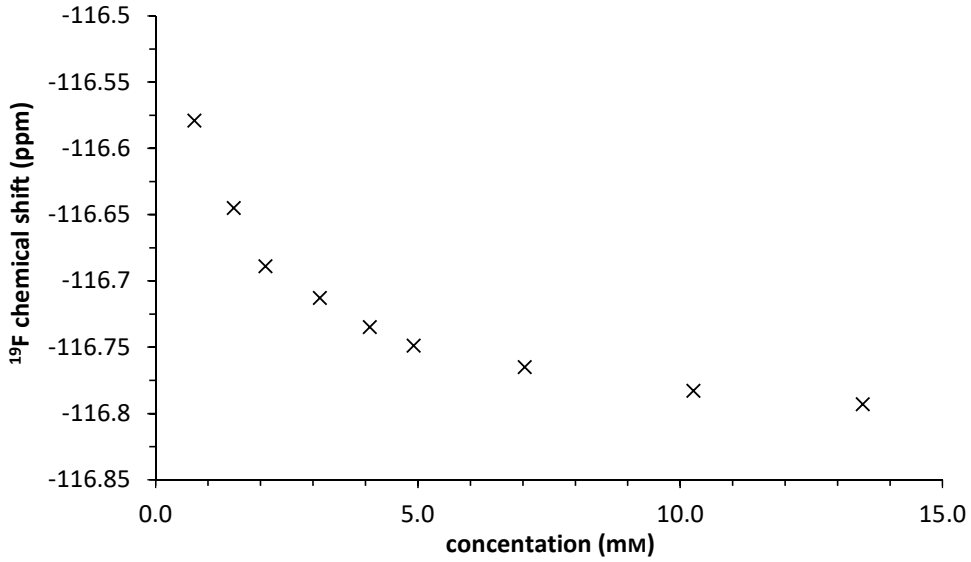


Figure 23. Plot showing ^{19}F chemical shift of **361**·HCl as a function of [**361**·HCl]; Key: × = **361**·HCl.

The concentration of the 'free' catalyst in the reaction mixture could therefore be calculated as a function of chemical shift according to equation (2):

$$[\mathbf{361}]_{free} = [\mathbf{361}]_{total} \times (\delta_{\mathbf{361}measured} - \delta_{\mathbf{361}\cdot HCl}) / (\delta_{\mathbf{361}free} - \delta_{\mathbf{361}\cdot HCl}) \quad (2)$$

where: $[\mathbf{361}]_{total}$ and $\delta_{\mathbf{361}measured}$ are measured variables; $\delta_{\mathbf{361}free}$ is a constant (− 122.68) and

$$\delta_{\mathbf{361}\cdot HCl} \approx -0.073 \times \ln([\mathbf{361}\cdot HCl]) - 116.62$$

It was found however that inputting an approximation of $\delta_{\mathbf{361}\cdot HCl} = -116.62$ into equation 2 gave very similar calculated data for $[\mathbf{361}]_{free}$ to using equation 1 to estimate $\delta_{\mathbf{361}\cdot HCl}$, and therefore this approximation was used throughout the calculations for simplicity.

4.9.3.4 Acyl ammonium intermediates

While monitoring the reaction, two distinct intermediates with significantly downfield shifts (δ_F = −111.79 and −111.97 ppm) were observed in low concentrations (≤ 0.4 mM). Based on reference to fluorinated BTM-derived acyl ammonium intermediate (δ_F = −113.40), previously identified within the Smith group,[9] it was proposed these may represent *N*-acylated isothiourea derivatives, namely α,β-unsaturated acyl ammonium **363** and post-Michael addition acyl ammonium **364** intermediates respectively (Figure 24). Over the reaction course the signal assigned to α,β-unsaturated acyl ammonium **363** decreased in intensity, whilst the intensity of the signal assigned to post-Michael addition acyl ammonium **364** intermediate was increased. This behaviour could be used as preliminary evidence for the assignment of the detected intermediates.

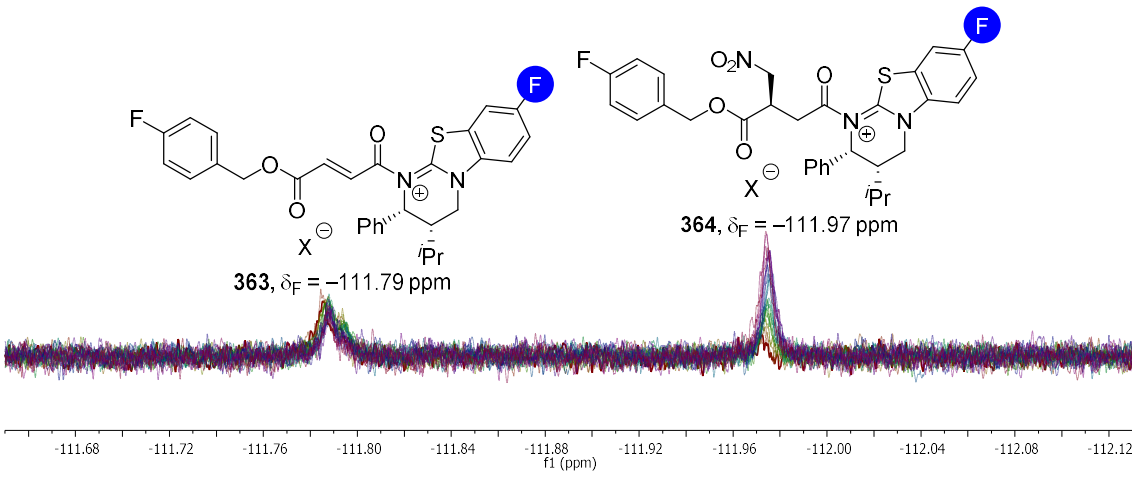
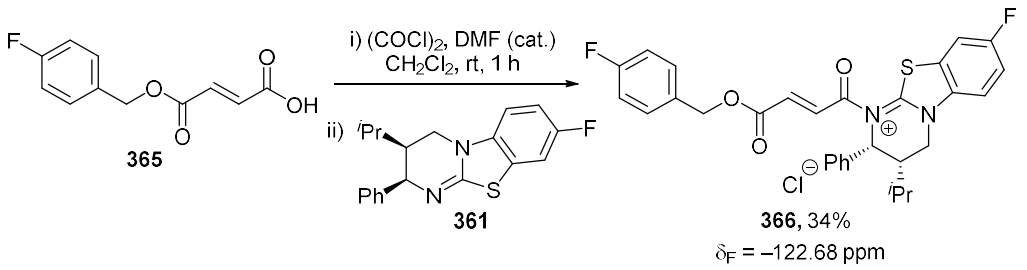


Figure 24. Typical superimposed reaction profile (−112.13-−111.65 ppm); proposed acyl ammonium species labelled.

To provide further evidence for this assignment, α,β-unsaturated acyl isothiouronium **363** was synthesised independently and isolated as a chloride salt (where X = Cl, −111.81 ppm) (Scheme 77).[39a]



Scheme 77. Synthesis of α,β-unsaturated acyl isothiouronium chloride salt **366**.

In keeping with **361**·HCl, it was found that the chemical shift of the fluorine on the isothiouronium ion part of **366** was concentration dependant. Upon incrementally increasing the concentration of **366**, an upfield shift was observed, the magnitude of which was approximately proportional to the concentration of **366**. The addition of Bu_4NCl (0 → 50 mM) to a sample of **366** (~ 1 mM) in $MeNO_2$ resulted in a similar upfield shift upon increasing [Bu_4NCl], suggesting the chemical shift of the isothiouronium fluorine may be particularly sensitive to the ionic strength of the solvent, as previously observed whilst analysing the chemical shift of **361**·HCl sample.

To test isolated α,β-unsaturated acyl ammonium chloride **366** as a precatalyst, the compound was dissolved in nitromethane, however, no formation of Michael addition product observed. Upon addition of Bu_4NOPNP rapid formation of Michael addition product **362** and α,β-unsaturated PNP ester **360**, along with release of 8F-HyperBTM **361**, was observed. These findings suggest that phenoxide acts as the base in the reaction to generate the active nitronate species which can undergo conjugate addition.

Next, isolated α,β-unsaturated acyl ammonium chloride **366** (20 mM) was added to a reaction in progress (after ~30 min). The signals assigned to α,β-unsaturated acyl ammonium **363** and post-Michael addition acyl ammonium **364** were both enhanced and underwent an upfield shift. Over the remaining reaction course both signals decreased in intensity (in particular, the signal assigned to α,β-unsaturated acyl ammonium **363**) and underwent a gradual downfield shift (Figure 25). This behaviour is consistent with the chemical shift of both acyl ammonium intermediates being concentration dependant. The persistence of both signals in this experiment indicates significantly higher concentrations of both species compared to usual reaction conditions, which can be rationalised due to suppression of catalyst turnover considering the 20 mM deficiency in 4-nitrophenoxide relative to acyl ammonium species.

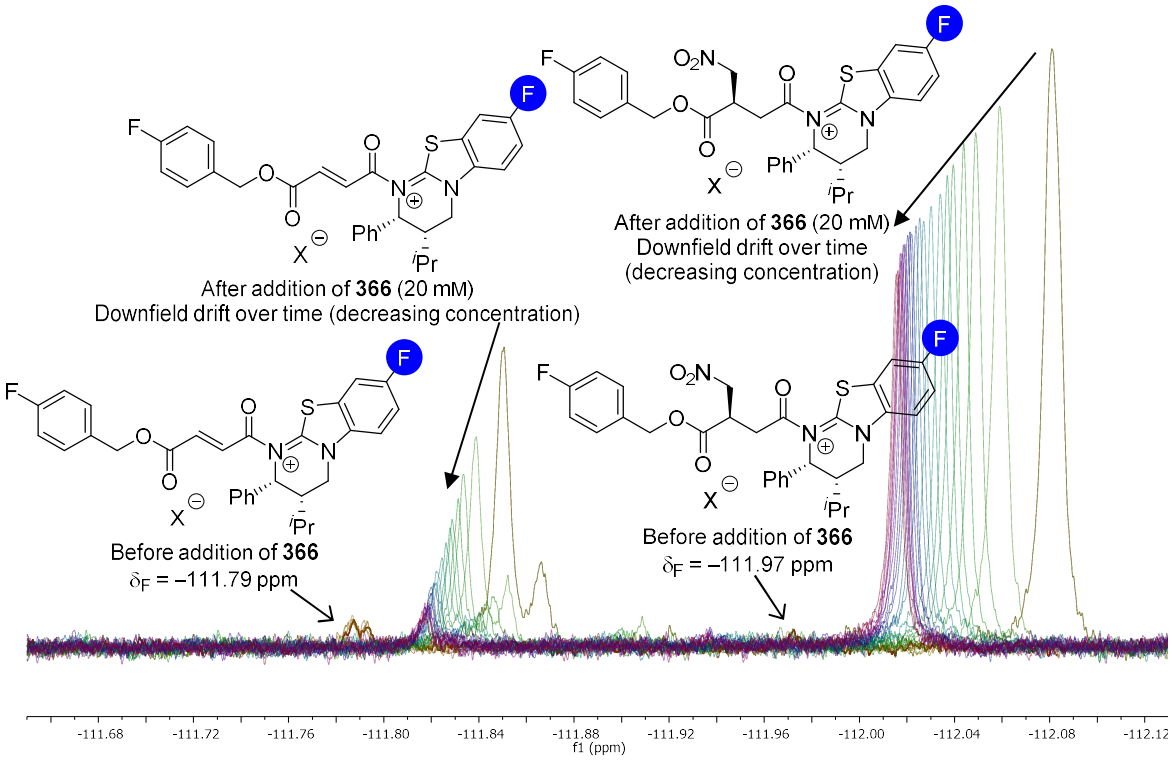
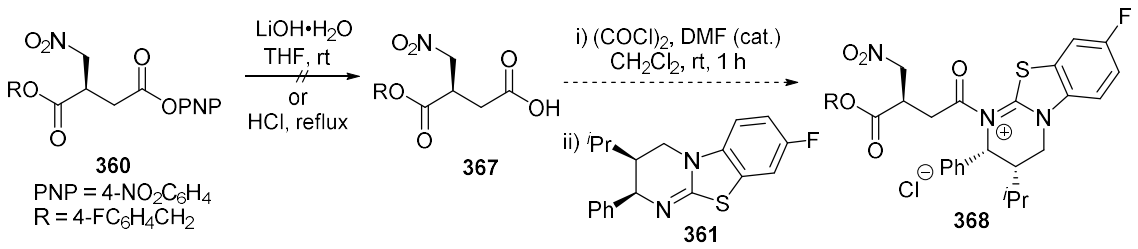


Figure 25. Addition of acyl ammonium **366** (20 mM) to reaction in progress at ~30 min. Reaction profile superimposed (−112.13-−111.65 ppm); all identified species labelled.

To probe the post-Michael addition intermediate in catalysis, independent synthesis of its chloride salt **368** was also attempted. However, isolation of acid **367** after hydrolysis of PNP ester **360** under acidic or basic conditions was unsuccessful with the complex mixture of decomposition products observed in the crude mixture by ^{1}H NMR spectroscopy (Scheme 78).



Scheme 78. Attempted synthesis of post-Michael addition acyl isothiouronium chloride salt **368**.

To provide support for the assignment of the post-Michael addition intermediate, 8F-HyperBTM **361** was added to a solution of Michael addition product **362** in $MeNO_2$ [C_6D_6-filled capillary and PhF internal reference (−114.05 ppm)]. This resulted in appearance of a peak at −111.97 ppm matching the chemical shift of the proposed post-Michael addition acyl isothiouronium **364** observed under reaction conditions.

4.9.3.5 Hydrolysis products

Given the susceptibility of PNP esters to hydrolysis, a series of experiments were undertaken to identify possible products of hydrolysis and account for their quantity in subsequent kinetic analysis. First, the hydrolysis products of α,β-unsaturated PNP ester **360** were investigated. This PNP ester is derived from (*E*)-4-((4-fluorobenzyl)oxy)-4-oxobut-2-enoic acid **365** with a chemical shift of −114.54 ppm. To provide insight into the chemical shift of the corresponding carboxylate, the effect of the base was investigated. Addition of $^{i}Pr_2NEt$ (0.5–2.0 equiv.) to a solution of α,β-unsaturated acid **365** resulted in an upfield shift, tending towards −115.03 ppm (Figure 26). Under catalytic conditions two peaks were observed in this range which underwent downfield drifts over time (Figure 27). Based on the relative chemical shifts of the α,β-unsaturated PNP ester **360** (more upfield) and Michael addition product **362** (more downfield), the higher intensity and more upfield signal was assigned to an equilibrating mixture of the carboxylic acid and carboxylate of the starting α,β-unsaturated PNP ester **360**. The lower intensity and more downfield signal was assigned to an equilibrating mixture of the carboxylic acid **367** and carboxylate of post-Michael addition PNP ester **362**. A signal in this range was also observed upon addition of 8F-HyperBTM to a solution of post-Michael addition PNP ester **362** in $MeNO_2$. As previously stated, the carboxylic acid **367** of post-Michael addition intermediate **364** could not be obtained, therefore this assignment is not unambiguous.

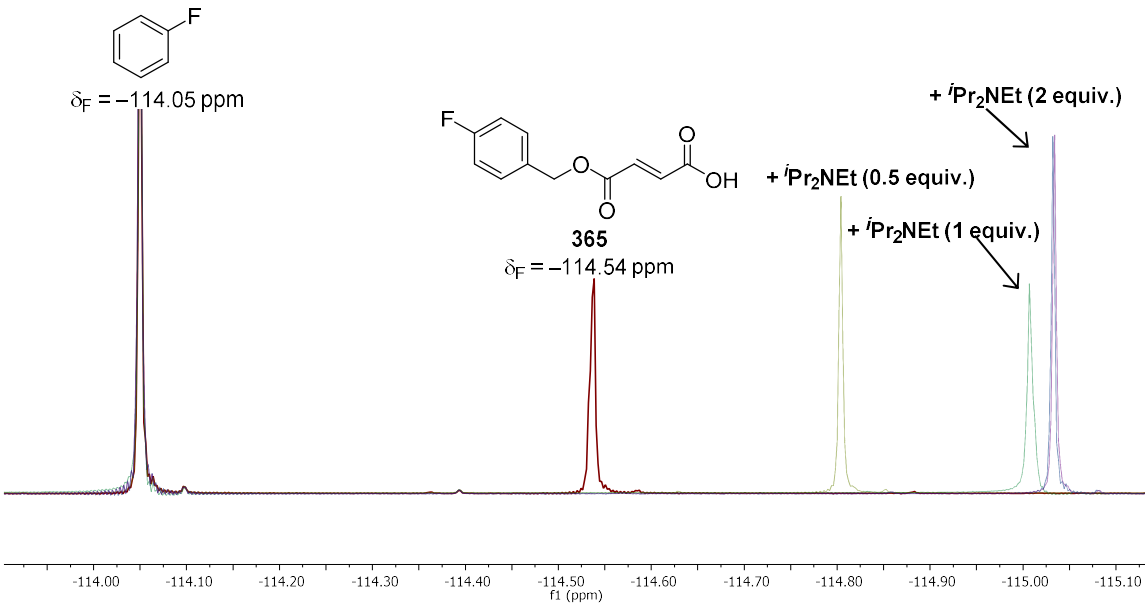


Figure 26. Addition of $^{i}Pr_2NEt$ (0.5-2 equiv.) to (*E*)-4-((4-fluorobenzyl)oxy)-4-oxobut-2-enoic acid **365** in $MeNO_2$. NMR spectra superimposed (−115.13-−113.91 ppm); all identified species labelled.

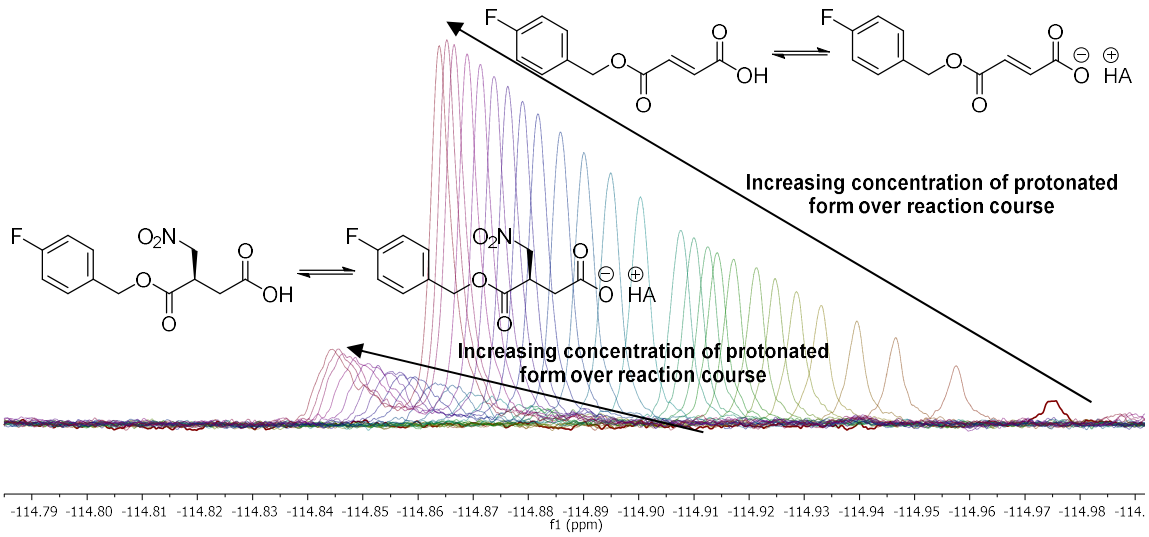


Figure 27. Typical superimposed reaction profile (−114.99-−114.78 ppm range); all identified species labelled.

4.9.3.6 Typical reaction profile

Having identified the potential reaction species, a typical kinetic profile of the model reaction (Scheme 79) shows gradual consumption of PNP-ester **360** (●), formation of Michael addition product **362** (▲), the proportion of freebase isothiourea catalyst **361** (×) calculated using equation 2, hydrolysis products of the starting PNP ester (◆) and product **362** (●) as well as low concentrations (≤ 0.4 mm) of the proposed acyl isothiouronium species **363** (●) and **364** (▲) (Figure 28).

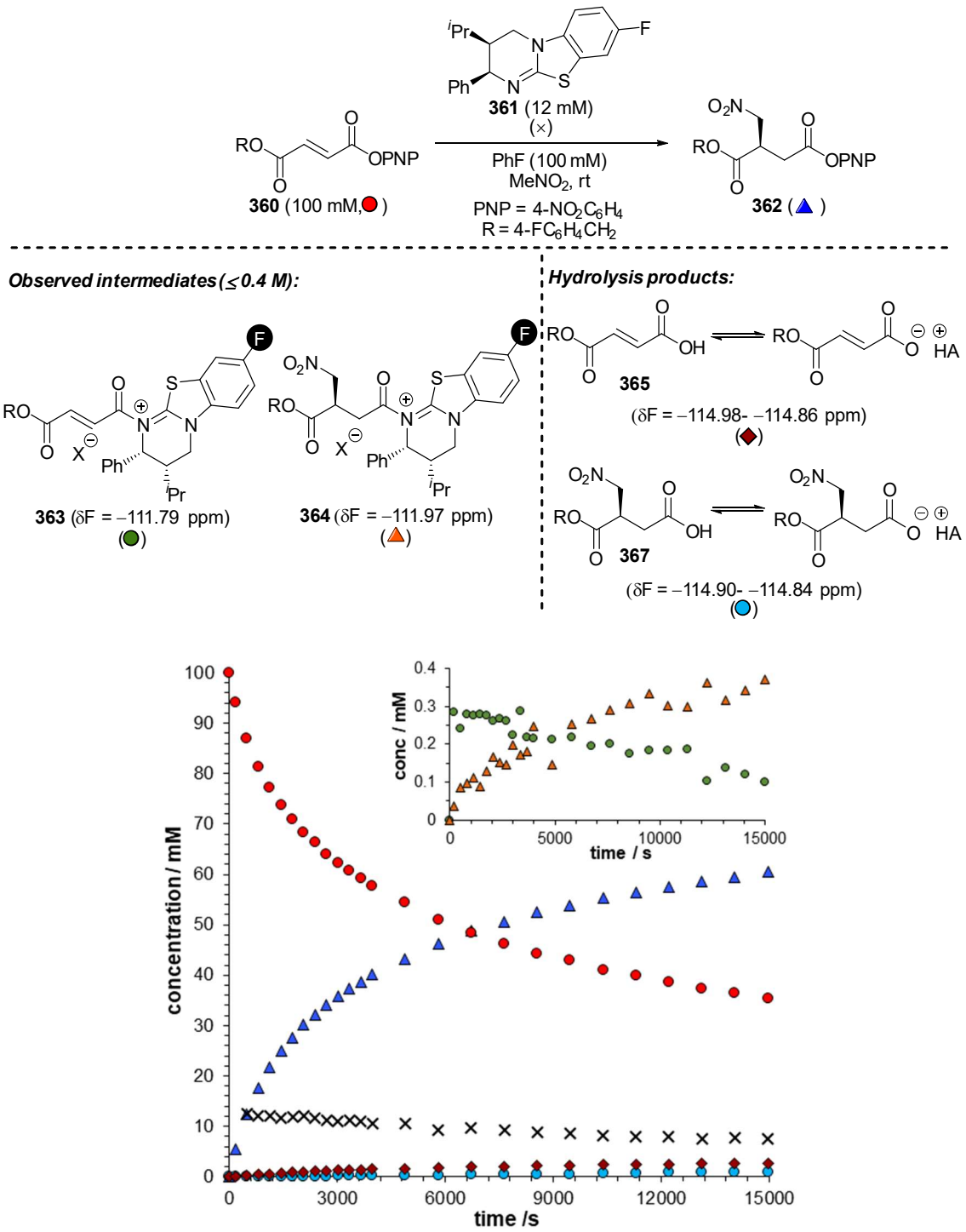


Figure 28. Typical reaction profile: conditions: **360** (100 mM), **361** (12 mM) in $MeNO_2$ (0.6 mL), PhF (100 mM), C_6D_6 capillary reference, rt; Key: ● = **360**; × = freebase **361** (calculated); ◆ = **365**; ● = **367**; ▲ = **362**; inset: ● = **363**; ▲ = **364**.

4.9.3.7 Determination of reaction orders using variable time normalisation graphical analysis

Next, the determination of reaction orders with respect to each component was attempted using an established method for quantifying the temporal concentration of reaction components. The complex catalyst speciation between four observable species, including freebase and protonated 8F-HyperBTM as well as isothiouronium intermediates **363**-**364**, in addition to slow hydrolysis of starting material over the reaction course indicated that kinetic analysis may be challenging. However, as the temporal concentrations of each component were quantifiable, the innovative variable time normalisation kinetic analysis method (VTNKA) reported recently by Burés was considered to be applicable.[40] The method is based on normalisation of the time axis to take into account the changing concentration of each reaction component. As many variable components can be added into the normalised time axis as required, with each component raised to a different index. The following equation (3) is used for the normalised time axis, where $[A]_i$, $[B]_i$ and $[C]_i$ are the concentrations of the reaction components at the certain time point; $[A]_{i-1}$, $[B]_{i-1}$ and $[C]_{i-1}$ are the concentrations of the reaction components at the time point before (i); t_i and t_{i-1} are the certain time points, at which the concentrations were measured; α, β, γ are the indices that represent the reaction orders of each component.

$$\sum_{i=1}^{n} \left(\frac{[A]_i + [A]_{i-1}}{2}\right)^{\alpha} \left(\frac{[B]_i + [B]_{i-1}}{2}\right)^{\beta} \left(\frac{[C]_i + [C]_{i-1}}{2}\right)^{\gamma} (t_i - t_{i-1}) \qquad (3)$$

To apply this method, a series of reactions were performed using different starting concentrations of each reaction component. The reaction order with respect to each component was then determined by systematically changing the indices in the normalised time axis, to obtain a plot in which all reaction profiles overlay and are linear.

Kinetic analysis was performed for three reactions with different starting concentrations of α,β-unsaturated ester **360** (100–150 mM) and (2*R*,3*S*)-8F-HyperBTM **361** (7–12 mM), with the concentration of $MeNO_2$ assumed to remain constant (pseudo-zero order in $MeNO_2$). A plot of concentration of product **362** against a normalised time axis of $\Sigma[\mathbf{360}]^{\alpha}[\mathbf{361}]^{\beta}\Delta t$ (where α and β represent the respective reaction orders of each component) allowed graphical interrogation of the kinetic profiles. Systematically varying α and β provided optimal overlay for α = 1.0 and β = 1.0, indicating the reaction is first order in both ester substrate and catalyst (Figure 29).

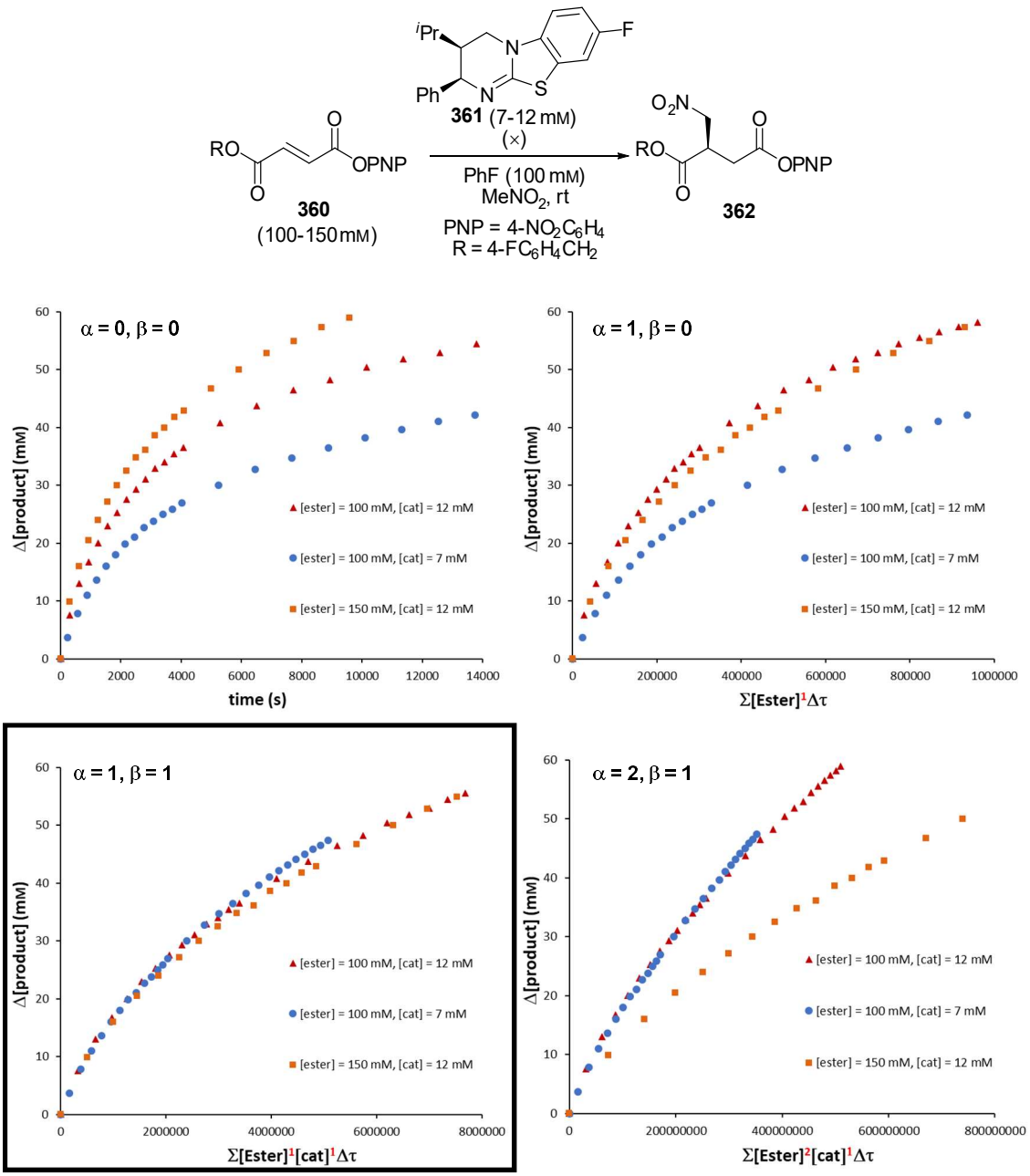


Figure 29. VTNKA: x-axis normalisation for [**360**] and [**361**].

Despite good overlay, the curvature of the plot suggested an additional reaction variable had been omitted from the analysis. Further studies showed that addition of product **362** (10 mM) at the start of the reaction resulted in rate retardation, consistent with product inhibition. As identified in crossover studies, product **362** can readily undergo competitive acylation by HyperBTM **361**, which decreases concentration of the free catalyst in the reaction mixture. Indeed, incorporation of $[\mathbf{362}]^{\gamma}$ into the normalised time axis ($\Sigma[\mathbf{360}]^{\alpha}[\mathbf{361}]^{\beta}[\mathbf{362}]^{\gamma}\Delta t$) resulted in good overlay and linearity at an arbitrary value of $\gamma = -0.5$ (Figure 30).

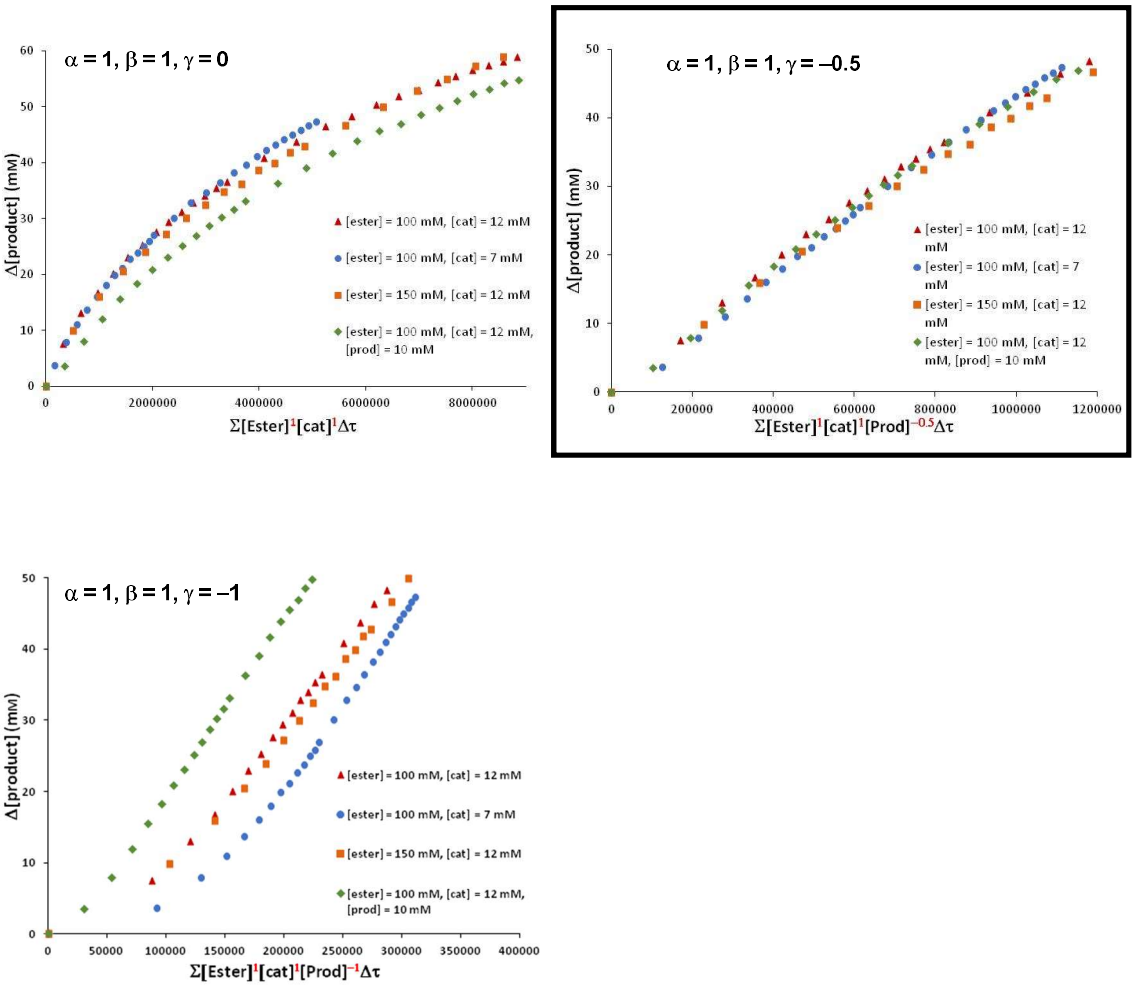
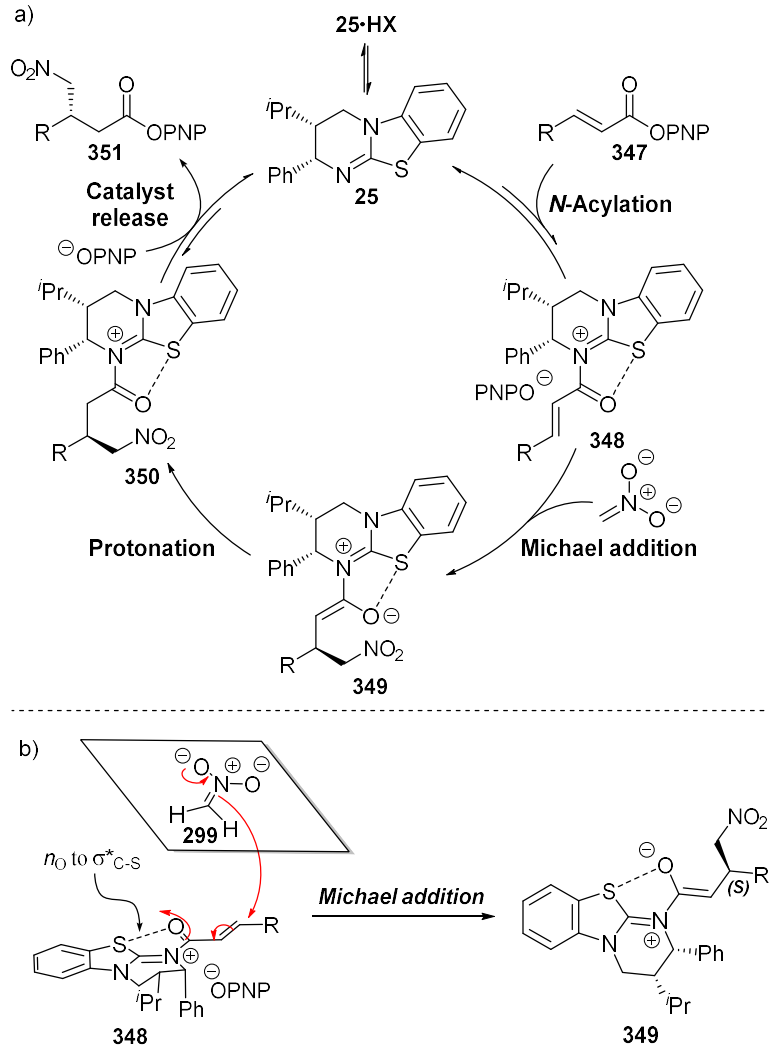


Figure 30. Normalisation plots for [**360**], [**361**] and [**362**].

4.9.4 Proposed mechanism

Having determined the reversibility of key catalytic steps, the structure of reaction intermediates, and orders of each reaction component, the following catalytic cycle is postulated (Scheme 79). Based on kinetic studies, HyperBTM **25** speciates between four observable species, mainly an equilibrating mixture of protonated and freebase isothiourea along with small amount of α,β-unsaturated acyl ammonium **363** and post-Michael addition acyl ammonium **364** intermediates. At the beginning of the reaction free HyperBTM **25** is the predominant resting state of the catalyst, however the proportion of protonated HyperBTM increases over the course of the reaction with a roughly 1:1 ratio of protonated species **25**·HCl and free catalyst present after 6 h (Figure 22). The process begins with rapid and reversible catalyst acylation by α,β-unsaturated PNP ester **347** to form α,β-unsaturated acyl isothiouronium **348**. The results of the crossover studies suggest that the equilibrium position favours the free catalyst **25** and α,β-unsaturated PNP ester **347**. The subsequent Michael addition of nitronate to α,β-unsaturated acyl isothiouronium **348** is proposed to be an irreversible process, due to the crossover experiment between reaction products (Scheme

75), which suggests formation of α,β-unsaturated esters **352-355** was not observed. In addition, whilst reaction of (2*R*,3*S*)-8F-HyperBTM **361** with Michael addition product **362** gave post-Michael addition acyl isothiouronium **364**, the formation of α,β-unsaturated acyl isothiouronium **363** or PNP ester **360** was not observed. Both of these experiments indicate that one or both steps in the catalytic cycle between **348** and **350** are irreversible. The 4-nitrophenoxide counterion released upon acylation is proposed to facilitate deprotonation of nitromethane,[41] whilst protonation of isothiouronium enolate **349** may be facilitated by either nitromethane or 4-nitrophenol. Finally, nucleophilic attack of 4-nitrophenoxide into acyl ammonium **350** facilitates catalyst turnover to afford Michael addition product **351** and regenerate HyperBTM **25**. Supported by kinetic studies and the rapid crossover between ^{19}F-labeled α,β-unsaturated PNP esters **353** and **353** relative to the overall rate of reaction, Michael addition of nitronate to α,β-unsaturated acyl isothiouronium **348** could be the turnover rate-limiting step. Previous experimental and computational studies strongly suggest that α,β-unsaturated acyl isothiouronium **348** adopts an s-*cis* conformation, with a *syn*-coplanar non-covalent 1,5-S···O interaction between the acyl O and catalyst S providing a conformational lock.[10] As a result, the configuration of the products obtained in this process can be rationalised by Michael addition of the nitronate to α,β-unsaturated acyl isothiouronium **348** *anti*- to the stereodirecting phenyl group of HyperBTM **25** generating an (*S*)-configured stereocentre at *C*(3)-carbon.



Scheme 79. a) Proposed catalytic cycle; b) Stereochemical rationale.

4.10 Conclusions and outlook

In this Chapter, the development of a new general concept for α,β-unsaturated acyl ammonium catalysis was described. Previous literature studies have used α,β-unsaturated acyl ammonium intermediates in formal cycloadditions, enantioselective Michael addition-annulation reactions, and complex cascade processes. The common feature of these methodologies is the inherent requirement of the Michael donor component to contain at least two distinct nucleophilic functionalities to (i) undergo conjugate addition to the α,β-unsaturated acyl ammonium intermediate, and (ii) enable turnover of the Lewis base catalyst. In the methodology developed here, the release of 4-nitrophenoxide from an α,β-unsaturated 4-nitrophenyl ester substrate was exploited to facilitate catalyst turnover. The new method was applied for the enantioselective isothiourea-catalysed Michael addition of nitroalkanes to (*E*)-α,β-unsaturated 4-nitrophenyl esters in generally good yield and with excellent enantioselectivity (27 examples, up to 79% yield,

99:1 er). The effect of changing the olefin configuration was also studied by using a (*Z*)-α,β-unsaturated 4-nitrophenyl ester, which gave the product in the same enantiomeric form as the corresponding (*E*)-configured PNP ester. Control reactions revealed rapid *in situ* isomerisation of (*Z*)- to (*E*)-α,β-unsaturated PNP ester, which was proposed to take place following reversible Michael addition-β-elimination of 4-nitrophenoxide. Although, a range of highly enantioenriched γ-nitro derivatives were accessed, the substrate scope was limited to ester or amide β-substituted PNP esters and generally simple nitroalkanes used as solvents. Product derivatisation gave straightforward access to stereodefined pyrrolidinones in good yield and excellent er. Detailed mechanistic investigations involved kinetic analysis using *in situ* $^{19}F\{^{1}H\}$ NMR spectroscopy, the use of ^{19}F-labelled catalyst and substrates, as well as crossover experiments. These studies allowed identification of reaction intermediates and the catalyst resting state. Furthermore, product inhibition and catalyst deactivation by protonation were identified under the reaction conditions. A variable time normalisation graphical analysis method, reported recently by Burés, was utilised to elucidate reaction orders of each component, providing deeper insight into the complex kinetics and reaction mechanism of the new process. Identified limitations in the scope of the described nitro-Michael addition provide an opportunity for improvements of the new method to allow the use of a wider range of Michael acceptors and more complex nitronates. Finally, the developed methodology opens an opportunity to explore the nucleophiles that require alternative catalyst turnover, which will broaden the current scope of α,β-unsaturated acyl ammonium catalysis.

4.11 References

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5 Silyl nitronates in enantioselective α,β-unsaturated acyl ammonium catalysis

5.1 Structure, properties and synthesis of silyl nitronates

O-Silyl nitronates are a masked activated form of an alkyl nitronate, bearing a silyl protecting group at one of the oxygens and derived from a corresponding nitroalkane. (Figure 31).[1,2]

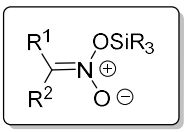


Figure 31. Structure of silyl nitronates.

Although thermally stable, silyl nitronates are very sensitive to hydrolysis and solvolysis, reacting readily with water, alcohols, acids, primary and secondary amines.[2] In general, the stability of most common silyl ethers (Figure 32) depends on the steric bulk of the silyl group and increases as indicated:[3]

- Towards hydrolysis and acidic media:

TMS < TES < TBS < TIPS < TBDPS

- Towards basic media:

TMS < TES < TBS ~ TBDPS < TIPS

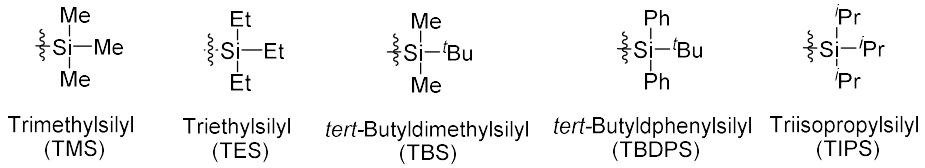
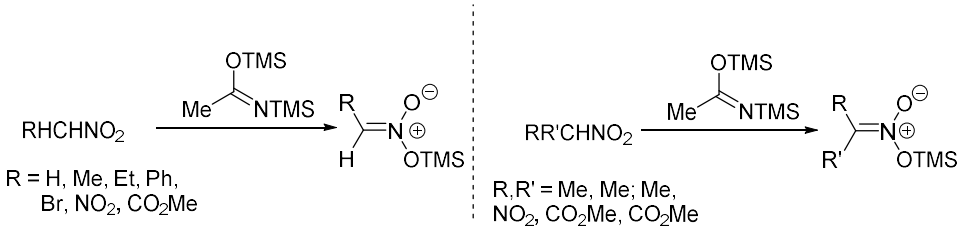


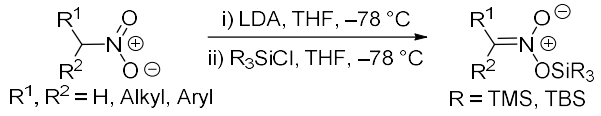
Figure 32. Common silyl ether protective groups.

Silyl nitronates were first prepared by Tartakovskii in 1974 (Scheme 80).[4] Their method of synthesis was to heat the appropriate nitroalkane in *N*,*O*-bis (trimethylsilyl)acetamide with close to quantitative yields obtained, however product purification proved problematic due to unavoidable contamination by excess silylating agent and acetamide by-products. Although only a limited range of compounds was described, both primary and secondary nitroalkanes could be employed.



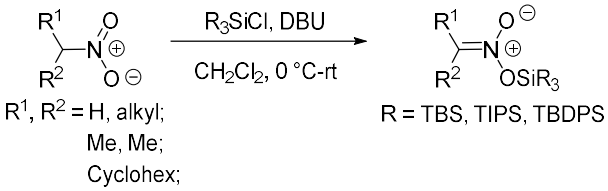
Scheme 80. Initial strategy for the preparation of silyl nitronates.

A more simple and efficient synthesis affording a variety of silylated nitronates in quantitative conversion was reported later involving low temperature deprotonation of primary or secondary nitroalkanes with a solution of lithium diisopropylamide in THF and trapping the resulting anion with a chlorotrialkylsilane. As an additional advantage, both trimethylsilyl esters and the more stable (*tert*-butyl)dimethylsilyl esters could be equally well prepared. (Scheme 81).[1]



Scheme 81. Synthesis of silyl nitronates from trialkylsilylchloride.

In an alternative and operationally simple approach, organic bases can be applied to generate silyl nitronates, as reported by Torssell and Zeuthen[5] using triethylamine in benzene; and Palomo[6] and MacMillan[7] using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane. Applying this final method, a range of trialkylsilyl groups could be introduced when using both primary and more hindered secondary nitroalkanes (Scheme 82).



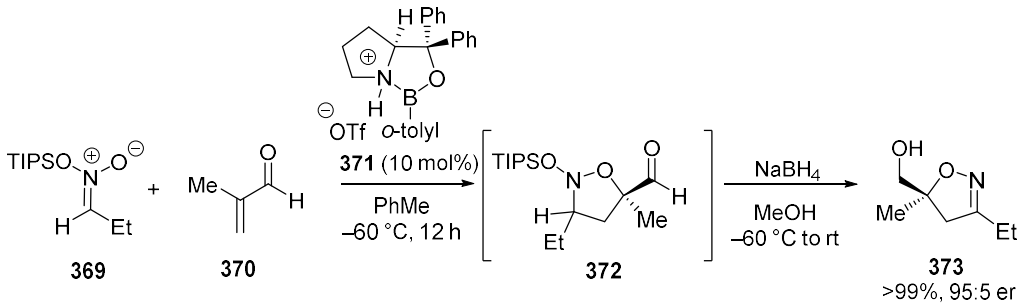
Scheme 82. Improved synthesis of silyl nitronates.

5.2 Silyl nitronates in enantioselective catalysis

5.2.1 Cycloaddition reactions

Silyl nitronates can be used as a surrogate for nitrile oxides in 1,3-dipolar cycloadditions, benefiting from their improved stability in comparison with nitrile oxides.[8] In his pioneering work, Torssell reported the reactions of silyl nitronates with various alkenes under thermal conditions with the corresponding isoxazolines obtained in racemic form.[5] Asymmetric syntheses of isoxazolines from silyl nitronates have been scarcely reported, in which a chiral auxiliary or a chiral dipolarophile was used to induce asymmetry.[9] In 2015, Jiao reported the first catalytic enantioselective synthesis of isoxazolines,[10] using triisopropylsilyl (TIPS) nitronate **369** derived from 1-nitropropane, and methacrolein **370** in the presence of Corey's chiral oxazaborolidine **371** activated by TfOH. Due to poor stability, the resulting cycloadduct **372** was reduced with $NaBH_4$ to generate isoxazoline product **373** in >99% yield and 95:5 er, in which triisopropylsilanol had been eliminated from the proposed *N*-silyloxy isoxazolidine intermediate

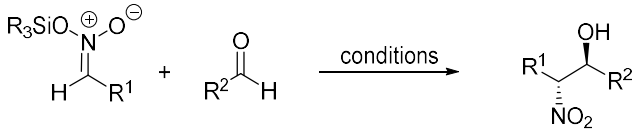
(Scheme 83). The protocol was successfully extended to the use of silyl nitronates bearing an α-aryl group.[11]



Scheme 83. Asymmetric 1,3-dipolar cycloaddition of TIPS-nitronate **350** with methacrolein.

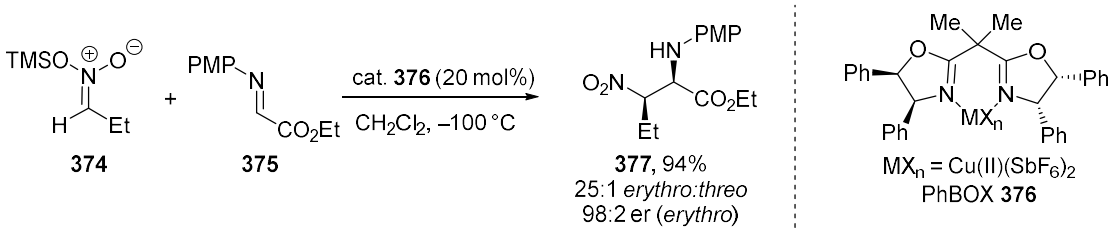
5.2.2 Henry reaction

β-Hydroxynitroalkanes, prepared by the Henry (nitroaldol) reaction, are valuable synthetic intermediates in organic synthesis.[12] Catalytic enantioselective Henry reactions of nitromethane with aldehydes have been developed by Shibasaki[13] and Trost[14] to provide access to optically-active β-nitro-α-hydroxy esters and β-amino-α-hydroxy esters. One drawback of these catalytic enantioselective Henry reactions is that the majority of examples are restricted to using nitromethane as the nucleophile. An alternative approach to the Henry reaction is the application of more reactive nucleophiles, such as silyl nitronates (Scheme 84).



Scheme 84. General Henry reaction using silyl nitronates.

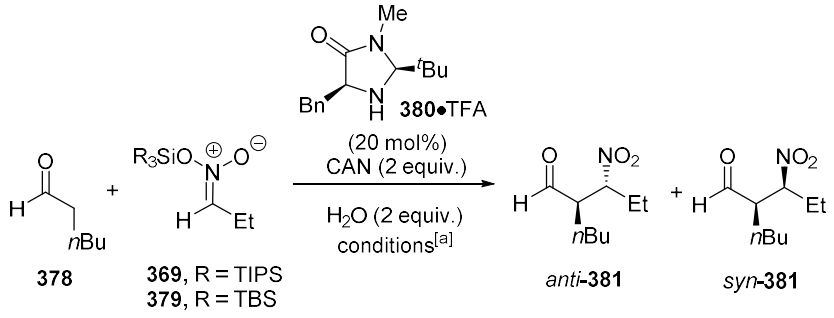
Building on work from Seebach[15] and Paece,[16] Jørgensen developed the first enantioselective Aza-Henry reaction as a novel approach to β-nitro-α-amino acid and α,β-diamino acid derivatives utilising silyl nitronates with imines in the presence of a chiral Lewis acid (Scheme 85).[17] The reaction of trimethylsilyl nitronate **374** with *N*-(4-methoxyphenyl) (PMP)-α-imino ester **375** catalysed by chiral PhBOX (*N*,*N*-chelating bisoxazoline) copper complex **376** gave the corresponding *N*-protected β-nitro-α-amino ester **377** in 95% yield with excellent dr (25:1 *erythro:threo*) and 98:2 er for the major diastereoisomer. This protocol was extended to the diastereo- and enantioselective Henry reaction with aromatic aldehydes with minimal eprimerisation of the generated nitroaldol products reported.[18]



Scheme 85. Enantioselective aza-Henry reaction using silyl nitronates.

5.2.3 Enantioselective nitroalkylation

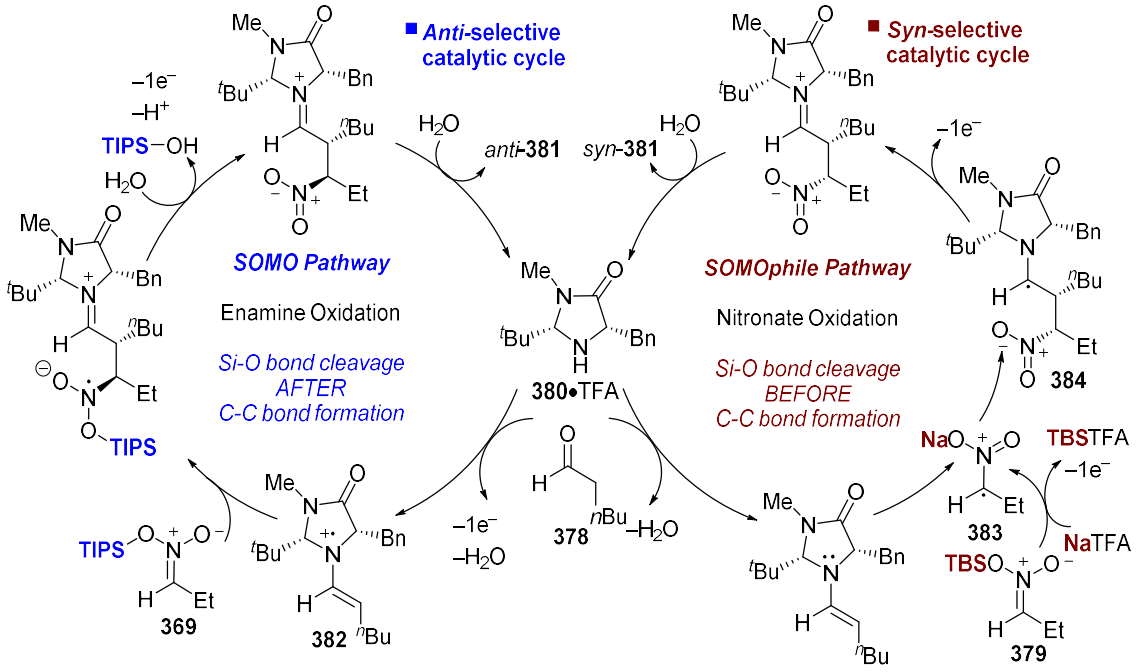
MacMillan and co-workers demonstrated the successful application of silyl-protected nitronates in oxidative SOMO catalysis that allowed rapid and generic access to β-aminocarbonyl moieties.[19] In this work, a transiently-generated three-π-electron radical cation enamine can undergo enantioselective bond formation with silyl nitronates as π-SOMOphiles to furnish a range of α-functionalised aldehyde adducts.[20] Enantioselective nitroalkylation was accomplished using hexanal **378**, imidazolidinone catalyst **380**, ceric ammonium nitrate (CAN) as the stoichiometric oxidant, and silyl nitronates **369** and **379** in the presence of a mildly basic additive NaO_2CCF_3 or $NaHCO_3$ (Scheme 86). An interesting observation was the apparent relationship between the diastereocontrol of the reaction and the inherent lability of the silyl nitronate employed. For example, relatively labile silyl species such as TBS nitronate **379** preferentially provided the *syn*-diastereomer **381** while TIPS nitronate **369** provided good *anti*-diastereocontrol.



SiR_3	yield (%)	er[b]	*anti:syn*
TIPS	84	96:4	5:1
TBS	78	97:3	1:7

Scheme 86. Asymmetric aldehyde nitroalkylation. [a] For TIPS nitronates: $NaHCO_3$ (2 equiv.), THF (0.13 M), –40°C, 24–48 h. For TBS nitronates: NaO_2CCF_3 (3 equiv.), acetone (0.13 M), –40 or –50 °C, 4–16 h. [b] The er of the major isomer.

To rationalise the observed change in diastereoselectivity as a function of the silyl group, the operation of two distinct reaction pathways was proposed that led to the observed *syn*- and *anti*-selectivities (Scheme 87).



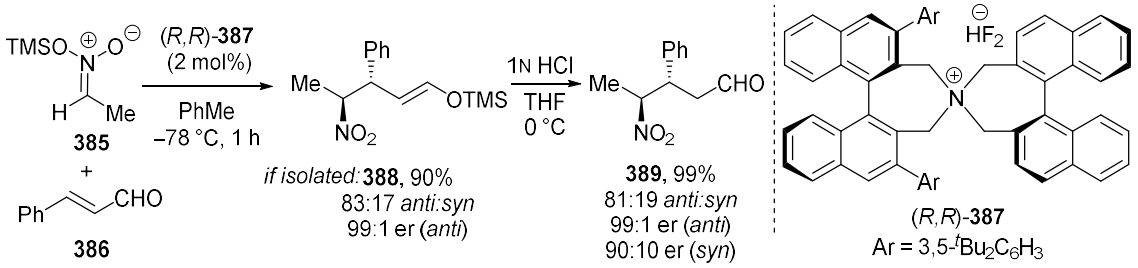
Scheme 87. Proposed divergence of mechanistic pathways.

It was postulated that for the *anti*-selective coupling, the primary pathway involves enamine oxidation and coupling of the resulting radical cation **382** with TIPS nitronate **369** (Scheme 87, SOMO pathway). In contrast, for *syn*-selective reactions, it is believed that the TBS nitronate is desilylated to form a sodium nitronate **383**, which undergoes rapid oxidation to generate nitronate radical cation **384**. In this case, the catalyst-derived enamine presumably functions as a SOMOphile to intercept this highly electrophilic radical (Scheme 8, SOMOphile pathway). The evidence for this mechanistic rationale was gained from a series of control experiments employing an internal SOMOphilic probe. The reaction of aldehyde **378** with excess allyl trimethylsilane resulted in exclusive aldehyde allylation using TIPS nitronate **369** and predominantly nitronate allylation from the reaction with TBS nitronate **379**, which supports the role of enamine- and nitronate radical cation species **382-384** in the mechanistic divergence.[19]

5.2.4 Enantioselective Michael addition

Despite extensive studies on the development of Michael addition reactions,[21] the catalytic asymmetric Michael addition of nitronates to α,β-unsaturated aldehydes has remained a difficult task, mainly because of the ready participation of aldehydes in 1,2-addition reactions with these nucleophiles.[22] Maruoka and co-workers addressed this problem by developing a new strategy, where the regio- and stereoselectivity of the fluoride-initiated addition of silyl nitronate **385** to α,β-unsaturated aldehyde **386** can be controlled by using chiral quaternary ammonium bifluoride **387** (Scheme 88). Fluoride-mediated desilylation of the silyl nitronate was proposed to provide a chiral ion pair of the nitronate and the catalyst counterion. Nitronate addition is followed by

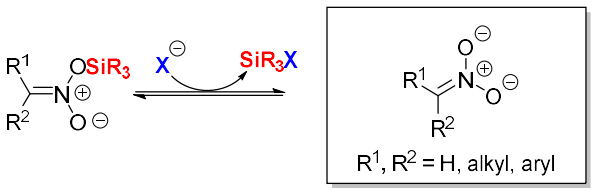
formation of enolate, which desilylates silyl nitronate to regenerate the ammonium nitronate ion and release the enol ester product **388** quantitatively with a high degree of diastereo- and enantioselectivity. This can be either isolated or hydrolysed to afford enantioenriched aldehyde **389**. A significant synthetic advantage of this method is the direct access to asymmetric enol silyl ethers as valuable Mukaiyama donors, which may be applied in subsequent transformations.



Scheme 88. Chiral quaternary ammonium bifluoride **387**-catalysed addition of silyl nitronate **385** to *trans*-cinnamaldehyde.

5.3 Aims and objectives

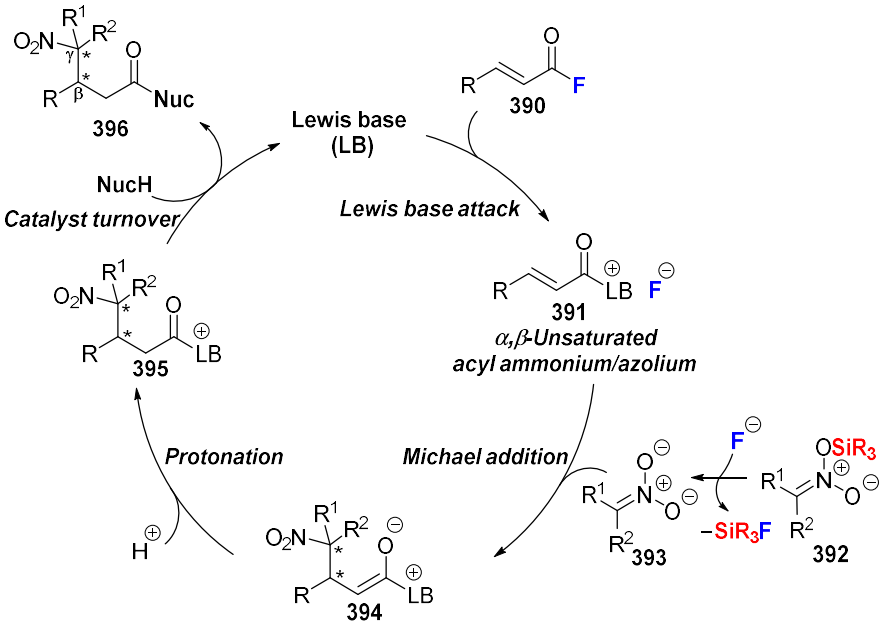
Considering the great potential of silyl nitronates as masked alkyl nitronates and their relatively rare reports in enantioselective catalysis, their application in enantioselective organocatalytic Michael addition was envisioned. As discussed in Chapter 4 the strategy of aryloxide-facilitated catalyst turnover using α,β-unsaturated aryl esters, allowed the use of nitroalkanes as simple nucleophiles. However, the scope of this methodology was restricted to generally simple, inexpensive and commercially-available nitroalkanes, which were used as a solvent to achieve the desired reactivity. To address this limitation, more activated silyl nitronates could be utilised as stoichiometric reagents, potentially providing access to a wider variety of nitronates. As shown previously in the literature, silyl nitronates can undergo desilylation mediated by a suitable counterion, such as fluoride, to generate the nitronate anion *in situ* (Scheme 89).



Scheme 89. Generation of active nitronate anion.

Previous work within the Lupton group had shown that α,β-unsaturated acid fluorides **390** are suitable precursors of α,β-unsaturated acyl azolium or acyl ammonium intermediates **391** that can be generated from the nucleophilic attack of a Lewis base, such as an N-heterocyclic carbene (NHC) or tertiary amine catalyst onto the carbonyl compound.[23] As part of a collaborative research project with Lupton and co-workers, the use of α,β-unsaturated acid fluorides as an α,β-

unsaturated acyl ammonium precursor and a fluoride source was envisioned as an approach to apply silyl nitronates in α,β-unsaturated acyl ammonium catalysis. The catalytically active α,β-unsaturated ammonium or azolium intermediate **391** could be intercepted by nitronate **393**, generated upon desilylation of **392** with a fluoride anion (Scheme 90). Formation of enolate **394** and subsequent protonation would give intermediate **395**, followed by attack of a suitable nucleophile to release the Lewis base and afford enantioenriched γ-nitro-functionalised products **396**, potentially bearing two stereogenic centres. The main challenges of this transformation would be to (i) achieve activation of the silyl nitronate; (ii) overcome direct reaction of the silyl nitronate with the α,β-unsaturated acid fluoride; (iii) identify a suitable nucleophilic source that can enable catalyst turnover; (iv) induce diastereo- and enantiocontrol of stereogenic centres at the β- and γ-position.

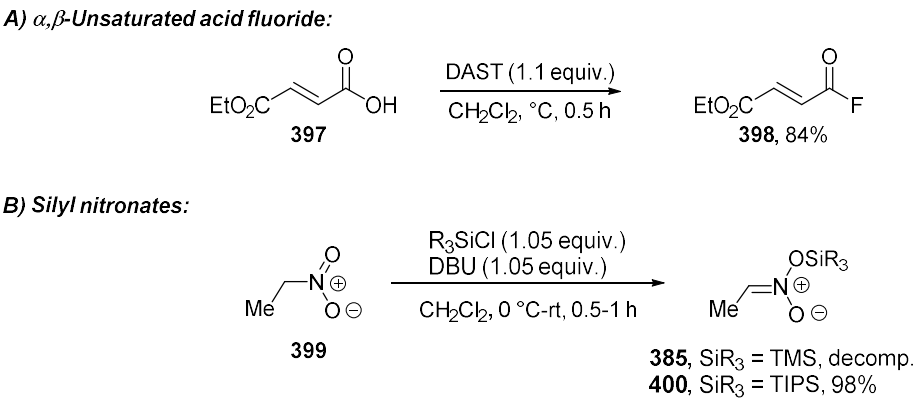


Scheme 90. Reaction design of the organocatalytic enantioselective Michael addition of silyl nitronates to α,β-unsaturated acid fluorides.

5.4 Preliminary studies

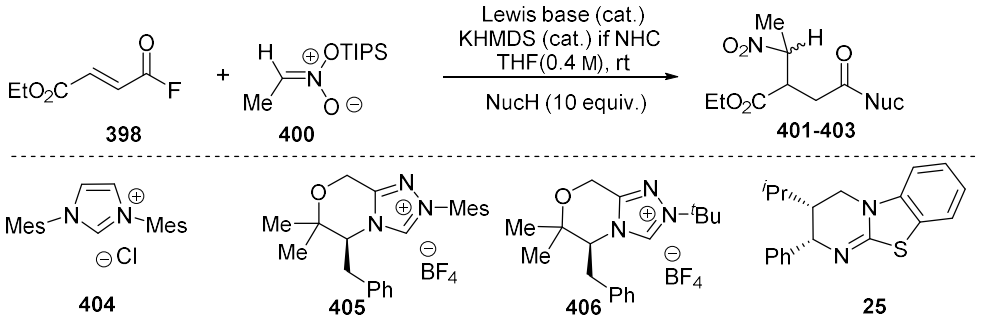
Studies commenced with the preparation of the required starting materials, with both α,β-unsaturated acid fluoride and silyl nitronates synthesised according to known literature procedures[23a][7] (Scheme 91). A β-ester functionality in the model acid fluoride **398** was chosen on the basis of the previous study with unsaturated aryl esters[24] and was readily accessed from the corresponding carboxylic acid **397** and diethylaminosulfur trifluoride (DAST) as a fluorinating reagent. Silyl nitronates were prepared from nitroalkanes using Palomo's protocol (Scheme 3). Nitroethane **399**-derived TMS-nitronate **385** was found to be very unstable at room

temperature, however the analogous TIPS-nitronate **400** was relatively stable and could be isolated in high yield. Notably, silyl nitronate **400** was obtained as a single isomer.



Scheme 91. Synthesis of the starting materials.

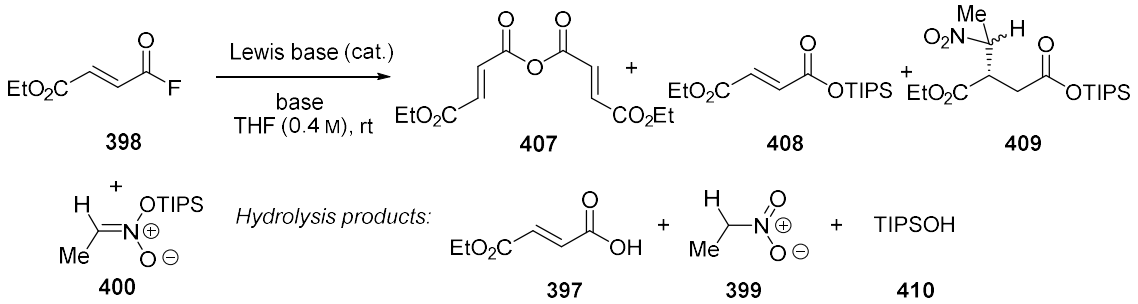
With the starting materials in hand, several reaction conditions were screened using a combination of α,β-unsaturated acid fluoride **398**, nitronate **400**, Lewis base catalyst and nucleophilic source. Notably, a nucleophile was added directly at the start of the reactions (Table 13). First, the reaction was tested in the presence of achiral IMes·HCl precatalyst (**404**·HCl), KHMDS as a base and an excess of methanol as the nucleophile (Table 13, entries 1-4). Pleasingly, methyl ester product **401** was formed, however as a 1:1 mixture of diastereoisomers and in low 12% yield (entry 1). Increasing the catalyst loading to 50% did not improve the yield and no product could be isolated (entry 2). Changing the nucleophile to ethanol or isopropanol resulted in comparable yields of the corresponding ethyl **402** and isopropyl **403** esters (entries 3-4). Chiral morpholine catalysts **405** and **406** with different *N*-substituents were not viable, and only gave a trace of Michael addition product **401** as a racemate (entries 5-6). Interestingly, when isothiourea catalyst, HyperBTM **25**, was used, product **401** was obtained in 93:7 er for both diastereoisomers (entry 7). Although acid fluoride **398** was fully consumed, the yield remained low, possibly due to insufficient catalyst turnover and competitive reaction of the nucleophile with the acid fluoride in addition to hydrolysis.



Entry	Cat	(mol%)	NucH	Yield (%)[a]	dr	er
1	**404**	10	MeOH	12	50:50	-
2	**404**	50	MeOH	-	50:50	-
3	**404**	10	EtOH	8	50:50	-
4	**404**	10	^{i}PrOH	13	50:50	-
5	**405**	10	MeOH	<10	50:50	56:44[b]
6	**406**	10	MeOH	<10	50:50	51:49[b]
7	**25**	20	MeOH	12	50:50	93:7[b]

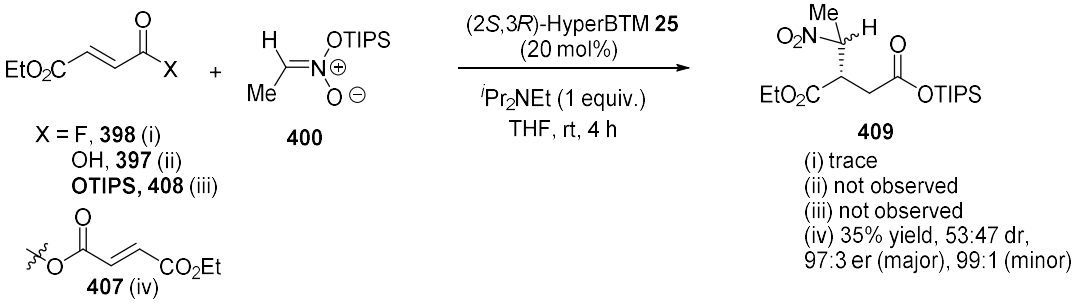
Table 13. Screening of Lewis bases and nucleophilic sources. [a] Isolated yields; [b] er for both diastereoisomers.

Analysing the crude mixtures from these reactions by ^{1}H NMR, hydrolysis products, such as carboxylic acid **397**, nitroethane **399** and triisopropylsilanol **410** were identified. Along with hydrolysis, new α,β-unsaturated systems were formed and identified as α,β-unsaturated homoanhydride **407** and α,β-unsaturated TIPS ester **408**. Assignment of these products was based on independent syntheses of these compounds (see experimental section). Importantly, Michael addition product **409** was formed as a TIPS ester and detected in trace quantities as two diastereomeric species, with the exact ratio difficult to determine at this stage (Scheme 92).



Scheme 92. Identified species in the reaction mixture.

To understand the origin of all the observed species, in particular formation of the TIPS ester-substituted Michael addition product **409**, each α,β-unsaturated system identified in the reaction mixture was tested as a potential α,β-unsaturated acyl ammonium precursor in the presence of base ($^{i}Pr_2NEt$) and HyperBTM **25** (Scheme 93). While carboxylic acid **397** and TIPS ester **408** did not give any product, reaction of homoanhydride **407** with 1 equiv. of TIPS nitronate **400** gave nitro-adduct **409** in 35% isolated yield. This implies that at least one catalytic turnover must have occurred in the reaction. At this stage, a mechanism for the formation of TIPS ester product **409** was not obvious but will be discussed later. Although the diastereoselectivity of the reaction was low (53:47 dr), both stereoisomers were formed with high levels of enantiocontrol (97:3; 99:1 er). With this promising result in hand, attention was turned to reaction optimisation.

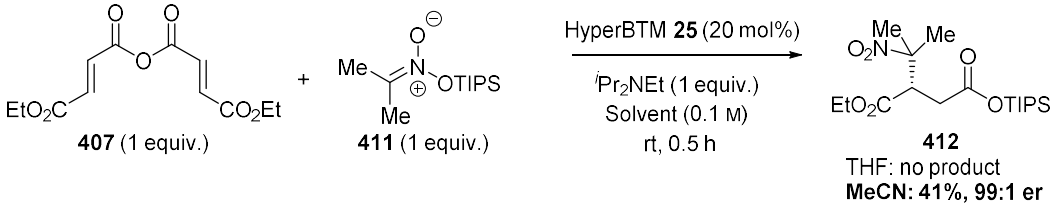


Scheme 93. Identification of a suitable α,β-unsaturated acyl ammonium precursor.

5.5 Reaction optimisation

5.5.1 Substrate choice

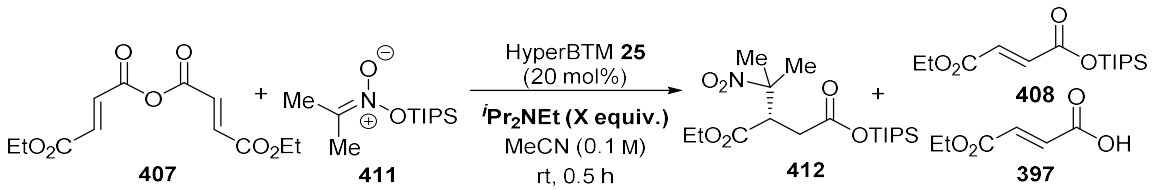
Given the challenging isolation and analysis of the Michael addition product as a mixture of diastereoisomers, the use of alternative silyl nitronates, which would not lead to an additional stereocentre in the γ-position of the product was envisaged. Due to the explosive nature of nitromethane-derived silyl nitronates,[20] 2-nitropropane-derived silyl nitronate **411** was tested under catalytic conditions. Notably, no product was obtained under the previously used reaction conditions, however, by using a more polar solvent (MeCN) full conversion of nitronate **411** was observed after 0.5 h. In this case Michael addition product **412** was formed in 41% yield and 99:1 er, with this result used for subsequent reaction optimisation (Scheme 94).



Scheme 94. Choice of silyl nitronate.

5.5.2 Reaction stoichiometry

Further reaction optimisation focused on the stoichiometry of the reaction and its influence on the product distribution. As shown in Table 14, when an excess of anhydride was used, only 20% of the desired product **412** was obtained, with predominantly hydrolysis of the anhydride and nitronate occurring in the reaction (entry 2). In contrast, when 2 equiv. of silyl nitronate **411** was employed, the product yield increased to 66% by ^{1}H NMR spectroscopy, with a higher amount of unsaturated TIPS ester **408**, and decreased hydrolysis of the anhydride (entry 3). Interestingly, using just 1.5 equiv. of nitronate gave higher yield of **412** (73%), accompanied by only 19% of α,β-unsaturated TIPS ester **408** (entry 4). The presence of base proved crucial to induce the desired reactivity and minimise the formation of by-products (entry 5). However, using 2 equiv. of ^{i}Pr$_2$NEt gave reduced yield of the Michael adduct (41%) and increased hydrolysis of homoanhydride **407**, so reaction optimisation continued with 1 equiv. of the base.



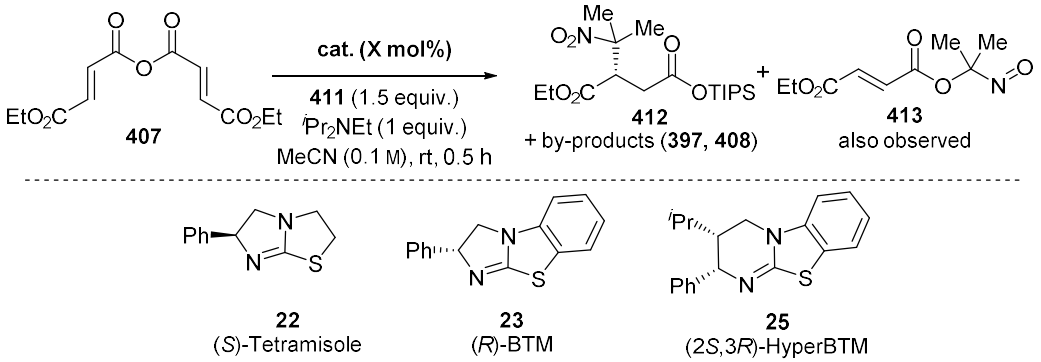
Entry	**407**:**411**:Base	**412** (%)[a]	er[b]	**408** (%)[a]	**397** (%)[a]
1	1:1:1	43 (41)	99:1	20	45
2	1.3:1:1	21	ND	46	76
3	1:2:1	66 (59)	99:1	36	34
4	1:1.5:1	73 (70)	99:1	19	35
5	1:1.5:0	20	ND	74	29
6	1:1.5:2	41	ND	33	50

Table 14. Variation of reaction stoichiometry. [a] Determined by ^{1}H NMR of the crude mixture using 1,4-dinitrobenzene as internal standard. The yields calculated with respect to **407** as 1 equiv., except for entry 2 where 1.3 equiv. of **407** was used (isolated yields given in parentheses). [c] Determined by chiral HPLC analysis. ND = not determined.

5.5.3 Catalyst screening and loading

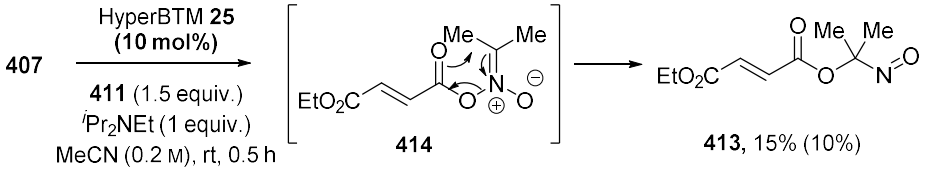
A survey of alternative chiral isothioureas was performed using 20 mol% of the Lewis base, under previously optimised reaction conditions (Table 15). From this study it was clear that catalytic efficiency and selectivity using HyperBTM **25** was superior for this process, as both tetramisole **22** and BTM **23** gave much lower yields (27-39%) and enantioselectivity of product **412**, accompanied by extensive formation of hydrolysis products (entries 2-3). Reducing the catalyst loading of HyperBTM to 10 mol% did not affect enantioselectivity, however, the yield of **412** decreased to 60% and an additional product **413** was observed, which was formed with a

characteristic deep blue colour.[25] Nitroso-derivative **413** was isolated and its structure was confirmed by 2D NMR and HRMS. Related compounds are described in the literature[26] and could result from *O*-acylation of the nitronate anion by an α,β-unsaturated species to form intermediate **414**, followed by [2,3]-rearrangement (Scheme 95). Due to co-elution of side-product **413** with Michael addition product **412** by flash silica column chromatography, efficient isolation of the Michael addition product in this case was difficult to achieve.



Entry	Cat.	mol%	**412** (%)[a]	er[b]	**408** (%)[a]	**397** (%)[a]	**413** (%)[a]
1	**25**	20	73 (70)	99:1	19	35	trace
2	**22**	20	27	91:9	44	58	trace
3	**23**	20	39	92:8	37	53	trace
4[c]	**25**	10	60	99:1	48	37	15 (10)

Table 15. Catalyst screening and loading. [a] Determined by ^{1}H NMR of the crude mixture using 1,4-dinitrobenzene as internal standard. The yields calculated with respect to **407** as 1 equiv. (isolated yields given in parentheses). [b] Determined by chiral HPLC analysis. [c] Additional side-product was observed.

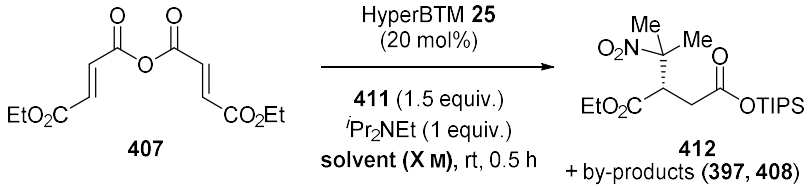


Scheme 95. Proposed mechanism for formation of nitroso-derivative **413** as a side-product *via* **414**.

5.5.4 Variation of solvent and concentration

As mentioned above, THF was not a viable solvent for this catalytic system as no γ-nitro product **412** was obtained with the homoanhydride and nitronate mainly hydrolysed or converted to TIPS ester **408** (Table 16, entry 2). Similarly, dichloromethane gave only traces of the desired product (entry 3). Good reactivity was obtained using a more polar solvent, DMF (entry 4), affording moderate yield but high enantioselectivity (98:2). However, the yield of Michael addition product **412** was lower in this case (59%), relative to the reaction in MeCN (73%). When using anhydrous MeCN (distilled over CaH_2), a crucial effect on the yield was observed, with TIPS ester **412**

isolated in 91% yield in almost enantiomerically pure form (99:1 er) (entry 5). Notably, the amount of by- and hydrolysis products was reduced in this case. When performing the reaction under inert conditions in a glovebox, the nitronate reacted more slowly, as after 1 h the starting material was still present (as monitored by TLC), however the eventual reaction yield was high, and no hydrolysis products were detected (entry 6). While a more dilute reaction (0.05 M) resulted in 81% of **412** (entry 7), slight yield improvement (92%) and still excellent er (99:1) was achieved by increasing the reaction concentration to 0.2 M (entry 8). This concentration in MeCN was selected as the optimal reaction medium for further investigation.



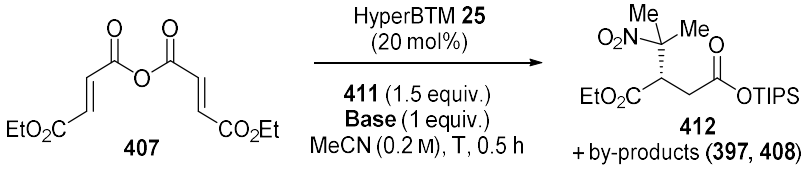
Entry	Solvent	[M]	**412** (%)[a]	er[b]	**408** (%)[a]	**397** (%)[a]
1	MeCN	0.1	73 (70)	99:1	19	35
2	THF	0.1	-	-	65	77
3	CH_2Cl_2	0.1	8	ND	63	52
4	DMF	0.1	59	98:2	41	36
5	anh. MeCN	0.1	95 (91)	99:1	28	11
6	MeCN[c]	0.1	75	ND	64	-
7	anh. MeCN	0.05	81	99:1	34	20
8	anh. MeCN	0.2	97 (92)	99:1	24	14

Table 16. Variation of solvent and concentration. [a] Determined by ^{1}H NMR of the crude mixture using 1,4 dinitrobenzene as internal standard. The yields calculated with respect to **407** as 1 equiv. (isolated yields given in parentheses). [b] Determined by chiral HPLC analysis. [c] Reaction performed in a glovebox; reaction time 1 h. ND = not determined. anh. = anhydrous.

5.5.5 Base and temperature screen

Next, the use of both organic and inorganic bases was investigated (Table 17). Triethylamine with a similar pK_{aH} (10.75) as diisopropylethylamine, gave comparable results, including exceptional stereocontrol in the β-position of **412**, however slightly lower yield according to ^{1}H NMR (80%) (entry 2). 2,6-Lutidine (pK_{aH} = 6.65), gave product **412** in drastically decreased 20% yield, whereas α,β-unsaturated TIPS ester **408** was formed in 97%, with the rest of homoanhydride **407** hydrolysed under reaction conditions (entry 3). Inorganic base K_2CO_3 could also be applied to afford Michael addition product **412**, albeit in lower yield (50%) and enantioselectivity (88:12) (entry 4). Interestingly, changing the temperature had a negative impact on reactivity. When

testing the reaction at –20 ºC and +40 ºC, **412** was formed in moderate ~50% yield in both cases (entries 5-6).

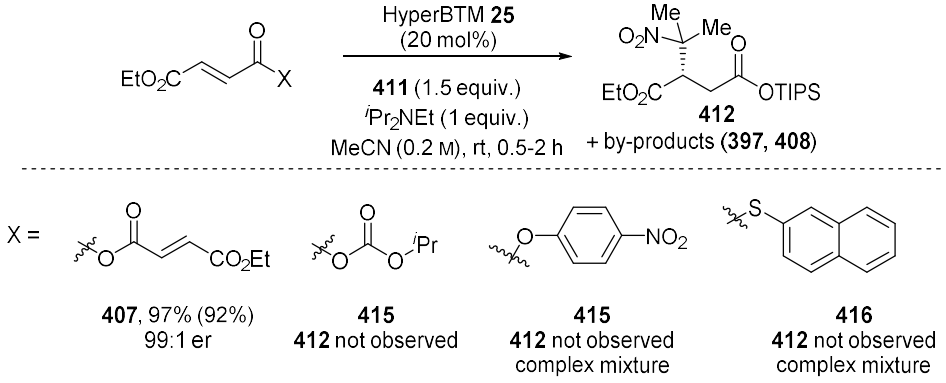


Entry	Base	T [ºC]	**412** (%)[a]	er[b]	**408** (%)[a]	**397** (%)[a]
1	$^{i}Pr_2NEt$	rt	97 (92)	99:1	24	14
2	NEt_3	rt	80	98:2	39	24
3	2,6-Lutidine	rt	19	ND	97	38
4	K_2CO_3	rt	50	88:12	21	25
5	$^{i}Pr_2NEt$	–20	50	ND	52	97
6	$^{i}Pr_2NEt$	40	52	ND	40	44

Table 17. Base and temperature screen. [a] Determined by ^{1}H NMR of the crude mixture using 1,4-dinitrobenzene as internal standard. The yields calculated with respect to **407** as 1 equiv. (isolated yields given in parentheses). [b] Determined by chiral HPLC analysis. ND = not determined.

5.5.6 α,β-Unsaturated acyl ammonium precursors

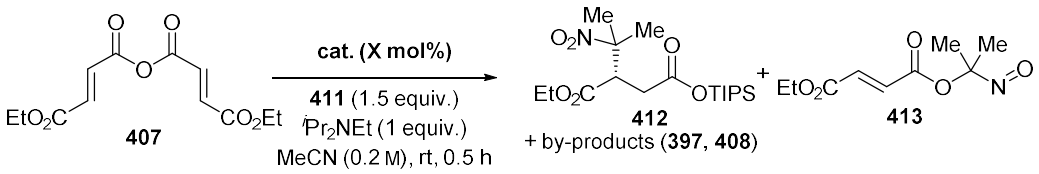
Next, the role of the homoanhydride was explored by applying alternative α,β-unsaturated derivatives (Scheme 96). Although previously reported by Matsubara in α,β-unsaturated acyl ammonium catalysis,[27] isopropyl-substituted carbonic anhydride **415** proved an inefficient precursor in this case with only starting materials returned. Using 4-nitrophenyl ester **283** or naphthyl-substituted thiol **416** resulted in complex mixture of products in each case, however TIPS ester **412** was not observed.



Scheme 96. Screening of α,β-unsaturated acyl ammonium precursors.

5.5.7 Further optimisation of catalyst loading

Using the improved reaction conditions, an attempt to decrease the catalyst loading was revisited (Table 18). In the presence of 10 mol% of HyperBTM **25** product **412** was formed in 78% yield after 0.5 h (entry 2) and in 83% after 1 h, when full conversion of both starting materials was observed by monitoring by TLC (entry 3). However, in both cases formation of nitroso derivative **413** as a side-product could not be suppressed, which complicated product purification. Increasing the equivalents of silyl nitronate **411** resulted in a higher yield (93%), however the amount of **413** increased as well, and isolated product **412** contained 15% of this impurity by ^{1}H NMR. Finally, the reaction was performed with slow addition of the nitronate *via* a syringe pump, however this experiment did not give better results than the fast addition.

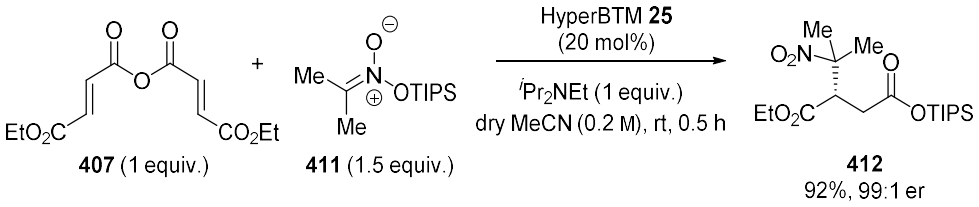


Entry	**25** (mol%)	Time (h)	**412** (%)[a]	er[b]	**408** (%)[a]	**397** (%)[a]	**413** (%)[a]
1	20	0.5	97 (92)	99:1	24	14	trace
2	10	0.5	78	99:1	34	8	15
3	10	1	83	99:1	30	7	18
4[c]	10	1	93 (85)[d]	99:1	44	8	22
5[e]	10	2	74	ND	97	28	33

Table 18. Optimisation of catalyst loading. [a] Determined by ^{1}H NMR of the crude mixture using 1,4-dinitrobenzene as internal standard. The yields calculated with respect to **407** as 1 equiv. (isolated yields given in parentheses). [b] Determined by chiral HPLC analysis. [c] 2 equiv. of **411** was used. [d] Product contains ~15% impurity of **413**. [e] 2.5 equiv. of **411** was used, slow addition with a syringe pump (1 mL/h). ND = not determined.

5.5.8 Optimised reaction conditions

α,β-Unsaturated homoanhydrides were the only suitable precursors of the α,β-unsaturated acyl ammonium intermediate in combination with silyl nitronates. Among the screened Lewis bases, HyperBTM **25** (20 mol%) showed the best catalytic efficiency and selectivity, however, attempts to decrease the catalyst loading proved challenging given the increased formation of the side-product. Moreover, the use of a polar solvent MeCN and organic base ^{i}Pr$_2$NEt was crucial to achieve optimal yield and enantioselectivity. Further studies into the enantioselective Michael addition of silyl nitronates were conducted with the finalised reaction conditions (Scheme 97).

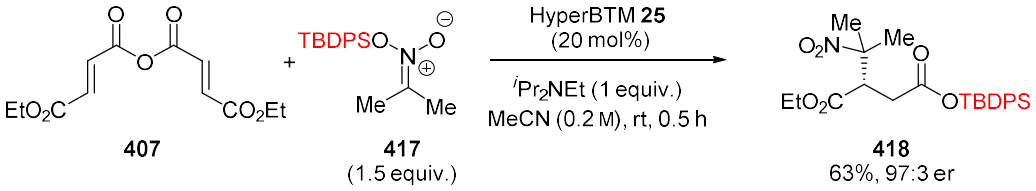


Scheme 97. Optimised reaction conditions for asymmetric Michael addition of silyl nitronates.

5.6 Reaction scope and limitations

5.6.1 Alternative silyl groups

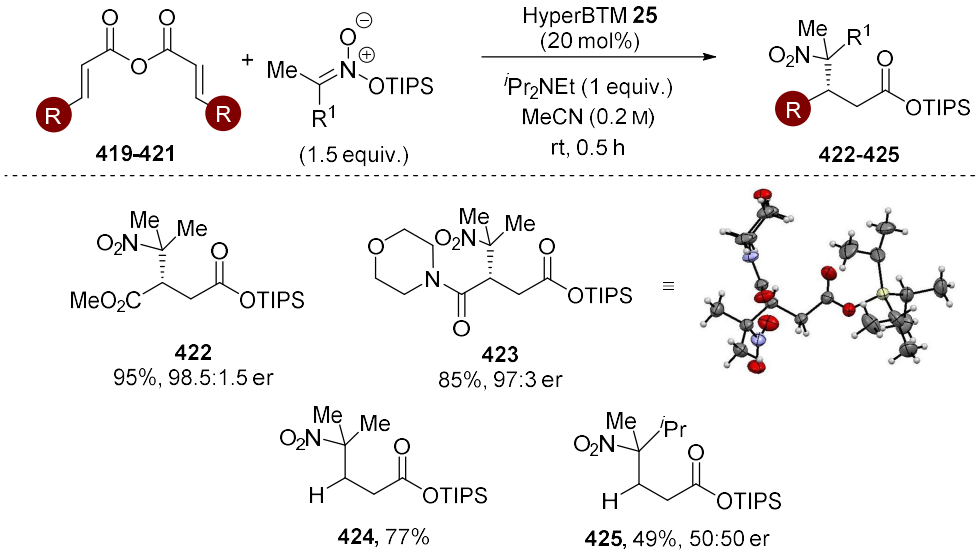
The use of alternative silyl protective groups was next investigated (Scheme 98). While trimethylsilyl nitronates were highly unstable and rapid decomposition was observed, *tert*-butyldiphenyl (TBDPS) silyl derivative **417** was moderately stable although had to be used directly as a crude mixture. Testing this nitronate in catalysis resulted in formation of new γ-nitro-substituted silyl ester **418** in 63% yield and excellent enantioselectivity (97:3 er). The decreased yield could be attributed to lower stability of nitronate **417** confirming the advantage of using TIPS protected nitronates to explore the reaction scope.



Scheme 98. Use of TBDPS nitronate **417**.

5.6.2 Variation of Michael acceptor

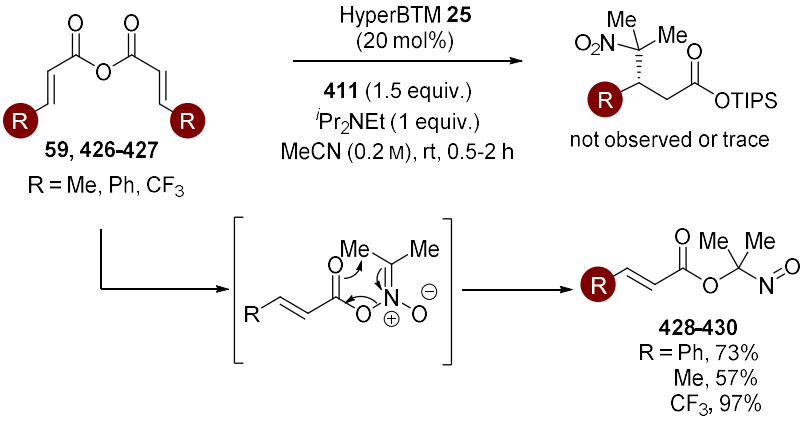
The next stage was to establish the sensitivity of the reaction to the steric and electronic properties of the Michael acceptor using TIPS nitronate **411** as a model nucleophile (Scheme 99). Homoanhydride **419** bearing a β-methyl ester provided TIPS ester **422** in 95% yield with excellent enantioselectivity (99:1 er). β-Amide-substituted acceptor **420** behaved comparably to the ester functionality affording corresponding amide **423** in 85% yield and 97:3 er. The constitution and absolute configuration of **423** was unambiguously determined by X-ray crystallographic analysis with all other compounds assigned by analogy. Acrylic anhydride **420** was also employed in the reaction with model nitronate **411** to give achiral Michael addition product **424** in 77% yield. However, product **425** bearing a stereogenic centre in the γ-position was formed as a racemate, indicating that formation of this centre was not controlled by the chiral isothiourea catalyst.



Scheme 99. Reaction scope: variation of Michael acceptor.

5.6.3 Unsuccessful Michael acceptors

In the previous work on the enantioselective Michael addition of nitroalkanes to α,β-unsaturated aryl esters, β-alkyl-, aryl- or CF_3-substituted aryl esters showed no or very little reactivity.[24] To test if this limitation could be overcome in the new methodology using more reactive silyl nitronates, the corresponding (*E*)-but-2-enoic, cinnamic and trifluoromethyl-substituted anhydrides were prepared. Unfortunately, they were not viable substrates in catalysis (Scheme 100) as α,β-unsaturated nitroso derivatives **428-430** were formed as the major products. Notably, analogous side-products were observed during the reaction optimisation, when the catalyst loading was reduced (Table 15, Scheme 95).

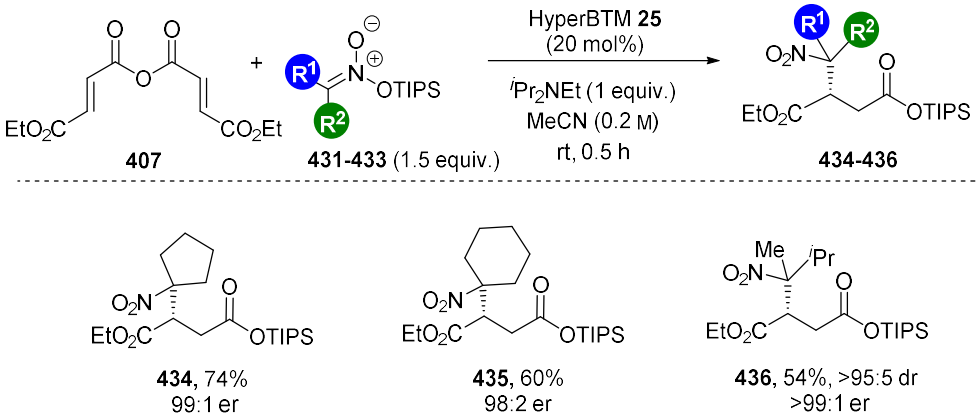


Scheme 100. Formation of nitroso-derivatives as side-products.

5.6.4 Alkyl-substituted nitronates

The scope of the new Michael addition protocol was further evaluated by employing different alkyl-substituted nitronates (Scheme 101), with substrates **431-433** readily prepared using the

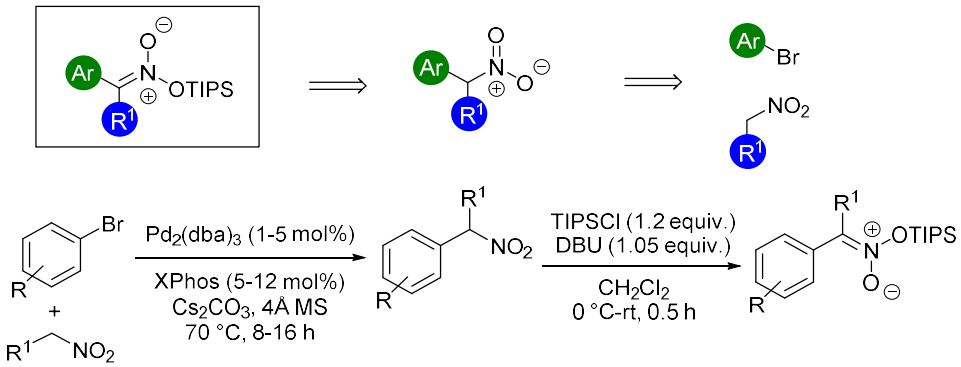
procedure described in Scheme 91. Pleasingly, the sterically-hindered cyclopentyl-derived nitronate was well tolerated, affording **434** in excellent enantiomeric purity (99:1 er) and isolated yield (74%). It should be noted that in the aryloxide-facilitated catalyst turnover strategy, outlined in Chapter 4, nitrocyclopentane gave only 42% yield of the corresponding product when used as a solvent. Nitrocyclohexane previously proved completely unreactive, however in this procedure, using nitrocyclohexane-derived silyl nitronate **432**, the corresponding product **435** was obtained in good yield (60%) and excellent enantiomeric ratio (98:2 er). Significantly, further increasing the steric bulk of the nitronate by changing R^2 substituent to an isopropyl group was still very well tolerated, producing TIPS ester **436** in good 54% yield, and with exceptional levels of diastereo- and enantioselectivity (the relative configuration of **436** yet to be determined).



Scheme 101. Reaction scope: alkyl nitronates.

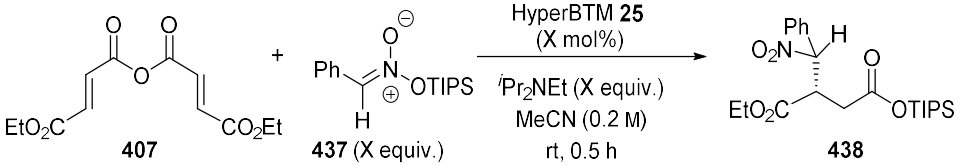
5.6.5 Monoaryl-substituted nitronates

To expand the scope of γ-nitro addition products, the use of monoaryl-substituted nitronates was envisaged. Aryl nitroalkanes were prepared through Pd(0)-catalysed coupling reaction of aryl bromides with nitroalkanes according to Kozlowski's method,[28ab] which was based on the strategy initially developed by Buchwald[28c] (Scheme 102). This method tolerates a number of functional groups including ketones, esters, and olefins. (*E*)-Configured aryl *O*-TIPS nitronates were prepared from aryl nitroalkanes and triisopropylsilyl chloride in the presence of a strong base.[6,7] These TIPS nitronates proved more stable than nitroalkane-derived silyl nitronates and could usually be purified by flash silica column chromatography.



Scheme 102. Preparation of aryl-substituted TIPS nitronates.

The reaction of homoanhydride **407** with α-phenyl-substituted nitronate **437** in the presence of 20 mol% HyperBTM afforded product **438** as an 85:15 diastereoisomeric mixture in moderate yield (37%) but high enantioselectivity for both stereoisomers. Notably, whilst with monoalkyl-substituted nitronate **409** (Scheme 93) gave poor diastereocontrol (53:47 dr), the diastereoselectivity using aryl derivative **437** was vastly improved (85:15 dr, with the relative configuration of **438** yet to be determined). A short optimisation demonstrated that the use of 2 equiv. of the silyl nitronate gave a higher yield of **438** (Table 19, entry 2). Interestingly, the reaction proceeded more efficiently in the absence of base, giving **438** in improved 51% isolated yield and excellent stereocontrol (entry 3). Reducing the catalyst loading did not affect the stereoselectivity, however resulted in decreased yield of product **438** (entry 4), hence the scope was evaluated using 20 mol% of HyperBTM **25**.



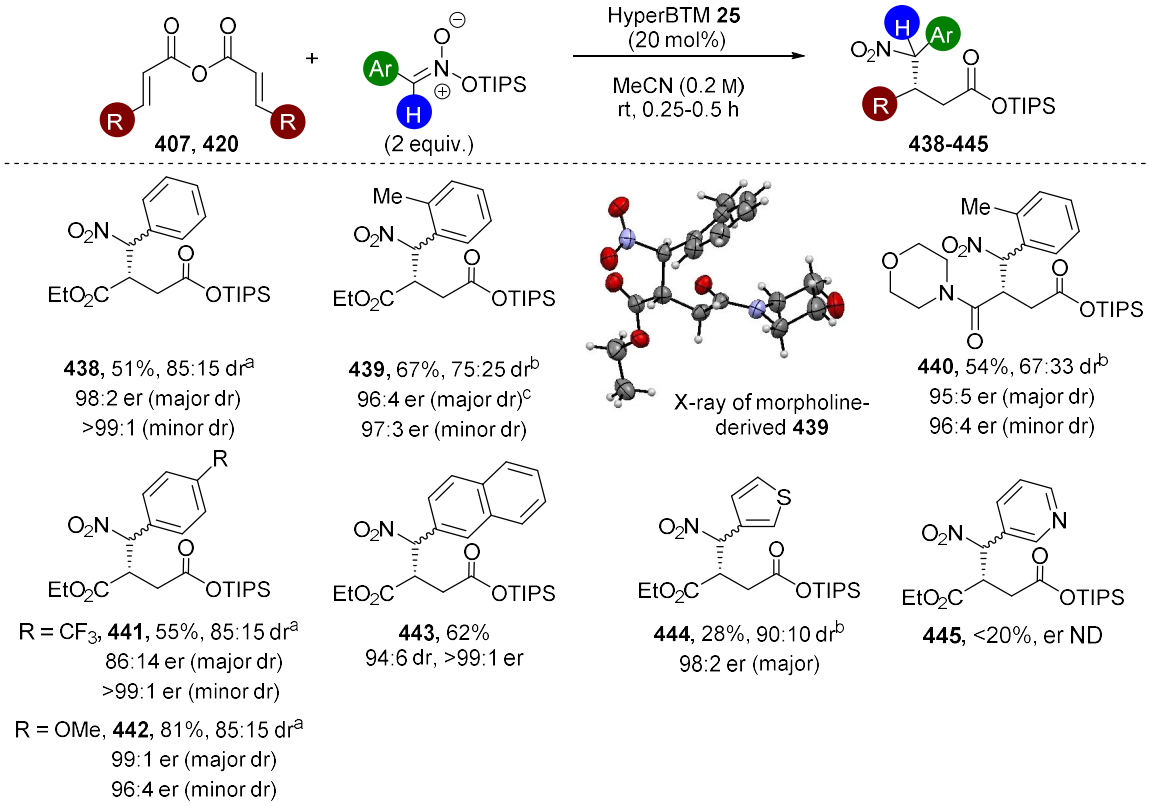
Entry	**cat.** (mol%)	**437** (equiv.)	^{i}Pr$_2$NEt (equiv.)	**438** (%)[a]	dr[a]	er[b]
1	20	1.5	1	43 (37)	85:15	98:2 (major) >99:1 (minor)
2	20	2	1	49 (46)	85:15	98:2 (major) >99:1 (minor)
3	20	2	0	58 (51)	85:15	98:2 (major) >99:1 (minor)
4	10	2	0	40 (33)	85:15	98:2 (major) >99:1 (minor)

Table 19. Reaction optimisation with aryl nitronates. [a] Determined by ^{1}H NMR of the crude mixture using 1,4-dinitrobenzene as internal standard. The yields calculated with respect to **407** as 1 equiv. (isolated yields given in parentheses). [b] Determined by chiral HPLC analysis.

A range of nitronates bearing different substituents on the aryl group were tested (Scheme 103). *o*-Tolyl derivative **439** (67% yield) was obtained with good diastereoselectivity (75:25 dr), with

both diastereoisomers highly enantioenriched and readily separable by flash silica column chromatography. The relative and absolute configuration of the major diastereoisomer of **439** was unambiguously determined by X-ray crystallographic analysis with all other examples in this series assigned by analogy. The diastereoselectivity for the formation of product **440** decreased slightly (67:33) when β-morpholine substituted homoanhydride was applied, with high er observed for both diastereoisomers. An interesting effect on enantioselectivity was observed by changing the electronic nature of the aryl group. While electron-donating 4-methoxy-aryl-substituted nitronate gave **442** in excellent yield, dr and er for both diastereoisomers, enantioselectivity was somewhat lower for the major diastereoisomer of electron-deficient 4-CF_3-aryl-substituted product **441** (86:14 er). To investigate if this lower er may be a result of a competitive background reaction, **401** and silyl nitronate were treated in absence of the catalyst. No product formation was observed, however this cannot rule out a background reaction promoted by side- or by-products formed under the reaction conditions.

Naphthyl-derived nitronate was a useful substrate as corresponding nitro adduct **443** was isolated in 62% yield in almost diastereo- and enantiopure form (94:6 dr, >99:1 er). One of the limitations of this reaction series became apparent when heteroaromatic TIPS nitronates were employed. γ-(2-Thiophene-nitro) derivative **444** was produced in a modest 28% yield, however both diastereo- and enantiopurity of this product was high. The low yield could be attributed to the poor stability of the thiophene-derived nitronate and the corresponding product **444**. Unfortunately, pyridine-derived nitronate was not an effective nucleophile in this process, as product **445** was formed in trace amounts, with mostly hydrolysis of the nitronate observed under reaction conditions.

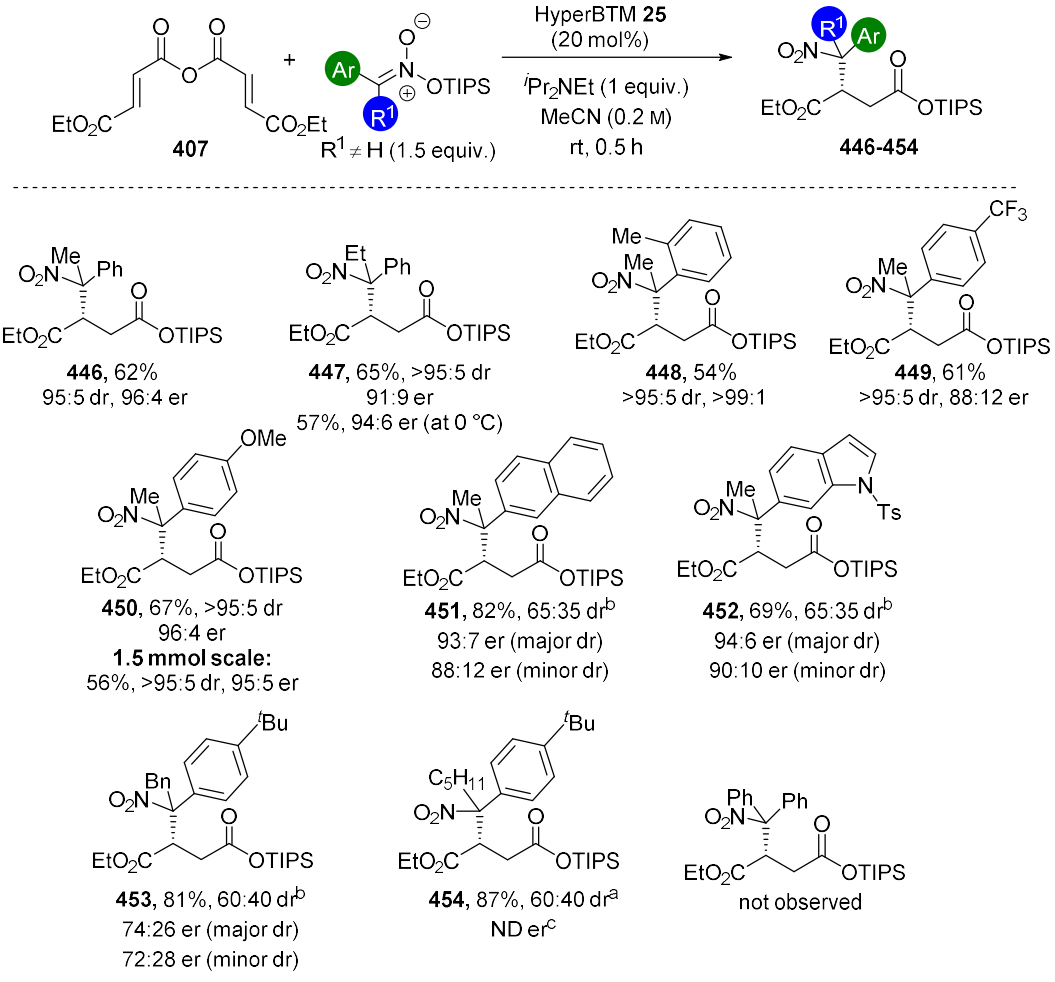


Scheme 103. Reaction scope: α-aryl nitronates. [a] Isolated as inseparable mixture of diastereomers. [b] Diastereomers were separated by flash silica column chromatography. [c] X-ray analysis of the major diastereoisomer derivatised to a morpholine amide. ND = not determined.

5.6.6 α,α-Aryl, alkyl disubstituted nitronates

The generality of this Michael addition protocol using more sterically-hindered disubstituted nitronates was next investigated (Scheme 104). Pleasingly, the use of phenyl, methyl-substituted silyl nitronate gave corresponding product **446** in 62% yield, excellent dr (95:5) and er (96:4). Even higher diastereoselectivity (>95:5) was observed by changing the methyl to an ethyl group, although product enantioselectivity was slightly eroded (91:9). This result was improved by performing the reaction at 0 ºC, giving **447** in 94:6 er. The steric and electronic influences of the α-aryl substituent in the presence of adjacent methyl group were also explored. *o*-Tolyl-substituted nitronate gave exceptional diastereo- and enantioselectivity (>95:5 dr, >99:1 er) but lower yield of **448** (54%), which could be ascribed to the steric hindrance of the *o*-tolyl group. In agreement with the previous observations, an electron-withdrawing CF_3-substituent in the aryl group led to lower enantioselectivity (88:12 er) of product **449**, however the diastereocontrol remained high (>95:5 dr). 4-Anisole-derived nitronate showed very good reactivity to afford Michael addition product **450** in 67% yield, >95:5 dr and 95:5 er. This compound was also prepared on a 1.5 mmol scale in similarly good yield and with no erosion of stereoselectivity. Product **451** bearing a naphthyl substituent was formed in high yield, moderate dr (65:35), and

good er for both major (93:7) and minor (88:12) diastereomers. Similar levels of diastereo- and enantiocontrol was obtained using indole-derived nitronate giving heterocycle-substituted TIPS ester **452** in 69% yield. The diastereo- and enantioselectivity dropped further for products **453** and **454**, which could be attributed to the sterics of the nitronates used. When nitronate bearing two phenyl groups was applied, no product was obtained, and the nitronate was returned unreacted. This could be attributed to severe steric hindrance of the two phenyl groups in this substrate. The product constituion in this series was assigned using 2D-NMR experiments (COSY, HSQC and HMBC) and by analogy between the NMR spectra of the monoaryl- and aryl,alkyl-substituted Michael addition products. However, both relative and absolute configuration of the major diastereoisomer in the di-substituted series is yet to be determined.

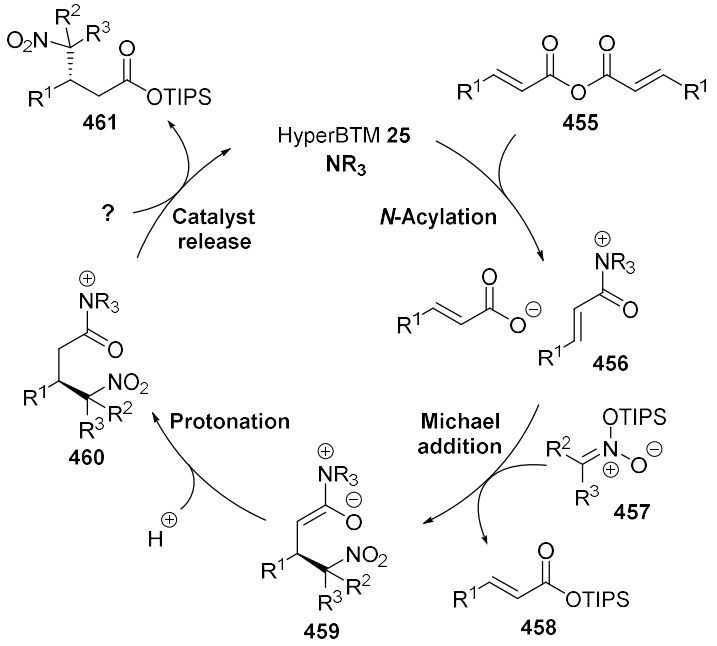


Scheme 104. Reaction scope: α,α-aryl,alkyl nitronates. [a] Isolated as inseparable mixture of diastereomers. [b] Diastereomers were separated by flash silica column chromatography. ND = not determined.

5.7 Mechanistic considerations

Having evaluated the substrate scope and limitations of the new Michael addition protocol, in-depth understanding of the reaction mechanism, in particular the origin of unprecedented catalyst turnover step in the absence of aryloxide was desired. A simplified catalytic cycle of the reaction

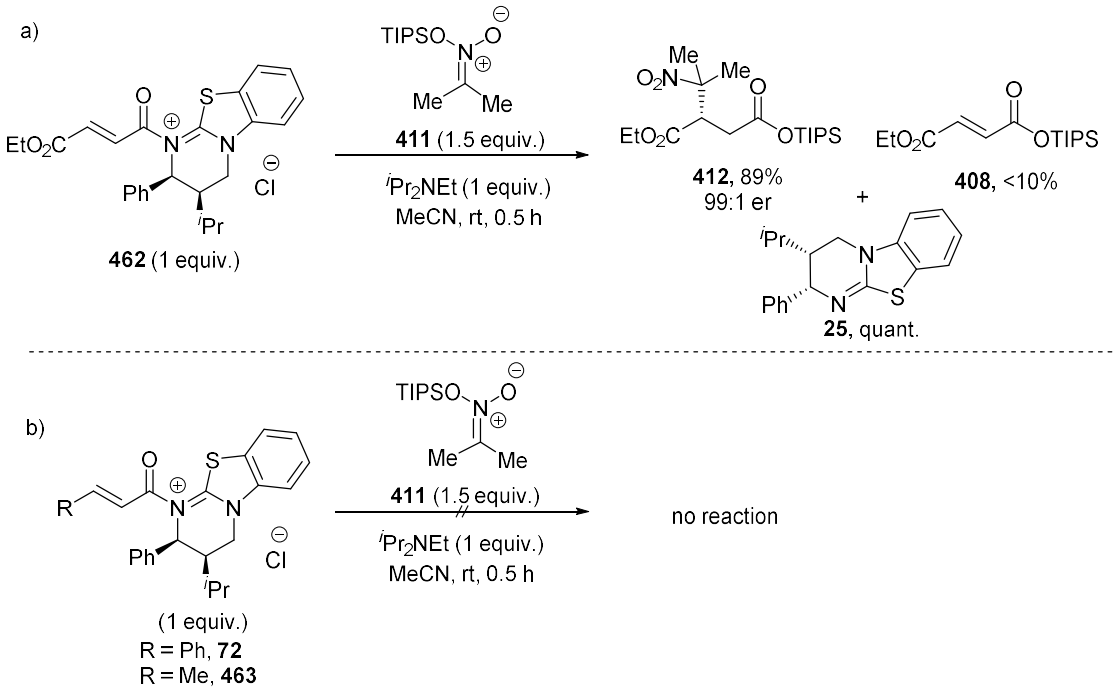
is detailed in Scheme 105. Reaction of the Lewis base with homoanhydride **455** is proposed to give α,β-unsaturated acyl isothiouronium-carboxylate ion pair **456**. Desilylation of the silyl nitronate **457** by the carboxylate generates nitronate anion and α,β-unsaturated TIPS ester **458**. Nucleophilic addition of nitronate to the α,β-unsaturated acyl isothiouronium species generates enolate **459**, followed by a protonation step to give acyl ammonium **460**. Catalyst turnover through an unknown mechanism then affords observed TIPS ester product **461**. To provide mechanistic insight into key steps, including the Michael addition, protonation and catalyst turnover steps, as well as explore the origin of diastereoselectivity observed in the reaction, a series of control experiments were undertaken.



Scheme 105. Simplified catalytic cycle for the asymmetric Michael addition of silyl nitronates.

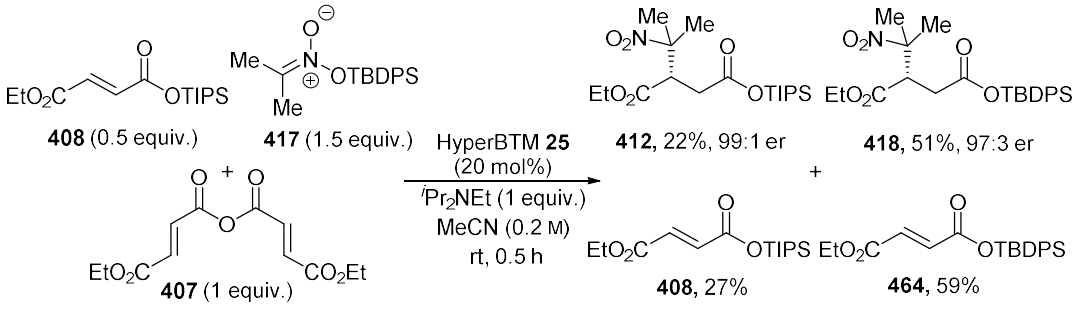
5.7.1 Studies of the Michael addition

To provide insight into a Michael addition step, α,β-unsaturated isothiouronium chloride salt **462**[24,30] was tested in a stoichiometric reaction with nitronate **411**. Pleasingly, the corresponding Michael addition product **412** was produced in 89% yield in 99:1 er with a quantitative release of free HyperBTM catalyst and a small amount of α,β-unsaturated TIPS ester **408** (Scheme 106a). To rationalise the origin of lack of reactivity using β-methyl and phenyl substituted homoanhydrides (Scheme 100), the corresponding α,β-unsaturated isothiouronium salts **72** and **463** were also prepared. They did not show any reactivity with a stoichiometric amount of silyl nitronate **411**, and the starting materials were returned unreacted or partially hydrolysed (Scheme 106b). This result is consistent with the observed limitation in the scope, where cinnamic and but-2-enoic homoanhydrides were not viable Michael acceptors for the nucleophilic addition of nitronates.



Scheme 106. a) Reaction of **462** with TIPS nitronate **411**. b) Reaction of **72**, **463** with with TIPS nitronate **411**.

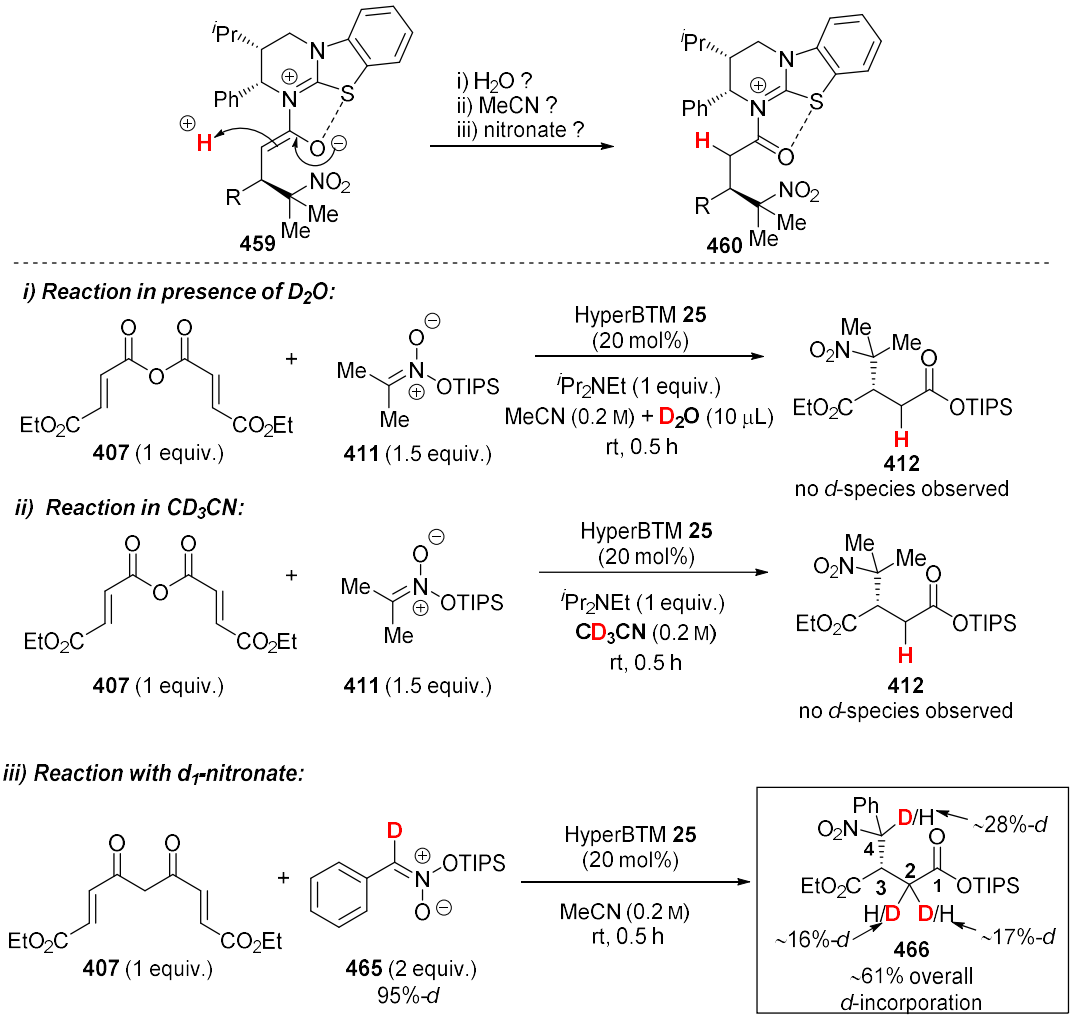
The role of the α,β-unsaturated TIPS ester **408** in the reaction mixture was also investigated by conducting a crossover experiment using homoanhydride **407** in the presence of HyperBTM **25**, TBDPS-derived nitronate **417** and an additional 0.5 equiv. of unsaturated TIPS ester **408** (Scheme 107). Intriguingly, Michael addition products **412** and **418**, bearing a TIPS group and TBDPS group respectively, were obtained with high enantioselectivity for both esters. α,β-Unsaturated TIPS **408** and TBDPS **464** esters were also observed in the product mixture. It should be noted that α,β-unsaturated TIPS ester **408** was not a competent α,β-unsaturated acyl ammonium precursor, as stated above (Scheme 93). This indicates the possibility of a dynamic silyl transfer between nitronate and carboxylate groups, where α,β-unsaturated TIPS ester **408** might undergo nucleophilic removal of the silyl group by a released nitronate anion to generate the TIPS-derived silyl nitronate, which could be potentially used further in the reaction. This would also explain the optimal stoichiometry identified in the reaction optimisation.



Scheme 107. Crossover experiment with homoanhydride, silyl nitronate and unsaturated TIPS ester.

5.7.2 Investigation of the protonation step

Among the key catalytic steps, protonation of enolate **459** to acyl ammonium **460** was of special interest, as there was no apparent proton source in the reaction mixture. Several mechanistic experiments were performed to determine whether i) water; ii) acetonitrile or iii) silyl nitronate were involved in the protonation step (Scheme 105). Performing the reaction of **407** with nitronate **411** in the presence of deuterium oxide in anhydrous MeCN or using d_3-MeCN as a solvent gave Michael addition product **412**, with no deuterium incorporation observed as analysed by ^{1}H, ^{2}H, and ^{13}C{^{1}H} NMR (Scheme 108, ii-iii). An attempt to synthesise the deuterated version (d_6) of model nitronate **411**, was unsuccessful, however d_1-nitronate **465** was prepared with ~95% of deuterium incorporation using CD_3NO_2 and the procedure described in Scheme 102 (see experimental section). Testing this nitronate under catalytic conditions resulted in formation of Michael addition product **466** as a mixture of deuterated and protonated species with partial deuterium incorporation at the C2 and C4 carbons (~61% overall) (Scheme 108, iii).



Scheme 108. Investigation of the protonation step.

The sample was characterised by ^{1}H, ^{2}H and $^{13}C\{^{1}H\}$ NMR spectroscopy. In ^{1}H NMR spectrum, the protons at C2 and C4 carbons for both diastereoisomers showed complex multiplets instead of the characteristic doublet of doublet and doublet splitting patterns respectively, observed for the corresponding non-deuterated product **438** (Figure 33). In addition, these protons integrated less than one (0.83–0.84 for C2-H and 0.72 for C4-H), consistent with the presence of deuterium at these centres. Based on the values of this integration, the approximate amount of deuterated species at C2 and C4 was ~16–17% and ~28% respectively.

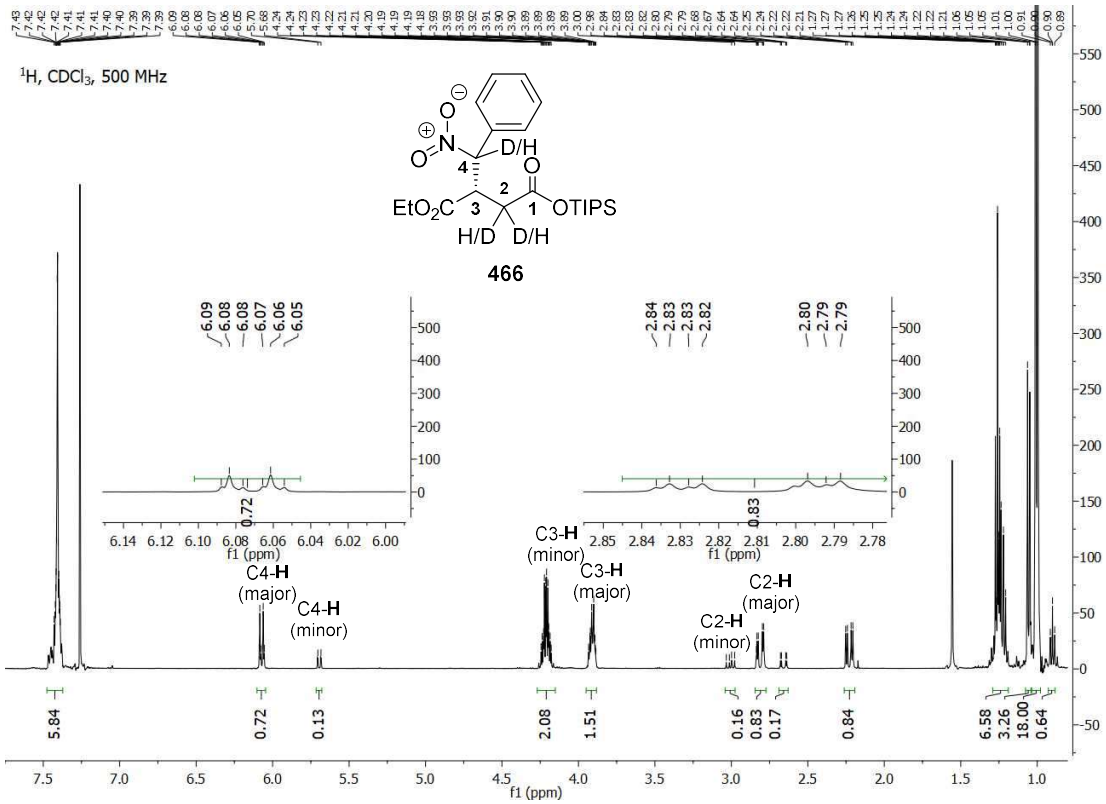


Figure 33. Section of ^{1}H NMR of partially deuterated Michael addition product **466**.

Analysing the sample **466** by ^{2}H NMR supported the presence of deuterium at C2- and C4-centres for both major and minor diastereoisomers (Figure 34). Notably, no deuterium signal was observed at C3-centre.

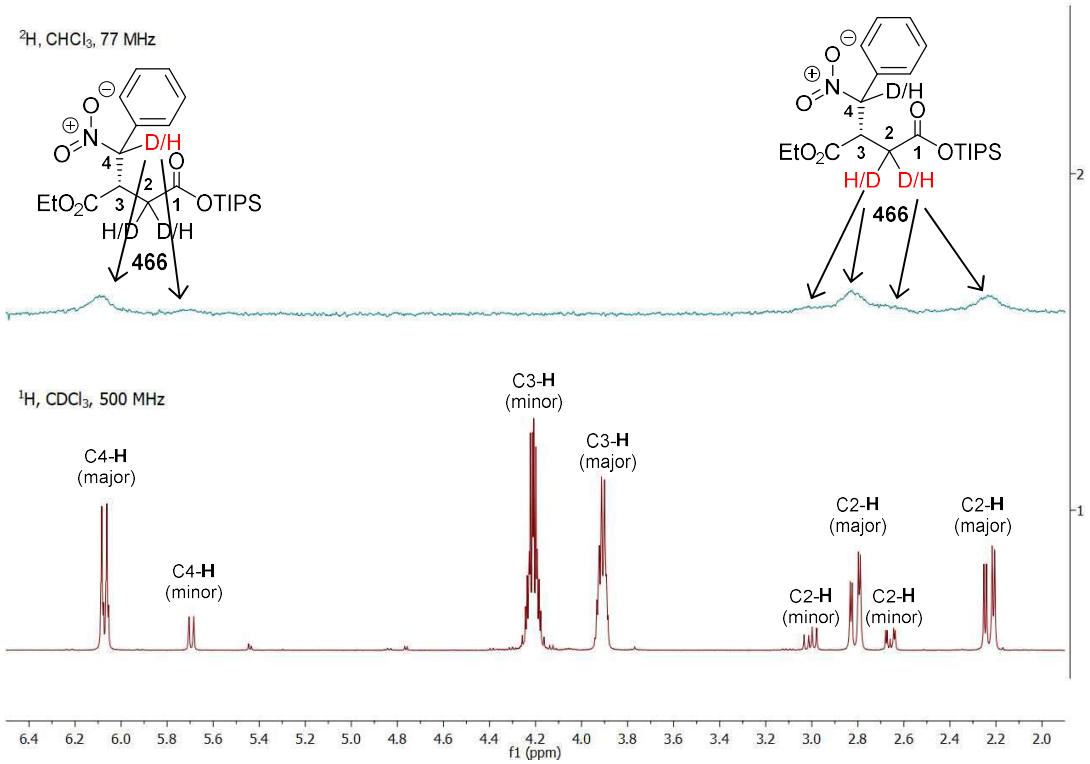


Figure 34. Section of ^{2}H NMR of partially deuterated Michael addition product **466**.

Further evidence for the deuterium incorporation was found in the $^{13}C\{^{1}H\}$ NMR spectrum, where a characteristic triplet signal at the C2-carbon of both diastereoisomers was observed (Figure 35). Moreover, multiple signals at the C3-centre indicates the presence of a complex mixture of partially deuterated Michael addition products **466** due to isotopic substitution of the heavy atom. The integration of these carbon signals was in qualitative accordance with the previous calculations to account for the amount of each deuterated species using ^{1}H NMR spectrum (Figures 33).

Supported by ^{1}H, ^{2}H and $^{13}C\{^{1}H\}$ NMR, unambiguous evidence of deuterium in compound **466** was obtained. Based on these findings, the nitronate species could potentially be involved in the protonation step, however, deuteration of 61% is less than expected (100%-*d* incorporation), which indicates that the presence of an additional proton source, such as water cannot be excluded.

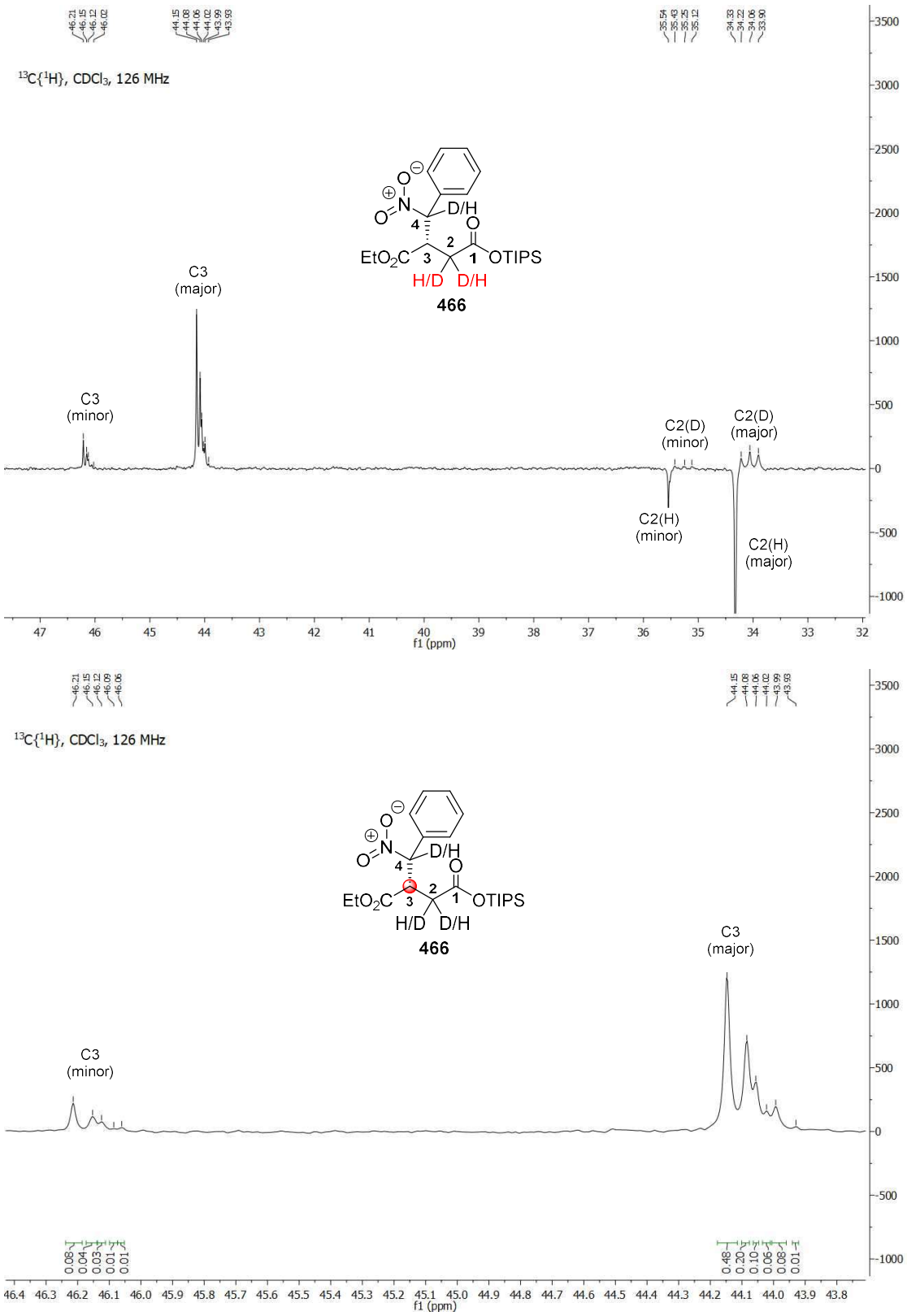
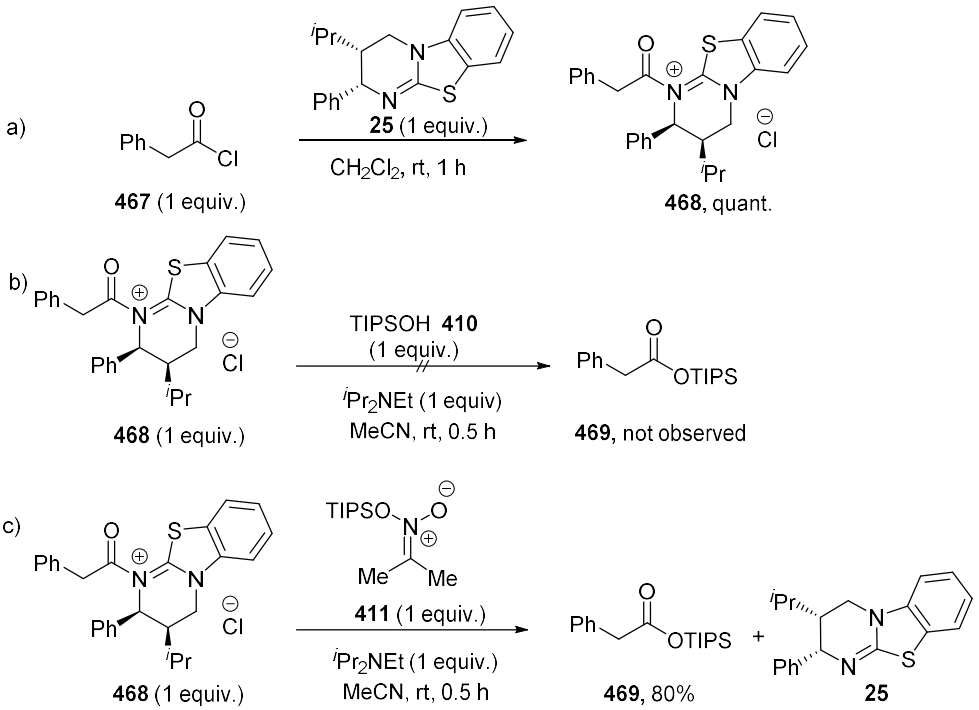


Figure 35. Sections of $^{13}C\{^{1}H\}$ NMR of partially deuterated Michael addition product **466**.

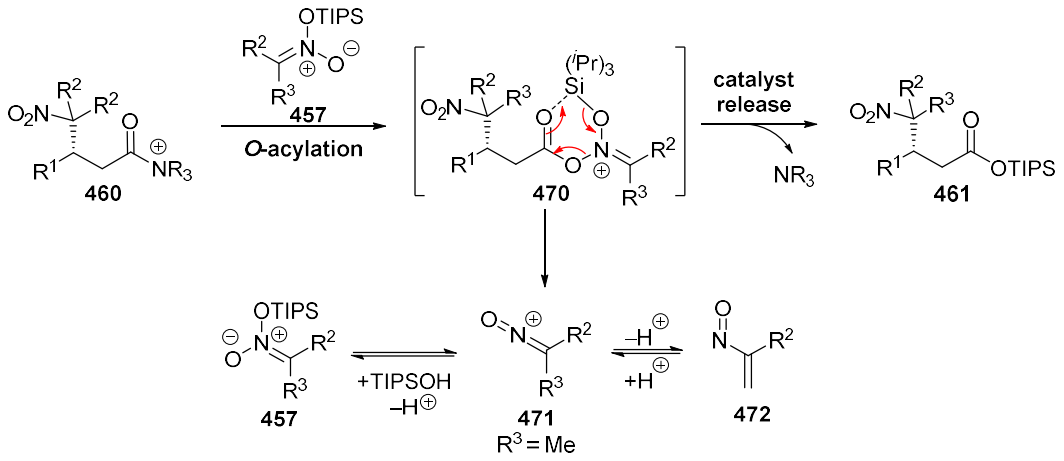
5.7.3 Studies of the catalyst turnover

To provide insight into the mechanism of the catalyst turnover, acyl isothiouronium **468** was chosen as a model of the post-Michael addition acyl isothiouronium intermediate. (2-Phenylacetyl) isothioronium **468** was prepared as a chloride salt from phenylacetyl chloride **467** and HyperBTM **25** (Scheme 109a). [24,29] The feasibility of triisopropylsilanol to facilitate the turnover was first investigated by reacting acyl isothiouronium salt **468** with silanol **410**. However, no TIPS ester was observed, and the salt remained stable in the reaction mixture, indicating that silanol is unlikely to be responsible for catalyst turnover (Scheme 109b). In contrast, subjecting the salt to the standard reaction conditions with TIPS nitronate **411** led to rapid formation of the free isothiourea and the corresponding TIPS phenylacetate **469** (80% yield) (Scheme 109c).



Scheme 109. a) Synthesis of acyl isothiouronium salt **468**. b) Reaction of **468** with TIPSOH **410**. c) Reaction of **468** with TIPS nitronate **411**.

Based on these findings, a possible mechanism for catalyst turnover can be proposed (Scheme 110). Silyl nitronate **457** is suggested to undergo *O*-acylation by post-Michael addition acyl ammonium **460** to generate intermediate **470**. Subsequent intramolecular silyl migration/[3,3] rearrangement of **470** releases the catalyst and gives enantioenriched γ-nitro silyl ester **461** along with *N*-oxoiminium species **471**, previously described in the literature.[26] This could either collapse to form nitroso derivative **472** or react with triiopropylsilanol to regenerate silyl nitronate **457**. Notably, as mentioned before, silanol **410** was both observed and isolated from the reaction mixture (Scheme 110).

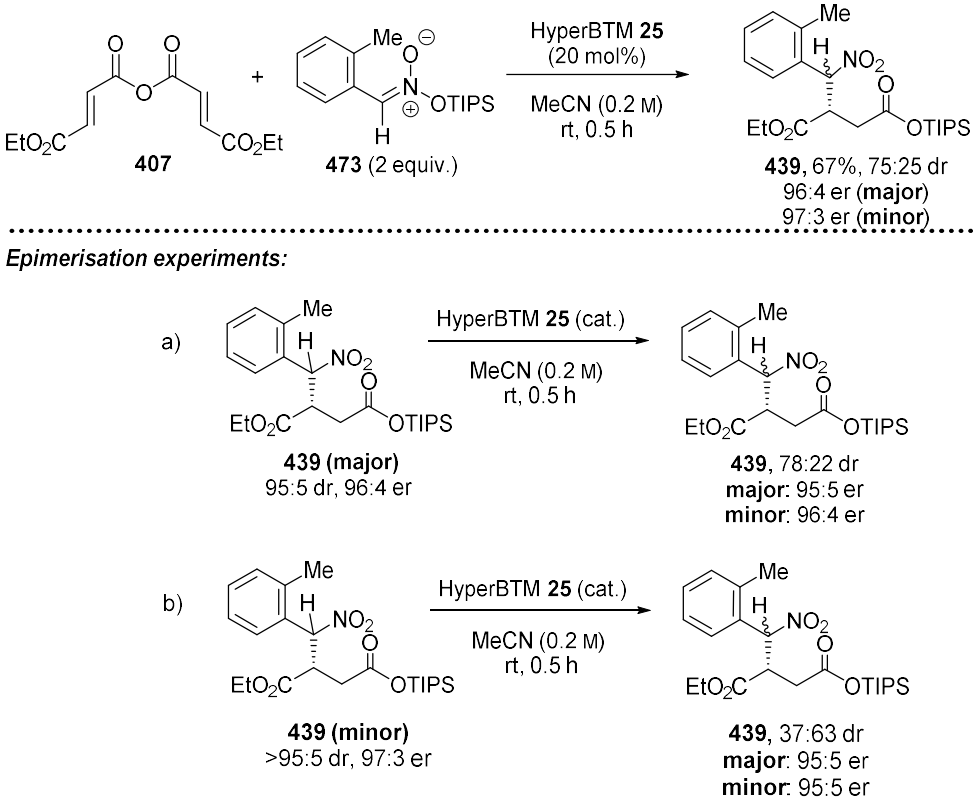


Scheme 110. Proposed mechanism for catalyst turnover and potential regeneration of silyl nitronate.

5.7.4 Origin of stereoselectivity

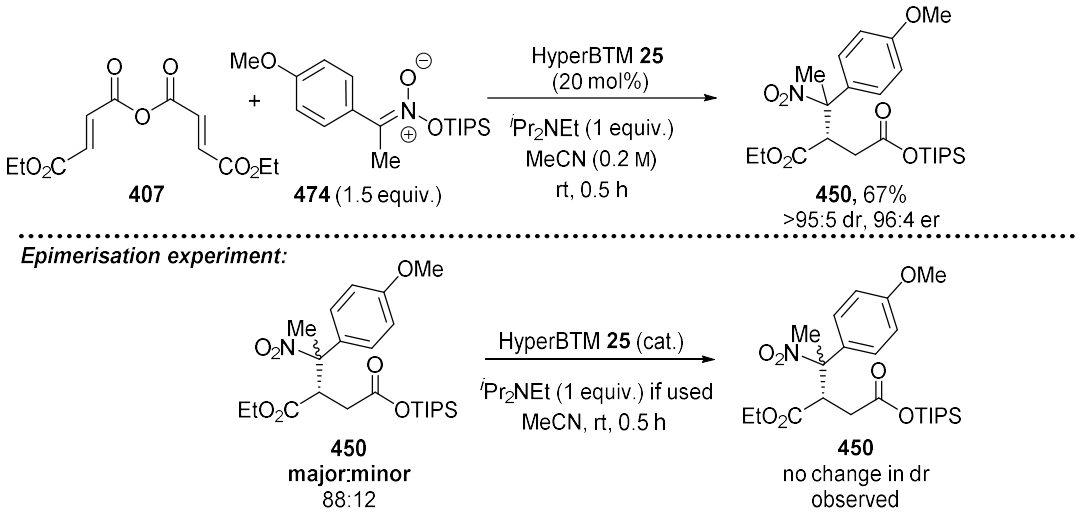
The stereochemical outcome of the (*S*)-configured stereocentre at C3 can be rationalised by a similar transition state to those previously proposed for the nucleophilic attack onto HyperBTM-derived α,β-unsaturated acyl isothiouronium intermediates (Chapter 4, Scheme 79b), with the absolute configuration of TIPS ester **423** (Scheme 99) consistent with this assignment.

To investigate if the observed diastereoselectivity was a result of kinetic or thermodynamic control, epimerisation studies were conducted. Michael addition product **439** which was formed as a mixture of diastereomers in 75:25 ratio, was used as a model compound for this study (Scheme 111). The major and minor stereoisomers were separated as enantioenriched esters both in ~95:5 dr. Subjection to the catalytic conditions resulted in substantial epimerisation of both esters after 0.5 h, with the sample enriched in the major diastereoisomer epimerised to 78:22 dr (major:minor) mixture, whilst the sample enriched in the minor diastereoisomer was epimerised to give a 37:63 dr (major:minor). Importantly, the enantiopurity of both stereoisomers remained high, indicating that epimerisation most likely occurs at the α-position to a nitro group,[31] with the stereocentre adjacent to the ester remaining unchanged. In addition, the absence of deuterium at C3 carbon in partially deuterated product **466** (Scheme 108, Figures 33-35) supports the stability of this centre towards epimerisation. It should be noted that the α-position with respect to a nitro group is most acidic and prone to epimerisation,[32] and therefore consistent with the results of this study. However, it is still inconclusive, whether the dr observed in the reaction is a result of kinetic control or epimerisation during the reaction. This study may potentially continue by monitoring the change of the diastereomeric ratio during the reaction course.



Scheme 111. Epimerisation experiments with monoarylated γ-nitro esters.

To investigate the origin of the diastereoselectivity further, Michael addition product **450**, which is fully substituted at the γ-position and formed in >95:5 dr, was selected to carry out an additional control experiment (Scheme 112). For this purpose, a minor diastereomer-enriched fraction (88:12 major:minor) was isolated and tested in the presence of HyperBTM **25**. No change in the diastereomeric ratio was observed with or without base, which confirms the stability of the C3-stereocentre adjacent to the ester functionality. This suggests the dr observed using fully-substituted nitronates is most likely kinetically-derived.



Scheme 112. Epimerisation experiment with all-substituted γ-nitro ester **450**.

5.8 Conclusions and outlook

In summary, this Chapter presents a novel approach to highly enantioenriched γ-nitro esters by exploiting the use of silyl nitronates and (*E*)-α,β-unsaturated homoanhydrides in the presence of a Lewis basic isothiourea catalyst, HyperBTM. A wide range of silyl nitronates bearing alkyl and aryl groups were prepared using simple and efficient strategies, and could be applied in the developed methodology to afford corresponding Michael addition TIPS esters (25 examples) with good to exceptional diastereo- and enantioselectivity (up to >95:5 dr, up to >99:1 er). The application of silyl nitronates allowed their use as stoichiometric reagents, which improves on the previous methodology developed in Chapter 4 where a nitroalkane was used as the reaction solvent. Notably, this strategy not only overcomes the limitation using only simple nitroalkanes in large excess, but also allows access to products containing highly substituted enantioenriched stereocentres. Among other advantages, the mild reaction conditions and short reaction times (<1 h) should be noted.

Mechanistic experiments were carried out to achieve a better understanding of the observed reactivity, in particular studying the Michael addition, protonation and catalyst turnover steps. Based on these studies, it was postulated that catalyst turnover is facilitated by the silyl nitronate through a proposed silyl migration/[3,3]-rearrangement pathway, unprecedented in enantioselective catalysis. In addition, epimerisation studies provided insight into the origin of the diastereoselectivity, showing that Michael addition products derived from mono-substituted nitronates can epimerise most likely at the stereocentre adjacent to the nitro rather than the ester group. In contract, fully-substituted nitronates give configurationally stable products under kinetic control. However, there is still great potential for further investigations of the reaction mechanism. Identification of possible reaction intermediates and studying the reaction kinetics might be challenging due to the highly reactive nature of silyl nitronates and the inability to conduct the reaction at lower catalyst loadings or temperatures due to the increased formation of alternative side-products. Of particular interest, is the dynamic silyl migration observed in this new process. Additional crossover experiments could provide further evidence for the *in situ* regeneration of silyl nitronate in the reaction mixture. This would also give a better understanding of the reaction stoichiometry.

Certain limitations of the new methodology were identified during this study, such as the requirement of an ester or an amide functionality in the β-position of the Michael acceptor to obtain the desired reactivity. In addition, the diastereo- and enantiocontrol of the additional stereocentre in the γ-position was dependent on the substrate rather than the catalyst. Although most aryl nitronates with various steric and electronic properties gave high yields and levels of stereoselectivity, heterocyclic and diaryl-substituted nitronates were not tolerated under the

reaction conditions. In conclusion, unprecedented reactivity within enantioselective α,β-unsaturated acyl ammonium catalysis was discovered, where both Michael addition and catalyst turnover are facilitated by a silyl nitronate. This methodology demonstrates a great potential in combining the powerful synthetic tool of Lewis base catalysis and the burgeoning area of external catalyst turnover with new unexpected reactivities yet to discover.

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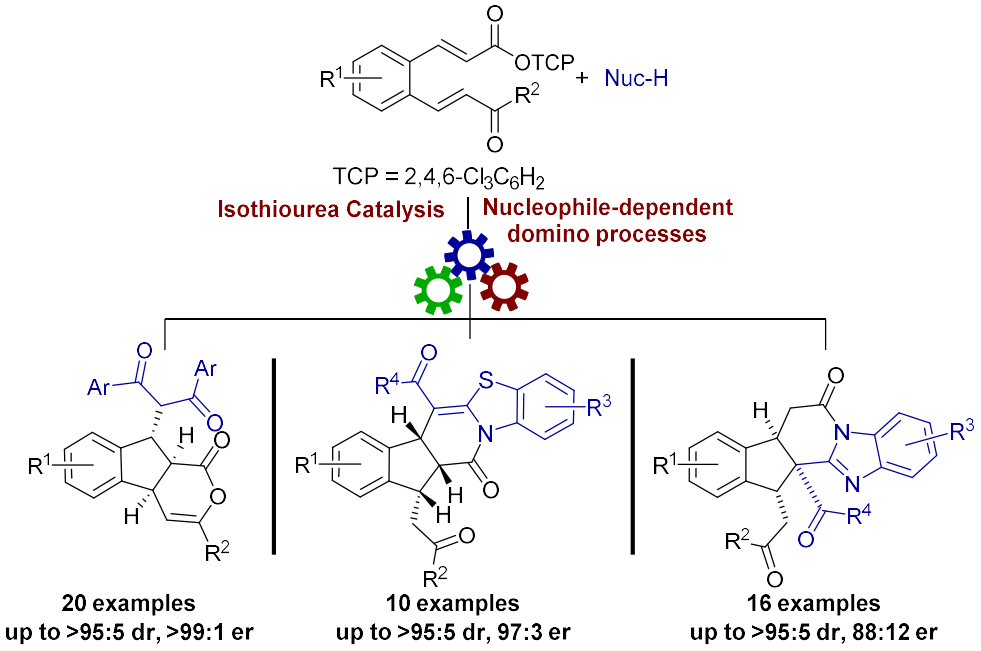
6 Conclusions and future prospectives

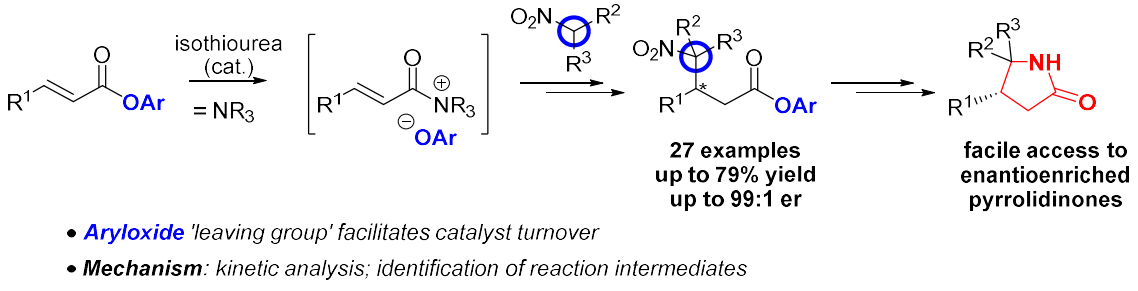
This thesis has described the studies into α,β-unsaturated acyl ammonium catalysis and showed the unique and divergent reactivity of chiral α,β-unsaturated acyl ammonium intermediates. These three-carbon synthons were readily derived from the reaction of either pre-formed bench-stable aryl esters bearing electron-deficient groups or homoanhydrides with an isothiourea catalyst. Addition of suitable nucleophiles into α,β-unsaturated acyl ammonium resulted in development of multiple novel methodologies for the efficient synthesis of highly enantioenriched polycyclic heterocycles and γ–amino acid derivatives, which have core structures found in natural products and drugs.

Firstly, the versatility of these intermediates was demonstrated by introducing a second Michael acceptor into α,β-unsaturated 2,4,6-trichlorophenol (TCP) esters as α,β-unsaturated acyl ammonium precursors. In the presence of the isothiourea catalyst HyperBTM, these esters undergo various enantioselective nucleophile-dependent domino reactions (Scheme 113). Three distinct, diastereodivergent pathways have been observed using either 1,3-dicarbonyls, acyl benzothiazoles, or acyl benzimidazoles as pro-nucleophiles to form fused polycyclic cores containing multiple contiguous stereocentres. The different domino processes make use of multiple catalytic intermediates, including α,β-unsaturated acyl ammonium, ammonium enolate and acyl ammoniums and rely upon the intrinsic differences in reactivity within each class of pro-nucleophile to selectively form the lactone or lactam products. A wide range of complex heterocycles were accessed using this methodology (46 examples) with good to exceptional levels of diastereo- and enantioselectivity (up to >95:5 dr, >99:1 er). Moreover, the resulting polycycles contain a stereodefined indane unit that can be found in a large number of biologically and pharmaceutically relevant molecules.



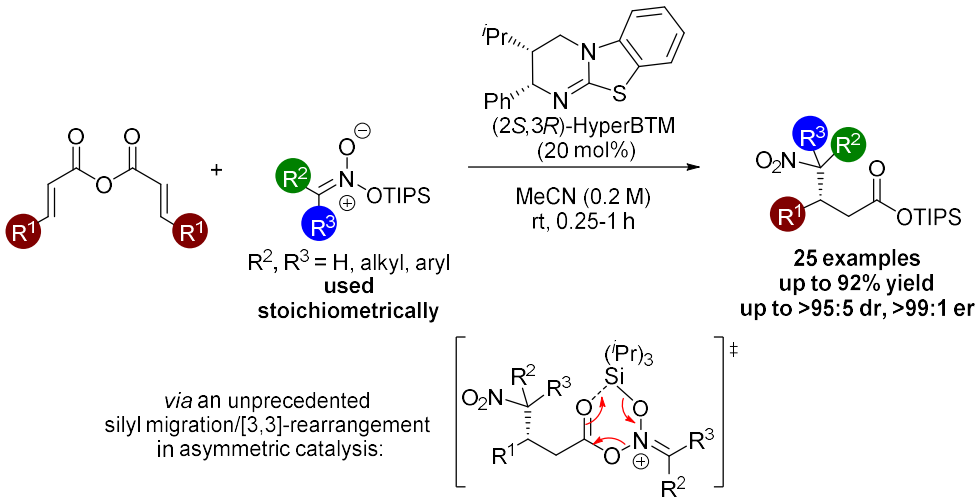
Scheme 113. Isothiourea-catalysed stereodivergent, nucleophile-dependent domino reactions.

Having demonstrated the utility and versatility of α,β-unsaturated acyl ammoniums in complex asymmetric cascade processes, the requirement of two distinct nucleophilic functionalities to facilitate catalyst turnover was recognised as an important limitation in the scope and addressed in the next part of this research. A new strategy within α,β-unsaturated acyl ammonium catalysis has been developed utilising the aryloxide release from an α,β-unsaturated aryl ester substrate to facilitate catalyst turnover (Scheme 114). This method allowed the use of simple non-tethered nucleophiles. The new protocol was applied for an enantioselective Michael addition of nitroalkanes to α,β-unsaturated 4-nitrophenyl esters. The resulting γ-nitro derivatives (27 examples) were generated in good yield (up to 79%) and excellent enantioselectivity (up to >99:1 er), with concomitant derivatisation of the products into optically active pyrrolidinones. Extensive mechanistic investiations including crossover studies and application of variable time normalisation graphical analysis delivered in-depth understanding of the reaction mechanism and complex reaction kinetics.



Scheme 114. A new general concept in α,β-unsaturated acyl ammonium catalysis.

Finally, the new strategy of catalyst turnover within α,β-unsaturated acyl ammonium catalysis was further explored using silyl nitronates as alternative simple nucleophiles. In combination with homoanhydrides and HyperBTM catalyst, these nitroalkane surrogates exhibited a unique reactivity to undergo enantioselective Michael addition and facilitate turnover of the Lewis base catalyst (Scheme 115). The postulated mechanism of the catalyst turnover through the silyl migration/[3,3]-rearrangement pathway was supported by the number of mechanistic experiments leading to a better understanding of this complex process. In contrast to the most nitro-Michael addition protocols, where the scope is limited to simple nitroalkanes used as reaction solvents, this methodology allowed the use of silyl nitronates as stoichiometric reagents to afford a wide range of γ-nitro-substituted silyl esters (25 examples) with good to excellent yields (up to 92%) and levels of stereoinduction (up to >95:5 dr, up to >99:1 er).



Scheme 115. Isothiourea-catalysed asymmetric Michael addition of silyl nitronates.

At the beginning of this PhD in late 2014, synthetic chemists have only begun to tap into the utility of α,β-unsaturated acyl ammonium intermediates for asymmetric catalysis and particularly domino processes. The research covered in this thesis has continued the exploration of this versatile activation mode by developing three distinct domino reactions with high stereodivergence of these processes through the use of suitable nucleophilic components. Most importantly, further development in this field was achieved by addressing the challenge of alternative catalyst turnover to allow for more diverse processes and application of simple nucleophiles. It can be envisioned that the scope can be further expanded in the area of α,β-unsaturated acyl ammonium catalysis through the use of previously unexplored nucleophiles. Furthermore, an apparent feature of the reactions described in this thesis is the limited number of β-substituents in the α,β-unsaturated substrate giving the desired reactivity. This provides an opportunity to explore alternative activation modes, which would allow this limitation to be

overcome. Since 2014, α,β-unsaturated acyl ammonium catalysis has emerged dramatically, and future work in this area will undoubtedly reveal hidden potential of this powerful and highly practical activation mode for unsaturated carboxylic acids.

7 Experimental

7.1 General information

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

Solvents (THF, CH_2Cl_2, PhMe) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Petroleum ether refers to the fraction of light petroleum ether boiling in the range 40-60 ºC.

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 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 Vacuubrand® 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 silica column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected.

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

Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids. Analysis was performed with Shimadzu IRsolution v1.50 software and only the characteristic peaks are quoted.

HPLC analyses were obtained on a Shimadzu HPLC consisting of a Shimadzu DGU-20A5 degasser, Shimadzu LC-20AT liquid chromatography, Shimadzu SIL-20AT auto sampler, Shimadzu CBM-20A communications bus module, Shimadzu SPD-M20A diode array detector, Shimadzu CTO-20A column oven and a Shimadzu FRC-10A fraction collector. Analysis was performed using Shimadzu LabSolutions v5.42 software and separation was achieved using the column described. All chiral HPLC traces were compared to the authentic racemic trace prepared in analogous fashion.

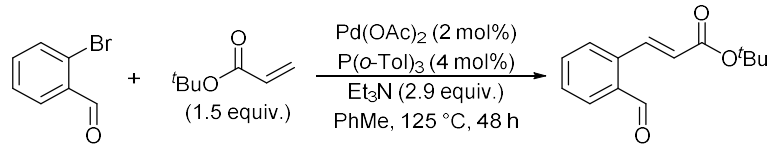
^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance II 400 (400 MHz, ^{1}H; 100 MHz, ^{13}C; 377 MHz, ^{19}F), Bruker Avance 500 (500 MHz, ^{1}H; 125 MHz, ^{13}C; 470 MHz, ^{19}F) or a Bruker Avance III 500 (500 MHz, ^{1}H; 125 MHz, ^{13}C; 470 MHz, ^{19}F) 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 and determined by analysis using MestReNova v 9.0.0 software. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), pent. (pentet), sept. (septet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets) 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 ^{1}H correlated spectroscopy (COSY), 2D ^{1}H nuclear Overhauser effect spectroscopy (NOESY), 2D ^{1}H–^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) where necessary.

Mass spectrometry (*m/z*) data were acquired by electrospray ionisation (ESI), electron impact (EI) or nanospray ionisation (NSI) at the EPSRC UK National Mass Spectrometry Facility at Swansea University. 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.

7.2 Experimental for Chapter 2

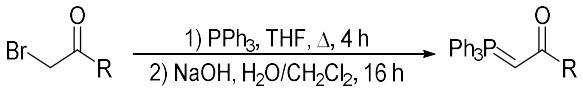
7.2.1 General procedures

General Procedure 1: *Heck Reaction*



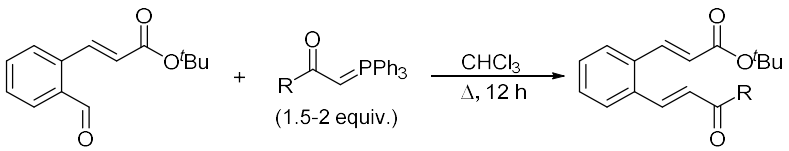
To a solution of the corresponding *o*-bromobenzaldehyde (1 equiv.) in anhydrous toluene (0.1 M) were successively added $Pd(OAc)_2$ (2 mol%), tri(*o*-tolyl)phosphine (4 mol%), (*E*)-*tert*-butyl acrylate (1.5 equiv.) and triethylamine (2.9 equiv.) at room temperature. The reaction mixture was heated at reflux for 2 days, cooled to rt, diluted with ether and filtered through a thin pad of Celite. The filtrate was diluted with water and extracted with ether. The organic layers were combined, dried over $MgSO_4$, and concentrated under vacuum. The dark thick oil obtained was purified by flash silica chromatography employing mixtures of *n*-hexane and ethyl acetate as eluents.

General Procedure 2: *Preparation of Phosphoranes*



A solution of the corresponding 2-bromoethanone (1 equiv.) and triphenylphosphine (1 equiv.) were heated at reflux in anhydrous THF for 4 h. After completion, the reaction mixture was allowed to cool to rt and the phosphonium salt was filtered and washed with Et_2O (3×100 mL). The phosphonium salt was then dissolved in H_2O:CH_2Cl_2 (1.5:1) and 2 M aq. NaOH (200 mL) was added. The mixture was stirred overnight at rt and then extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the corresponding phosphorane.

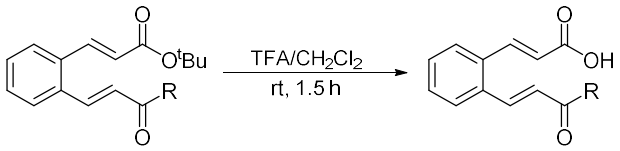
General Procedure 3: *Wittig Reaction*



To a solution of (*E*)-*tert*-butyl 3-(2-formylphenyl)acrylate (1 equiv.) in $CHCl_3$, was added the corresponding phosphorane (1.5–2.0 equiv). The reaction mixture was heated at reflux overnight

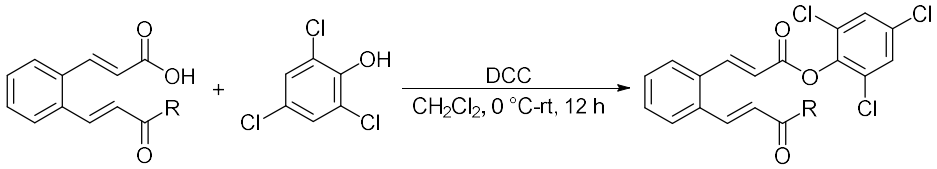
under Ar and then concentrated *in vacuo*. The residue was purified by flash silica column chromatography using a mixture of hexane and ethyl acetate (EtOAc) as eluents.

General Procedure 4: *Ester Hydrolysis*



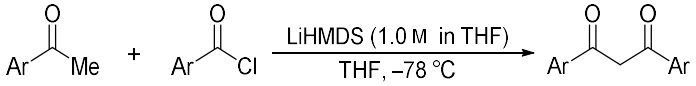
The appropriate ester was dissolved in a mixture of TFA : CH_2Cl_2 (1:2). The reaction was stirred at rt and monitored by TLC until completion. The crude mixture was concentrated *in vacuo* without further purification to give the corresponding carboxylic acid.

General Procedure 5: *Trichlorophenol (TCP) Esterification*



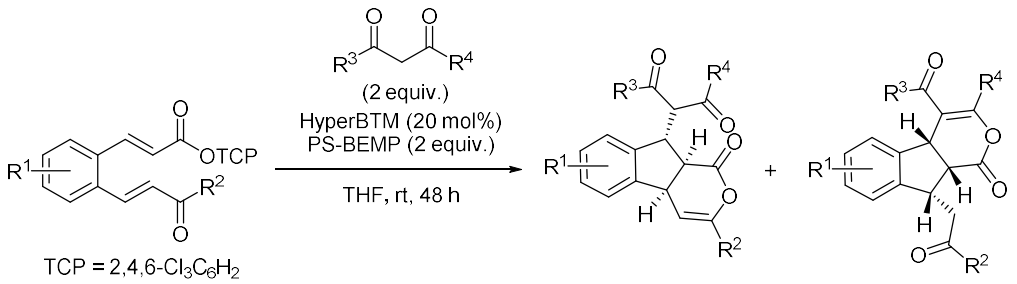
To a solution of the corresponding carboxylic acid (1 equiv.) and DCC (1.1 equiv) in CH_2Cl_2 at 0 °C was added 2,4,6-trichlorophenol (TCP-OH) (1.02 equiv) dissolved in CH_2Cl_2 dropwise. The reaction mixture was stirred for 12 h at rt. The crude mixture was filtered to remove the byproduct dicyclohexylurea and concentrated *in vacuo*. The residue was purified by flash silica column chromatography using a mixture of hexane and ethyl acetate (EtOAc) as eluents.

General Procedure 6: *Preparation of Diketones*



To a solution of arylketone (1 equiv.) in THF at −78 °C was added LiHMDS (1.0 M in THF, 1.5 equiv.) over 15 mins and the resulting mixture stirred at −78 °C for 1 h. Acid chloride (1.2 equiv.) was added dropwise as a solution in THF over 5 mins and the solution warmed to room temperature over 1 h and stirred for a further 17 h. The reaction was quenched with 10% citric acid (20 mL) and extracted with EtOAc (2 × 100 mL). The combined organics were washed with H_2O (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash silica column chromatography using a mixture of petroleum ether and diethylether (Et_2O) as eluents.

General Procedure 7: *Michael-Michael-Lactonisation Reaction with 1,3-Dicarbonyls*

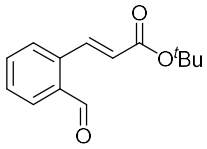


To a solution of the corresponding tricholorophenol-activated ester (1 equiv.) in anhydrous THF (0.4 M), was added isothiourea HyperBTM (20 mol%) and polymer-bound 2-*tert*-butylimino-2-diethylamino-1,3,dimethylperhydro,1,3,2,diazaphosphorine (PS-BEMP) (2 equiv.) followed by addition of the appropriate 1,3-diketone (2 equiv.). The reaction mixture was stirred for 48 h at room temperature. The crude mixture was filtered to remove the base and concentrated *in vacuo*. The residue was purified by flash silica column chromatography using mixtures of petroleum ether and ethyl acetate as eluents giving the products of approximatly 95% purity. Analytically pure compounds can be obtained after a second purification by flash silica column chromatography using dichloromethane as eluent.

7.2.2 Preparation of starting materials

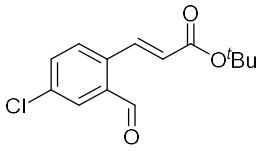
7.2.2.1 Data for *tert*-butyl acrylates

***tert*-Butyl (*E*)-3-(2-formylphenyl)acrylate (109)**



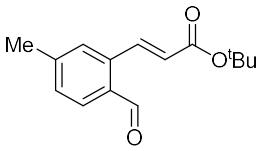
Following General Procedure 1, 2-bromobenzaldehyde (2.9 ml, 25 mmol), $Pd(OAc)_2$ (110 mg, 0.5 mmol), tri-*o*-tolylphosphine (305 mg, 1 mmol), (*E*)-*tert*-butyl acrylate (5.5 ml, 37.5 mmol) and triethylamine (10 ml, 71.7 mmol) in 50 mL PhMe and subsequent chromatography (90:10 hexane : EtOAc, R_f 0.2) afforded the title compound (5.3 g, 92%) as a brown oil. Data in agreement with the literature.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.53 (9H, s, C(CH_3)$_3$), 6.30 (1H, d, *J* 15.8, CH=C*H*–COO^{t}Bu), 7.52 (1H, td, *J* 7.4, 1.7, C*H*-Ar), 7.59 (2H, qd, *J* 7.8, 3.7, C*H*-Ar), 7.86 (1H, dd, *J* 7.6, 1.0, C*H*-Ar), 8.40 (1H, d, *J* 15.9, C*H*=CH–COO^{t}Bu), 10.30 (1H, s, CO*H*).

***tert*-Butyl (*E*)-3-(4-chloro-2-formylphenyl)acrylate (165)**



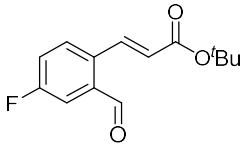
Following General Procedure 1, 5-chloro-2-bromobenzaldehyde (1.1 ml, 5 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), tri-*o*-tolylphosphine (61 mg, 0.2 mmol), (*E*)-*tert*-butyl acrylate (1.1 ml, 7.5 mmol) and triethylamine (2.0 ml, 14.3 mmol) in 10 mL PhMe and subsequent chromatography (90:10 hexane:EtOAc, R_f 0.2) afforded the title compound (908 mg, 68%) as a yellow solid. mp 55–57 °C; ν_{max} (film) 3003 (alkenyl C-H), 2978 (alkyl C-H), 1699 (C=O); 1636 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 6.30 (1H, d, *J* 15.8, CH=C*H*–COO^{t}Bu), 7.53–7.61 (2H, m, C*H*-Ar), 7.85 (1H, dd, *J* 7.6, 1.0, C*H*-Ar), 8.31 (1H, d, *J* 15.8, C*H*=CH–COO^{t}Bu), 10.30 (1H, s, CO*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (C(*C*H$_3$)$_3$), 81.4 (*C*(CH$_3$)$_3$), 126.0 (CH=*C*H–COO*t*Bu), 129.5 (*C*H-Ar), 131.1 (*C*H-Ar), 134.0 (*C*-Ar), 134.9 (*C*-Cl), 135.5 (*C*-Ar), 136.2 (*C*-Ar), 138.2 (*C*H=CH–COO^{t}Bu), 165.4 (*C*OO^{t}Bu), 190.2 (*C*OH); *m/z* (NSI$^+$) 289 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{14}H_{15}{}^{35}ClO_3Na$ [M+Na]$^+$, found 289.0604, requires 289.0602 (+0.7 ppm).

***tert*-Butyl (*E*)-3-(2-formyl-5-methylphenyl)acrylate (166)**



Following General Procedure 1, 4-methyl-2-bromobenzaldehyde (995 mg, 5 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), tri-*o*-tolylphosphine (61 mg, 0.2 mmol), (*E*)-*tert*-butyl acrylate (1.5 equiv.) and triethylamine (2.0 ml, 14.3 mmol) in 10 mL PhMe and subsequent chromatography (90:10 hexane : EtOAc, R_f 0.2) afforded the title compound (950 mg, 77%) as a yellow oil. ν_{max} (film) 3001 (alkenyl C-H), 2978 (alkyl C-H), 1697 (C=O), 1634 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 2.43 (3H, s, Ar-C*H*$_3$), 6.30 (1H, d, *J* 15.8, CH=C*H*–COO^{t}Bu), 7.33 (1H, d, *J* 7.8, C*H*-Ar), 7.42 (1H, s, C*H*-Ar), 7.77 (1H, d, *J* 7.8, C*H*-Ar), 8.40 (1H, d, *J* 15.8, C*H*=CH–COO^{t}Bu), 10.26 (1H, s, CO*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.9 (Ar-*C*H$_3$) 28.3 (C(*C*H$_3$)$_3$), 81.0 (*C*(CH$_3$)$_3$), 125.1 (CH=*C*H–COO^{t}Bu), 128.7 (*C*H-Ar), 130.6 (*C*H-Ar), 131.7 (*C*-Ar), 137.1 (*C*-Ar), 140.0 (*C*H=CH–COO^{t}Bu), 145.0 (*C*-Me), 165.7 (*C*OO^{t}Bu), 191.5 (*C*OH); *m/z* (NSI$^+$) 515 ([2M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{15}H_{18}O_3Na$ [M+Na]$^+$, found 269.1147, requires 269.1148 (–0.4 ppm).

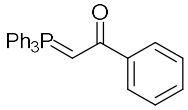
***tert*-Butyl (*E*)-3-(4-fluoro-2-formylphenyl)acrylate (167)**



Following General Procedure 1, 5-fluoro-2-bromobenzaldehyde (1.0 g, 5 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), tri-*o*-tolylphosphine (61 mg, 0.2 mmol), (*E*)-*tert*-butyl acrylate (1.5 eq) and triethylamine (2.0 ml, 14.3 mmol) in 10 mL PhMe and subsequent chromatography (90:10 hexane : EtOAc, R_f 0.2) afforded the title compound (878 mg, 70%) as a yellow oil. ν_{max} (film) 2980 (alkyl C-H), 1705 (C=O), 1605 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 6.28 (1H, d, *J* 15.8, CH=C*H*–COO^{t}Bu), 7.31 (1H, td, *J* 8.2, 2.8, C*H*-Ar), 7.58 (1H, dd, *J* 8.6, 2.8, C*H*-Ar), 7.63 (1H, dd, *J* 8.6, 5.1, C*H*-Ar), 8.30 (1H, d, *J* 15.8, C*H*=CH–COO^{t}Bu), 10.32 (1H, s, CO*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −109.7; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (C(*C*H$_3$)$_3$), 81.3 (*C*(CH$_3$)$_3$), 117.1 (d, $^2J_{CF}$ = 22.3, C_{Ar}-F), 117.2 (*C*H-Ar), 121.3 (CH=*C*H–COO^{t}Bu), 121.4 (d, $^2J_{CF}$ = 22.0, C_{Ar}-F), 125.7 (*C*H-Ar), 130.3 (*C*H-Ar), 133.5 (2×*C*-Ar), 138.1 (*C*H=CH–COO^{t}Bu), 163.4 (d, $^1J_{CF}$ = 252.8, C_{Ar}-F), 164.4 (*C*-F), 165.4 (*C*OO^{t}Bu), 190.0 (*C*OH); *m/z* (NSI$^+$) 273 ([M+Na]$^+$, 85%, 523 ([2M+Na]$^+$, 60%); HRMS (NSI$^+$) $C_{14}H_{15}F_1O_3Na$ [M+Na]$^+$, found 273.0903, requires 273.0897 (+2.0 ppm).

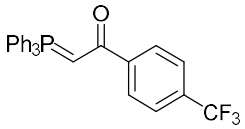
7.2.2.2 Data for phosphoranes

1-Phenyl-2-(triphenylphospharanylidene)ethanone (132)



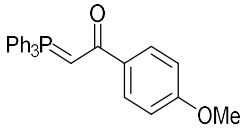
Following General Procedure 2, 2-bromo-1-phenylethanone (11.1 g, 55.5 mmol), triphenyphosphine (14.6 g, 55.5 mmol), anhydrous THF (250 mL) gave the title compound as a white solid (18.7 g, 88%). mp 177–179 °C; {Lit.[2] mp 178–180 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.43 (1H, d, *J* 24.6, C*H*), 7.34–7.37 (3H, m, Ar*H*), 7.45–7.58 (9H, m, Ar*H*), 7.70–7.75 (6H, m, Ar*H*), 7.96–7.99 (2H, m, Ar*H*). Data in agreement with the literature.[2]

1-(4-Trifluoromethyl)phenyl)-2-(triphenylphospharanylidene)ethanone (135)



Following General Procedure 2, 2-bromo-1-(4-trifluoromethyl)phenyl)ethanone (7.5 g, 28.1 mmol), triphenyphosphine (7.4 g, 28.1 mmol), anhydrous THF (100 mL) gave the title compound as a yellow solid (12 g, 95%). mp 156–158 °C; {Lit.[1] mp 158–160 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.46 (1H, d, *J* 24.5, C*H*), 7.47–7.51 (6H, m, Ar*H*), 7.57–7.61 (5H, m, Ar*H*), 7.69–7.73 (6H, m, Ar*H*), 8.04–8.06 (2H, m, Ar_{CF3}, *H*–2,6). Data in agreement with the literature.[3]

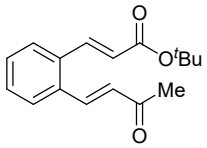
1-(4-Methoxyphenyl)-2-(triphenylphospharanylidene)ethanone (136)



Following General Procedure 2, 2-bromo-1-(4-methoxyphenyl)ethanone (15.0 g, 65.5 mmol), triphenyphosphine (17.2 g, 65.5 mmol), anhydrous THF (200 mL) gave the title compound as a white solid (23 g, 94%). mp 149–151 °C; {Lit.[1] mp 150–153 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.36 (1H, br.s, C*H*), 6.86–6.89 (2H, m, Ar*H*), 7.44–7.48 (6H, m, Ar*H*), 7.53–7.56 (3H, m, Ar*H*), 7.70–7.74 (6H, m, Ar*H*), 7.93–7.95 (2H, m, Ar*H*). Data in agreement with the literature.[4]

7.2.2.3 Data for enone *tert*-butyl esters

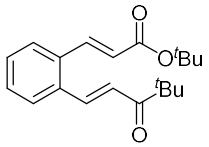
***tert*-Butyl (*E*)-3-(2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (111)**



Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(2-formylphenyl)acrylate (1.36 g, 5.88 mmol) in $CHCl_3$, was added a phosphorane, 1-(triphenylphosphanylidene)-2-propanone, (3.80 g, 11.8 mmol, 2 equiv.). The reaction mixture was refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.25) to give the title compound (1.52 g, 95%) as a brown oil. ν_{max} (film) 3087 (alkenyl C-H), 2976 (alkyl C-H), 1705 (C=O); 1672 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, $C(CH_3)_3$), 2.40 (3H, s, $COCH_3$), 6.29 (1H, d, *J* 15.8, CH=C*H*– $CO_2{}^t$Bu), 6.60 (1H, d, *J* 15.5, CH=C*H*-COMe), 7.37–

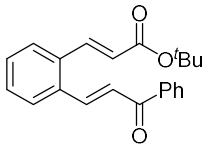
7.40 (2H, m, C*H*-Ar), 7.55–7.59 (2H, m, C*H*-Ar), 7.87 (1H, d, *J* 15.5, C*H*=CH–COMe), 7.94 (1H, d, *J* 15.8, C*H*=CH–CO_2*t*Bu); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 27.7 ($CO\mathit{C}H_3$), 28.3 ($C(\mathit{C}H_3)_3$), 81.0 ($\mathit{C}(CH_3)_3$), 124.0 (CH=*C*H–CO_2*t*Bu), 127.7 (*C*H-Ar), 127.8 (*C*H-Ar), 130.0 (*C*H-Ar), 130.3 (*C*H-Ar), 130.5 (CH=*C*H-CO-Me), 134.3 (*C*-Ar), 134.8 (*C*-Ar), 140.2 (*C*H=CH-CO-Me), 140.2 (*C*H=CH–COO*t*Bu), 165.9 ($\mathit{C}O_2$*t*Bu), 198.2 (*C*OC-Me); *m/z* (NSI^+) 567 ($[2M+Na]^+$, 100%), 290 ($[M+NH_4]^+$, 45%); HRMS (NSI^+) $C_{17}H_{24}O_3N_1$ $[M+NH_4]^+$, found 290.1755, requires 290.1751 (+1.5 ppm).

tert-Butyl (_E_)-3-(2-((_E_)-4,4-dimethyl-3-oxopent-1-en-1-yl)phenyl)acrylate (138)



Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(2-formylphenyl)acrylate (0.43 g, 1.86 mmol) in $CHCl_3$, was added a phosphorane, 1-(triphenylphospharanylidene)-3,3-dimethyl-2-butanone, (1.00 g, 2.79 mmol, 1.5 equiv.). The reaction mixture was refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.3) to give the title compound (0.43 g, 74%) as a yellow solid. mp 87–88 °C; ν_{max} (film) 3003 (alkenyl C-H), 2976 (alkyl C-H), 1703 (C=O); 1680 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.23 (9H, s, COC($\mathit{C}H_3$)$_3$), 1.54 (9H, s, $CO_2C(\mathit{C}H_3)_3$), 6.27 (1H, d, *J* 15.8, CH=C*H*–CO_2*t*Bu), 6.97 (1H, d, *J* 15.5, CH=C*H*-CO*t*Bu), 7.37–7.40 (2H, m, C*H*-Ar), 7.52–7.59 (2H, m, C*H*-Ar), 7.94 (1H, d, *J* 15.8, C*H*=CH–CO_2*t*Bu), 7.98 (1H, d, *J* 15.5, C*H*=CH–CO*t*Bu); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 26.4 (COC($\mathit{C}H_3$)$_3$), 28.3 ($CO_2C(\mathit{C}H_3)_3$), 43.4 ($CO\mathit{C}(CH_3)_3$), 80.9 ($CO_2\mathit{C}(CH_3)_3$), 123.7 (CH=*C*H–CO_2*t*Bu), 125.1 (CH=*C*H-CO*t*Bu), 127.9 (*C*H-Ar), 128.3 (*C*H-Ar), 129.8 (*C*H-Ar), 129.9 (*C*H-Ar), 135.1 (2×*C*-Ar), 140.0 (*C*H=CH-CO*t*Bu), 141.0 (*C*H=CH–CO_2*t*Bu), 165.8 ($\mathit{C}O_2$*t*Bu), 203.9 (*C*O*t*Bu); *m/z* (NSI^+) 332 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{20}H_{30}O_3N_1$ $[M+NH_4]^+$, found 332.2225, requires 332.2220 (+1.4 ppm).

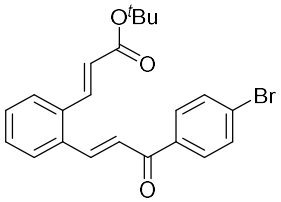
(_E_)-_tert_-Butyl 3-(2-((_E_)-3-oxo-3-phenylprop-1-en-1-yl)phenyl)acrylate (139)



Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(2-formylphenyl)acrylate (6.43 g, 27.7 mmol) in $CHCl_3$, was added a phosphorane, 1-phenyl-2-(triphenylphosphoranylidene)-ethanone, (15.8 g, 41.5 mmol, 1.5 equiv.). The reaction mixture was refluxed overnight under Ar and the

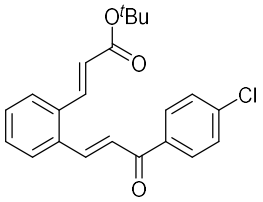
concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.25) to give the title compound (8.20 g, 88%) as a brown oil. ν_{max} (film) 3084 (alkenyl C-H), 2973 (alkyl C-H), 1703 (C=O); 1662 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 6.30 (1H, d, *J* 15.8, CH=C*H*–COO^{t}Bu), 7.41 (1H, d, *J* 15.5, CH=C*H*-COC-Ph), 7.41–7.42 (2H, m, C*H*-Ar), 7.50–7.53 (2H, m, C*H*-Ar), 7.57–7.62 (1H, m, C*H*-Ph), 7.66–7.69 (1H, m, C*H*-Ph), 7.72–7.69 (1H, m, C*H*-Ph), 8.00 (1H, d, *J* 15.8, C*H*=CH–CO-Ph) 8.02–8.05 (2H, m, C*H*-Ph), 8.13 (1H, d, *J* 15.6, C*H*=CH–COO^{t}Bu); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (C(*C*H$_3$)$_3$), 81.0 (*C*(CH$_3$)$_3$), 124.0 (CH=*C*H–COO^{t}Bu), 126.0 (CH=*C*H-CO-Ph), 128.0 (*C*H-Ar), 128.2 (*C*H-Ar), 128.7 (2×*C*H-Ph), 128.8 (2×*C*H-Ph), 129.9 (*C*H-Ar), 130.3 (*C*H-Ar), 133.1 (*C*H-Ph), 134.9 (*C*-Ar), 135.2 (*C*-Ar), 138.1 (*C*-Ph), 140.7 (*C*H=CH-CO-Ph), 141.8 (*C*H=CH–COO^{t}Bu), 165.8 (*C*OO^{t}Bu), 190.2 (*C*OC-Ph); *m/z* (NSI$^+$) 386 ([2M+NH$_4$]$^+$, 100%), 352 ([M+NH$_4$]$^+$, 60%); HRMS (NSI$^+$) $C_{22}H_{26}O_3N_1$ [M+NH$_4$]$^+$, found 352.1911, requires 352.1907 (+1.1 ppm).

tert-Butyl (*E*)-3-(2-((*E*)-3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylate (140)



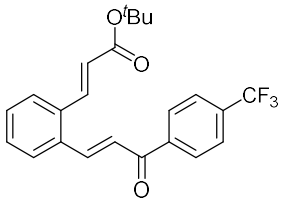
Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(2-formylphenyl)acrylate (0.47 g, 2 mmol) in $CHCl_3$, was added a phosphorane, 1-(4-bromo)-phenyl-2-(triphenylphosphoranylidene)ethanone, (1.8 g, 4.0 mmol, 2 equiv.). The reaction mixture was refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane:EtOAc, R_f 0.25) to give the title compound (0.67 g, 80%) as a pale peach solid. mp 116–117 °C; ν_{max} (film) 3061 (alkenyl C-H), 2982 (alkyl C-H), 1697 (C=O); 1607 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 6.30 (1H, d, *J* 15.8, CH=C*H*–CO$_2$^{t}Bu), 7.35 (1H, d, *J* 15.5, CH=C*H*-COC-Ph$_{Br}$), 7.40–7.45 (2H, m, C*H*-Ar), 7.58–7.60 (1H, m, C*H*-Ar), 7.64–7.67 (2H, m, C*H*-Ph$_{Br}$), 7.66–7.69 (1H, m, C*H*-Ar), 7.89–7.91 (1H, m, C*H*-Ph$_{Br}$), 7.99 (1H, d, *J* 15.8, C*H*=CH–CO$_2$^{t}Bu), 8.13 (1H, d, *J* 15.5, C*H*=CH–CO-Ph$_{Br}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (C(*C*H$_3$)$_3$), 81.1 (*C*(CH$_3$)$_3$), 124.1 (CH=*C*H–CO$_2$^{t}Bu), 125.4 (CH=*C*H-CO-Ph$_{Br}$), 128.0 (*C*H-Ar), 128.3 (*C*H-Ar), 129.9 (*C*H-Ar), 130.3 (2×*C*H-Ph$_{Br}$), 130.5 (*C*H-Ar), 132.2 (2×*C*H-Ph$_{Br}$), 134.7 (*C*-Ar), 135.3 (*C*-Ar), 136.8 (*C*-Ph$_{Br}$), 140.6 (*C*H=CH-CO-Ph$_{Br}$), 142.4 (*C*H=CH–CO$_2$^{t}Bu), 165.8 (*C*O$_2$^{t}Bu), 189.2 (*C*OC-Ph$_{Br}$); *m/z* (NSI$^+$) 849 ([2M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{21}O_3{}^{79}BrNa$ [M+NH$_4$]$^+$, found 435.0562, requires 435.0566 (−1.0 ppm).

tert-Butyl (_E_)-3-(2-((_E_)-3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylate (141)



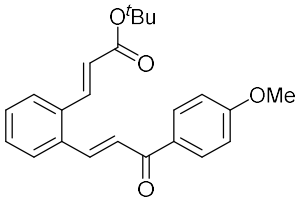
Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(2-formylphenyl)acrylate (0.45 g, 1.9 mmol) in $CHCl_3$, was added a phosphorane, 1-(4-chloro)-phenyl-2-(triphenylphosphornylidene)-ethanone, (1.6 g, 3.8 mmol, 2 equiv.). The reaction mixture was refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.25) to give the title compound (0.68 g, 95%) as a pale yellow solid. mp 118–119 °C; ν_{max} (film) 3113 (alkenyl C-H), 2981 (alkyl C-H), 1697 (C=O); 1665 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 6.30 (1H, d, *J* 15.8, CH=C*H*–$CO_2{}^t$Bu), 7.36 (1H, d, *J* 15.5, CH=C*H*-COC-Ph$_{Cl}$), 7.40–7.45 (2H, m, C*H*-Ar), 7.46–7.51 (2H, m, C*H*-Ph$_{Cl}$), 7.58–7.60 (1H, m, C*H*-Ar), 7.66–7.68 (1H, m, C*H*-Ar), 7.97–7.99 (1H, m, C*H*-Ph$_{Cl}$), 7.99 (1H, d, *J* 15.8, C*H*=CH–CO-Ph$_{Cl}$), 8.13 (1H, d, *J* 15.5, C*H*=CH–$CO_2{}^t$Bu); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (C(*C*H$_3$)$_3$), 81.1 (*C*(CH$_3$)$_3$), 124.1 (CH=*C*H–$CO_2{}^t$Bu), 125.5 (CH=*C*H-CO-Ph$_{Cl}$), 128.0 (*C*H-Ar), 128.3 (*C*H-Ar), 129.2 (2×*C*H-Ph$_{Cl}$), 129.9 (*C*H-Ar), 130.2 (2×*C*H-Ph$_{Cl}$), 130.5 (*C*H-Ar), 134.7 (*C*-Ar), 135.3 (*C*-Ar), 136.4 (*C*-Ph$_{Cl}$), 140.7 (*C*H=CH-CO-Ph$_{Cl}$), 142.3 (*C*H=CH–$CO_2{}^t$Bu), 165.8 (*C*O$_2{}^t$Bu), 188.8 (*C*OC-Ph$_{Cl}$); *m/z* (NSI$^+$) 759 ([2M+Na]$^+$, 100%), 775 ([2M+K]$^+$, 75%), 391 ([M+Na]$^+$, 70%); HRMS (NSI$^+$) $C_{22}H_{21}O_3{}^{35}ClNa$ [M+Na]$^+$, found 391.1074, requires 391.1071 (+0.7 ppm).

***tert*-Butyl (*E*)-3-(2-((*E*)-3-(4-trifluoromethyl)phenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylate (142)**



Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(2-formylphenyl)acrylate (0.47 g, 2.1 mmol) in $CHCl_3$, was added a phosphorane, 1-(4-trifluoro)-phenyl-2-(triphenylphosphoranylidene)ethanone, (0.89 g, 4.0 mmol, 2 equiv.). The reaction mixture was refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.25) to give the title compound (0.76 g, 90%) as a yellow solid. mp 95–97 °C; ν_{max} (film) 3103 (alkenyl C-H), 2982 (alkyl C-H), 1695 (C=O); 1668 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 6.30 (1H, d, *J* 15.8, CH=C*H*–$CO_2{}^t$Bu), 7.37 (1H, d, *J* 15.6, CH=C*H*-COC-Ph$_{CF3}$), 7.40–7.47 (2H, m, C*H*-Ar), 7.58–7.60 (1H, m, C*H*-Ar), 7.66–7.68 (1H, m, C*H*-Ar), 7.77–7.78 (2H, m, C*H*-Ph$_{CF3}$), 7.99 (1H, d, *J* 15.8, C*H*=CH–$CO_2{}^t$Bu), 8.11–8.13 (2H, m, C*H*-Ph$_{CF3}$) 8.15 (1H, d, *J* 15.6, C*H*=CH–CO-Ph$_{CF3}$); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −63.0 (C*F*$_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (C(*C*H$_3$)$_3$), 81.1 (*C*(CH$_3$)$_3$), 124.3 (CH=*C*H–$CO_2{}^t$Bu), 125.4 (CH=*C*H-CO-Ph$_{CF3}$), 125.9 (2×*C*H-Ph$_{CF3}$), 125.9 (q, $^3J_{CF}$ = 3.4, C_{Ar}-CF_3), 127.0 (q, $^1J_{CF}$ = 272.6, C_{Ar}-CF_3), 128.9 (*C*-Ph$_{CF3}$), 128.1 (*C*H-Ar), 128.3 (*C*H-Ar), 129.0 (2×*C*H-Ph$_{CF3}$), 130.0 (*C*H-Ar), 130.7 (*C*H-Ar), 134.3 (q, $^2J_{CF}$ = 31.2, C_{Ar}-CF_3), 134.4 (*C*-Ar), 135.4 (*C*-Ar), 140.5 (*C*H=CH-CO-Ph$_{CF3}$), 140.9 (*C*-Ph$_{CF3}$), 143.1 (*C*H=CH–$CO_2{}^t$Bu), 165.8 (*C*O$_2{}^t$Bu), 189.5 (*C*OC-Ph$_{CF3}$); *m/z* (NSI$^+$) 425 ([M+Na]$^+$, 100%), 827 ([2M+Na]$^+$, 45%); HRMS (NSI$^+$) $C_{23}H_{21}O_3F_3Na$ [M+Na]$^+$, found 425.1332, requires 425.1335 (–0.7 ppm).

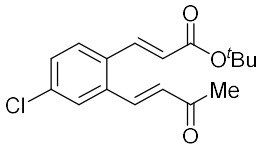
***tert*-Butyl (*E*)-3-(2-((*E*)-3-(4-methoxy)phenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylate (143)**



Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(2-formylphenyl)acrylate (0.47 g, 2.0 mmol) in $CHCl_3$, was added a phosphorane, 1-(4-methoxy)-phenyl-2-(triphenylphosphoranylidene)ethanone, (0.75 g, 4.0 mmol, 2 equiv.). The reaction mixture was

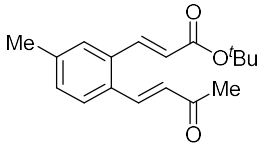
refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.20) to give the title compound (0.68 g, 93%) as a yellow solid. mp 84–85 °C; ν_{max} (film) 3057 (alkenyl C-H), 2980 (alkyl C-H), 1690 (C=O); 1661 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 3.89 (1H, s, OC*H*$_3$), 6.29 (1H, d, *J* 15.8, CH=C*H*–$CO_2{}^t$Bu), 7.39–7.43 (2H, m, C*H*-Ar), 7.41 (1H, d, *J* 15.5, CH=C*H*-COC-Ph$_{OMe}$), 7.56–7.59 (1H, m, C*H*-Ar), 7.66–7.68 (1H, m, C*H*-Ar), 8.00 (1H, d, *J* 15.8, C*H*=CH–$CO_2{}^t$Bu), 8.04–8.05 (2H, m, C*H*-Ph$_{OMe}$), 8.11 (1H, d, *J* 15.5, C*H*=CH–CO-Ph$_{OMe}$), ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (C(*C*H$_3$)$_3$), 55.7 (O*C*H$_3$), 81.0 (*C*(CH$_3$)$_3$), 114.0 (2×*C*H-Ph$_{OMe}$), 123.9 (CH=*C*H–$CO_2{}^t$Bu), 126.0 (CH=*C*H-CO-Ph$_{OMe}$), 127.9 (*C*H-Ar), 128.2 (*C*H-Ar), 129.8 (*C*H-Ar), 130.1 (*C*H-Ar), 131.0 (*C*-Ph$_{OMe}$), 131.1 (2×*C*H-Ph$_{OMe}$), 135.1 (2×*C*-Ar), 140.9 (*C*H=CH-CO-Ph$_{OMe}$), 141.0 (*C*H=CH–$CO_2{}^t$Bu), 163.7 (Ph*C*-OMe), 165.9 (*C*$O_2{}^t$Bu), 188.4 (*C*OC-Ph$_{OMe}$); *m/z* (NSI$^+$) 751 ([2M+Na]$^+$, 100%), 387 ([2M+K]$^+$, 50%), 387 ([M+Na]$^+$, 40%); HRMS (NSI$^+$) $C_{23}H_{25}O$ [M+H]$^+$, found 365.1750, requires 365.1747 (+0.7 ppm).

***tert*-Butyl (*E*)-3-(4-chloro-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (168)**



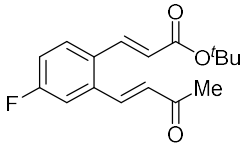
Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(4-chloro-2-formylphenyl)acrylate (828 mg, 3.30 mmol) in $CHCl_3$, was added a phosphorane, 1-(triphenylphosphanylidene)-2-propanone (2.1 g, 6.60 mmol, 2 equiv). The reaction mixture was refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.25) to give the title compound (841 mg, 83%) as a yellow solid. mp 127–129 °C; ν_{max} (film) 2978 (alkenyl C-H), 2931 (alkyl C-H), 1705 (C=O); 1674 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 2.41 (3H, s, COC*H*$_3$), 6.28 (1H, d, *J* 15.8, CH=C*H*– $CO_2{}^t$Bu), 6.61 (1H, d, *J* 16.0, CH=C*H*-COMe), 7.36 (1H, dd, *J* 8.4, 2.1, C*H*-Ar), 7.50–7.55 (2H, m, C*H*-Ar), 7.79 (1H, d, *J* 16.0, C*H*=CH–COMe), 7.94 (1H, d, *J* 15.8, C*H*=CH–$CO_2{}^t$Bu); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.1 (CO*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 81.3 (*C*(CH$_3$)$_3$), 124.4 (CH=*C*H–$CO_2{}^t$Bu), 127.6 (*C*H-Ar), 129.1 (*C*H-Ar), 130.3 (*C*H-Ar), 131.2 (CH=*C*H-CO-Me), 133.2 (*C*-Cl), 135.9 (*C*-Ar), 136.0 (*C*-Ar), 138.6 (*C*H=CH-CO-Me), 138.9 (*C*H=CH–COO^{t}Bu), 165.6 (*C*$O_2{}^t$Bu), 197.7 (*C*OC-Me); *m/z* (NSI$^+$) 635 ([2M+Na]$^+$, 100%), 329 ([M+Na]$^+$, 85%); HRMS (NSI$^+$) $C_{17}H_{19}{}^{35}ClO_3Na$ [M+Na]$^+$, found 329.0912, requires 329.0915 (–0.9 ppm).

tert-Butyl _(E)_-3-(5-methyl-2-((_E_)-3-oxobut-1-en-1-yl)phenyl)acrylate (169)



Following General Procedure 3, to a solution of *tert*-butyl (*E*)-3-(2-formyl-5-methylphenyl)acrylate (921 mg, 3.74 mmol) in $CHCl_3$, was added a phosphorane, 1-(triphenylphosphanylidene)-2-propanone (2.4 g, 7.48 mmol, 2.0 equiv). The reaction mixture was refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.25) to give the title compound (978 mg, 91%) as a yellow solid. mp 83–85 °C; ν_{max} (film) 2978 (alkenyl C-H), 2930 (alkyl C-H), 1703 (C=O); 1672 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 2.37 (3H, s, Ar-C*H*$_3$), 2.39 (3H, s, COC*H*$_3$), 6.28 (1H, d, *J* 15.7, CH=C*H*– $CO_2{}^t$Bu), 6.58 (1H, d, *J* 16.1, CH=C*H*-COMe), 7.20 (1H, d, *J* 7.9, C*H*-Ar), 7.38 (1H, s, C*H*-Ar), 7.49 (1H, d, *J* 7.9, C*H*-Ar), 7.85 (1H, d, *J* 16.1, C*H*=CH–COMe), 7.93 (1H, d, *J* 15.8, C*H*=CH–$CO_2{}^t$Bu); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.5 (Ar-*C*H$_3$), 27.6 (CO*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 81.0 (*C*(CH$_3$)$_3$), 123.8 (CH=*C*H–$CO_2{}^t$Bu), 127.6 (*C*H-Ar), 128.3 (*C*H-Ar), 129.6 (*C*H-Ar), 131.0 (CH=*C*H-CO-Me), 131.5 (*C*-Ar), 134.7 (*C*-Ar), 140.2 (*C*H=CH-CO-Me), 140.3 (*C*H=CH–COO*t*Bu), 140.7 (*C*-Me), 165.9 (*C*$O_2{}^t$Bu), 198.3 (*C*OCH$_3$); *m/z* (NSI$^+$) 595 ([2M+Na]$^+$, 100%), 309 ([M+Na]$^+$, 45%); HRMS (NSI$^+$) $C_{18}H_{22}O_3Na$ [M+Na]$^+$, found 309.1461, requires 309.1461 (–0.1 ppm).

tert-Butyl (_E_)-3-(4-fluoro-2-((_E_)-3-oxobut-1-en-1-yl)phenyl)acrylate (170)

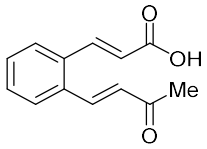


Following General Procedure 3, to a solution of (*E*)-*tert*-butyl 3-(4-fluoro-2-formylphenyl)acrylate (495 mg, 1.98 mmol) in $CHCl_3$, was added a phosphorane, 1-(triphenylphosphanylidene)-2-propanone (1.19 g, 3.75 mmol, 2.0 equiv). The reaction mixture was refluxed overnight under Ar and the concentrated *in vacuo*. The residue was purified by flash silica column chromatography (90:10 Hexane : EtOAc, R_f 0.25) to give the title compound (431 mg, 75%) as a yellow solid. mp 89–91 °C; ν_{max} (film) 2980 (alkenyl C-H), 2955 (alkyl C-H), 1705 (C=O); 1674 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (9H, s, C(C*H*$_3$)$_3$), 2.41 (3H, s, COC*H*$_3$), 6.24 (1H, d, *J* 15.8, CH=C*H*–$CO_2{}^t$Bu), 6.59 (1H, d, *J* 16.1, CH=C*H*-COMe), 7.10 (1H, td, *J* 8.3, 2.6, C*H*-Ar), 7.36 (1H, dd, *J* 9.5, 2.6, C*H*-Ar),

7.57 (1H, dd, *J* 8.7, 5.6, C*H*-Ar), 7.81 (1H, d, *J* 16.1, C*H*=CH–COMe), 7.87 (1H, d, *J* 15.8, C*H*=CH–$CO_2{}^t$Bu); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −110.3; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 27.9 (CO*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 81.2 (*C*(CH$_3$)$_3$), 114.1 (d, $^2J_{CF}$ = 22.5, C_{Ar}-F), 114.2 (*C*H-Ar), 117.7 (d, $^2J_{CF}$ = 22.0, C_{Ar}-F), 117.8 (*C*H-Ar), 123.8 (CH=*C*H–$CO_2{}^t$Bu), 129.9 (d, $^3J_{CF}$ = 8.5, C_{Ar}-F), 129.9 (*C*H-Ar), 131.0 (*C*-Ar), 131.2 (CH=*C*H-CO-Me), 136.4 (*C*-Ar), 138.8 (*C*H=CH-CO-Me), 139.0 (*C*H=CH–COO^{t}Bu), 164.6 (d, $^1J_{CF}$ = 252.1, C_{Ar}-F), 165.8 (*C*O$_2$*t*Bu), 197.8 (*C*OCH$_3$); *m/z* (NSI$^+$) 603 ([2M+Na]$^+$, 100%), 313 ([M+Na]$^+$, 45%); HRMS (NSI$^+$) $C_{17}H_{19}F_1O_3Na$ [M+Na]$^+$, found 313.1210, requires 313.1210 (−0.1 ppm).

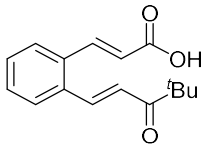
7.2.2.4 Data for enone acids

(*E*)-3-(2-((*E*)-3-Oxobut-1-en-1-yl)phenyl)acrylic acid (104)



Following General Procedure 4, *tert*-butyl (*E*)-3-(2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (1.52 g, 5.59 mmol) gave the corresponding carboxylic acid (1.16 g, 96%) as light green solid. mp 144–146 °C; ν_{max} (film) 3125–2485 br (carb. acid, O-H), 1672 (C=O), 1593 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.43 (3H, s, COC*H*$_3$), 6.39 (1H, d, *J* 15.8, CH=C*H*–COOH), 6.64 (1H, d, *J* 16.1, CH=C*H*-COMe), 7.42–7.46 (2H, m, C*H*-Ar), 7.53–7.71 (2H, m, C*H*-Ar), 7.88 (1H, d, *J* 16.1, C*H*=CH–CO-Me), 8.15 (1H, d, *J* 15.8, C*H*=CH–COOH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 28.0 (CO*C*H$_3$), 121.0 (CH=*C*H–COOH), 127.9 (*C*H-Ar), 128.0 (*C*H-Ar), 130.5 (CH=*C*H–COMe), 130.7 (*C*H-Ar), 130.8 (*C*H-Ar), 134.1 (*C*-Ar), 134.7 (*C*-Ar), 139.9 (*C*H=CH-CO-Me), 143.7 (*C*H=CH–COOH), 171.5 (*C*OOH), 198.3 (*C*O-Me); *m/z* (NSI$^+$) 215 ([M–H]$^-$, 100%), 431 ([2M–H]$^-$, 40%); HRMS (NSI$^+$) $C_{18}H_{15}O_3$[M+H]$^+$, found 279.1016, requires 279.1016 (+0.1 ppm).

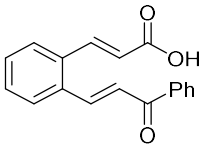
(*E*)-3-(2-((*E*)-4,4-Dimethyl-3-oxopent-1-en-1-yl)phenyl)acrylic acid (145)



Following General Procedure 4, *tert*-butyl (*E*)-3-(2-((*E*)-4,4-dimethyl-3-oxopent-1-en-1-yl)phenyl)-acrylate (0.43 g, 1.36 mmol) gave the corresponding carboxylic acid (0.36 g, quant.) as a light green solid. mp 147–148 °C; ν_{max} (film) 2976–2517 br (carb. acid, O-H), 1678 (C=O), 1624 (C=O); ^{1}H

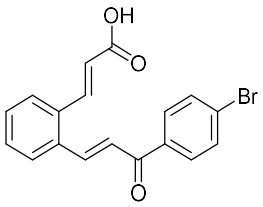
NMR (500 MHz, $CDCl_3$) δ_H: 1.24 (9H, s, COC(CH_3)$_3$), 6.39 (1H, d, *J* 15.8, CH=C*H*–COOH), 6.98 (1H, d, *J* 15.5, CH=C*H*-CO*t*Bu), 7.38–7.48 (2H, m, C*H*-Ar), 7.55–7.70 (2H, m, C*H*-Ar), 8.00 (1H, d, *J* 15.5, C*H*=CH–CO*t*Bu), 8.17 (1H, d, *J* 15.8, C*H*=CH–COOH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 26.2 (COC(CH_3)$_3$), 31.0 (CO*C*(CH_3)$_3$), 120.2 (CH=*C*H–COOH), 125.4 (CH=*C*H–CO*t*Bu), 127.8 (*C*H-Ar), 128.4 (*C*H-Ar), 129.9 (*C*H-Ar), 130.4 (*C*H-Ar), 134.1 (*C*-Ar), 135.4 (*C*-Ar), 139.6 (*C*H=CH-CO*t*Bu), 144.1 (*C*H=CH–COOH), 170.0 (*C*OOH), 192.3 (*C*O*t*Bu); *m/z* (NSI^+) 539 ($[2M+Na]^+$, 100%), 281 ($[M+Na]^+$, 40%); HRMS (NSI^+) $C_{16}H_{19}O_3[M+H]^+$, found 259.1329, requires 259.1331 (+0.9 ppm).

(*E*)-3-(2-((*E*)-3-Oxo-3-phenylprop-1-en-1-yl)phenyl)acrylic acid (146)



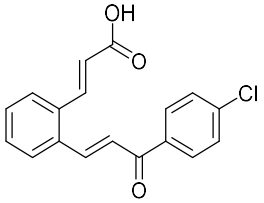
Following General Procedure 4, (*E*)-*tert*-butyl 3-(2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)phenyl)acrylate (7.09 g, 21.2 mmol) gave the corresponding carboxylic acid (5.58 g, 95%) as a yellow solid. mp 155–158 °C; ν_{max} (film) 3113–2523 br (carb. acid, O-H), 1678 (C=O), 1589 (C=O); ^1H NMR (500 MHz,$CDCl_3$) δ_H: 6.42 (1H, d, *J* 15.8, CH=C*H*–COOH), 7.42 (1H, d, *J* 15.5, CH=C*H*-CO-Ph), 7.45–7.48 (2H, m, C*H*-Ar), 7.52 (2H, t, *J* 7.6, C*H*-Ar), 7.60 (1H, dd, *J* 10.5, 4.2, C*H*-Ph), 7.64–7.66 (1H, m, C*H*-Ph), 7.69–7.72 (1H, m, C*H*-Ph), 8.04–8.06 (2H, m, C*H*-Ph), 8.15 (1H, d, *J* 15.6, C*H*=CH–COOH), 8.24 (1H, d, *J* 15.8, C*H*=CH–CO-Ph); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$)δ_C: 120.9 (CH=*C*H–COOH), 126.5 (CH=*C*H-CO-Ph), 128.1 (*C*H-Ar), 128.4 (*C*H-Ar), 128.8 (2×*C*H-Ph), 128.9 (2×*C*H-Ph), 130.4 (*C*H-Ar), 130.6 (*C*H-Ar), 133.3 (*C*H-Ph), 134.4 (*C*-Ar), 135.3 (*C*-Ar), 137.9 (*C*-Ph), 141.5 (*C*H=CH-COC-Ph), 144.1 (*C*H=CH–COOH), 171.5 (*C*OOH), 190.3 (*C*OC-Ph); *m/z* (NSI^+) 279 ($[M+H]^+$, 50%); HRMS (NSI^+) $C_{18}H_{15}O_3[M+H]^+$, found 279.1016, requires 279.1016 (+0.1 ppm).

(*E*)-3-(2-((*E*)-3-(4-Bromophenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylic acid (147)



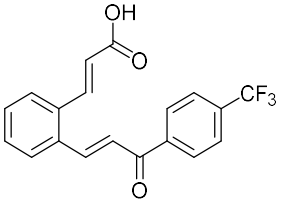
Following General Procedure 4, (*E*)-*tert*-butyl 3-(2-((*E*)-3-oxo-3-(4-bromophenyl)prop-1-en-1-yl)phenyl)acrylate (0.66 g, 1.59 mmol) gave the corresponding carboxylic acid (0.53 g, 93%) as a yellow solid. mp 158–160 °C; ν_{max} (film) 3065–2579 br (carb. acid, O-H), 1682 (C=O), 1584 (C=O); ^{1}H NMR (500 MHz,$CDCl_3$) δ_H: 6.42 (1H, d, *J* 15.8, CH=C*H*–COOH), 7.37 (1H, d, *J* 15.5, CH=C*H*-CO-Ph_{Br}), 7.45–7.49 (2H, m, C*H*-Ar), 7.65–7.67 (3H, m, 2×C*H*-Ph_{Br} + C*H*Ar), 7.69–7.70 (1H, m, C*H*-Ar), 7.91–7.92 (2H, m, C*H*-Ph_{Br}), 8.15 (1H, d, *J* 15.6, C*H*=CH–CO-Ph_{Br}), 8.22 (1H, d, *J* 15.8, C*H*=CH–COOH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 120.8 (CH=*C*H–COOH), 125.8 (CH=*C*H-CO-Ph_{Br}), 128.1 (*C*H-Ar), 128.4 (*C*-Ph_{Br}), 128.5 (*C*H-Ar), 130.3 (2×*C*H-Ph_{Br}), 130.5 (*C*H-Ar), 130.6 (*C*H-Ar), 132.2 (2×*C*H-Ph_{Br}), 134.4 (*C*-Ar), 135.1 (*C*-Ar), 136.6 (*C*-Ph_{Br}), 142.0 (*C*H=CH-COC-Ph_{Br}), 144.1 (*C*H=CH–COOH), 170.8 (*C*OOH), 189.0 (*C*OC-Ph_{Br}); *m/z* (NSI^+) 737 ([2M+Na]$^+$, 100%), 715 ([2M+H]$^+$, 15%); HRMS (NSI^+) $C_{18}H_{13}O_3{}^{79}BrNa$ [M+Na]$^+$, found 378.9941, requires 378.9940 (+0.2 ppm).

(*E*)-3-(2-((*E*)-3-(4-Chlorophenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylic acid (148)



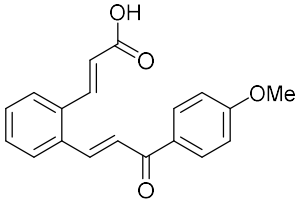
Following General Procedure 4, (*E*)-*tert*-butyl 3-(2-((*E*)-3-oxo-3-(4-chlorophenyl)prop-1-en-1-yl)phenyl)acrylate (0.65 g, 1.78 mmol) gave the corresponding carboxylic acid (0.55 g, quant.) as a green solid. mp 178–181 °C; ν_{max} (film) 3067–2570 br (carb. acid, O-H), 1684 (C=O), 1654 (C=O); ^{1}H NMR (500 MHz,$CDCl_3$) δ_H: 6.42 (1H, d, *J* 15.8, CH=C*H*–COOH), 7.38 (1H, d, *J* 15.5, CH=C*H*-CO-Ph_{Cl}), 7.43–7.52 (4H, m, 2×C*H*-Ar + 2×C*H*-Ph_{Cl}), 7.64–7.66 (1H, m, C*H*Ar), 7.69–7.70 (1H, m, C*H*-Ar), 7.98–8.00 (2H, m, C*H*-Ph_{Cl}), 8.15 (1H, d, *J* 15.6, C*H*=CH–CO-Ph_{Cl}), 8.22 (1H, d, *J* 15.8, C*H*=CH–COOH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 120.7 (CH=*C*H–COOH), 125.9 (CH=*C*H-CO-Ph_{Cl}), 128.1 (*C*H-Ar), 128.5 (*C*H-Ar), 129.2 (2×*C*H-Ph_{OMe}), 130.2 (2×*C*H-Ph_{Cl}), 130.5 (*C*H-Ar), 130.6 (*C*H-Ar), 134.5 (*C*-Ar), 135.1 (*C*-Ar), 136.3 (*C*-Ph_{Cl}), 139.7 (*C*-Ph_{Cl}), 142.0 (*C*H=CH-COC-Ph_{Cl}), 144.0 (*C*H=CH–COOH), 170.5 (*C*OOH), 188.8 (*C*OC-Ph_{Cl}); *m/z* (NSI^+) 647 ([2M+Na]$^+$, 100%); HRMS (NSI^+) $C_{18}H_{13}O_3{}^{35}ClNa$[M+Na]$^+$, found 335.0450, requires 335.0445 (+1.4 ppm).

(*E*)-3-(2-((*E*)-3-(4-Trifluoromethyl)phenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylic acid (149)



Following General Procedure 4, (*E*)-*tert*-butyl 3-(2-((*E*)-3-oxo-3-(4-trifluoromethyl)phenyl)prop-1-en-1-yl)phenyl)acrylate (0.76 g, 1.88 mmol) gave the corresponding carboxylic acid (0.66 g, quant) as a yellow solid. mp 118–120 °C; ν_{max} (film) 3065–2365 br (carb. acid, O-H), 1682 (C=O), 1659 (C=O); ^{1}H NMR (500 MHz,$CDCl_3$) δ_H: 6.42 (1H, d, *J* 15.8, CH=C*H*–COOH), 7.39 (1H, d, *J* 15.5, CH=C*H*-CO-Ph_{CF3}), 7.46–7.52 (2H, m, C*H*-Ar), 7.65–7.67 (1H, m, C*H*Ar), 7.70–7.72 (1H, m, C*H*-Ar), 7.78–7.79 (2H, m, C*H*-Ph_{CF3}), 8.13–8.15 (2H, m, C*H*-Ph_{CF3}), 8.18 (1H, d, *J* 15.5, C*H*=CH–CO-Ph_{CF3}), 8.22 (1H, d, *J* 15.8, C*H*=CH–COOH); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −63.1 (C*F*$_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 120.9 (CH=*C*H–COOH), 125.8 (CH=*C*H-CO-Ph_{CF3}), 125.9 (q, $^{3}J_{CF}$ = 3.6, C_{Ar}-CF_3), 126.0 (2×*C*H-Ph_{CF3}), 127.1 (q, $^{1}J_{CF}$ = 279.5, C_{Ar}-CF_3), 128.2 (*C*H-Ar), 128.5 (*C*H-Ar), 129.0 (2×*C*H-Ph_{CF3}), 130.2 (2×*C*H-Ph_{Cl}), 130.6 (*C*H-Ar), 130.7 (*C*H-Ar), 134.5 (2×*C*-Ar), 134.7 (q, $^{2}J_{CF}$ = 45.0, C_{Ar}-CF_3), 134.9 (2×*C*-Ph_{CF3}), 142.7 (*C*H=CH-COC-Ph_{CF3}), 144.0 (*C*H=CH–COOH), 170.5 (*C*OOH), 189.2 (*C*OC-Ph_{CF3}); *m/z* (NSI^+) 691 ([2M−H]$^-$, 100%); HRMS (NSI^+) $C_{19}H_{12}O_3F_3$ [M−H]$^-$, found 345.0740, requires 345.0733 (+2.0 ppm).

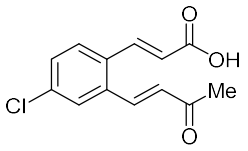
(*E*)-3-(2-((*E*)-3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylic acid (150)



Following General Procedure 4, (*E*)-*tert*-butyl 3-(2-((*E*)-3-oxo-3-(4-methoxyphenyl)prop-1-en-1-yl)phenyl)acrylate (0.68 g, 1.85 mmol) gave the corresponding carboxylic acid (0.57 g, quant) as a yellow solid. mp 194–195 °C; ν_{max} (film) 3063–2515 br (carb. acid, O-H), 1682 (C=O), 1607 (C=O); ^{1}H NMR (500 MHz,$CDCl_3$) δ_H: 3.89 (3H, s, OC*H*$_3$), 6.41 (1H, d, *J* 15.8, CH=C*H*–COOH), 6.99 (2H, m, C*H*-Ph_{OMe}), 7.42 (1H, d, *J* 15.5, CH=C*H*-CO-Ph_{OMe}), 7.44–7.48 (2H, m, C*H*-Ar), 7.61–7.66 (1H, m, C*H*Ar), 7.68–7.72 (1H, m, C*H*-Ar), 8.05–8.07 (2H, m, C*H*-Ph_{OMe}), 8.12 (1H, d, *J* 15.5, C*H*=CH–CO-Ph_{OMe}), 8.24 (1H, d, *J* 15.8, C*H*=CH–COOH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 55.7 (O*C*H$_3$), 114.1 (2×*C*H-Ph_{OMe}), 120.5 (CH=*C*H–COOH), 126.5 (CH=*C*H-CO-Ph_{OMe}), 128.0 (*C*H-Ar),

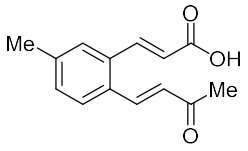
128.4 (*C*H-Ar), 130.2 (*C*H-Ar), 130.6 (*C*H-Ar), 130.9 (*C*-Ph_{OMe}), 131.2 (2×*C*H-Ph_{OMe}), 134.3 (*C*-Ar), 135.6 (*C*-Ar), 140.7 (*C*H=CH-COC-Ph_{OMe}), 144.2 (*C*H=CH–COOH), 163.8 (*C*-Ph_{OMe}), 170.5 (*C*OOH), 188.5 (*C*OC-Ph_{OMe}); *m/z* (NSI^+) 639 ($[2M+Na]^+$, 100%), 331 ($[M+Na]^+$, 50%); HRMS (NSI^+) $C_{19}H_{17}O_4$ $[M+H]^+$, found 309.1125, requires 309.1121 (+1.2 ppm).

(*E*)-3-(4-Chloro-2-((*E*)-3-Oxobut-1-en-1-yl)phenyl)acrylic acid (171)



Following General Procedure 4, *tert*-butyl (*E*)-3-(4-chloro-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (827 mg, 2.70 mmol) gave the corresponding carboxylic acid (676 mg, quant.) as a yellow solid. mp 131–133 °C; ν_{max} (film) 3068–2569 br (carb. acid, O-H), 1697 (C=O), 1622 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.42 (3H, s, COCH_3), 6.38 (1H, d, *J* 15.8, CH=C*H*–COOH), 6.64 (1H, d, *J* 16.0, CH=C*H*-COMe), 7.41 (1H, dd, *J* 8.4, 2.1, C*H*-Ar), 7.56–7.58 (2H, m, C*H*-Ar), 7.80 (1H, d, *J* 16.0, C*H*=CH–CO-Me), 8.06 (1H, d, *J* 15.8, C*H*=CH–COOH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (CO*C*H_3), 121.0 (CH=*C*H–COOH), 127.7 (*C*H-Ar), 129.1 (*C*H-Ar), 130.3 (CH=*C*H–COMe), 131.3 (*C*H-Ar), 132.3 (*C*-Cl), 136.1 (*C*-Ar), 136.7 (*C*-Ar), 138.2 (*C*H=CH-CO-Me), 142.4 (*C*H=CH–COOH), 170.2 (*C*OOH), 200.4 (*C*O-Me); *m/z* (NSI^+) 273 ($[M+Na]^+$, 100%), 523 ($[2M+Na]^+$, 60%); HRMS (NSI^+) $C_{13}H_{11}O_3{}^{35}ClNa[M+Na]^+$, found 273.0291, requires 273.0289 (+0.8 ppm).

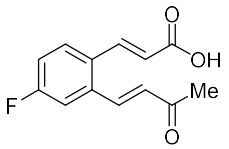
(*E*)-3-(5-Methyl-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylic acid (172)



Following General Procedure 4, *tert*-butyl (*E*)-3-(5-methyl-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (941 mg, 3.28 mmol) gave the corresponding carboxylic acid (755 mg, quant.) as a yellow solid. mp 173–175 °C; ν_{max} (film) 3061–2506 br (carb. acid, O-H), 1689 (C=O), 1622 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, Ar-C-CH_3), 2.42 (3H, s, COCH_3), 6.39 (1H, d, *J* 15.8, CH=C*H*–COOH), 6.62 (1H, d, *J* 16.0, CH=C*H*-COMe), 7.16–7.18 (1H, m, C*H*-Ar), 7.43 (1H, s, C*H*-Ar), 7.52 (1H, d, *J* 8.0, C*H*-Ar), 7.86 (1H, d, *J* 16.0, C*H*=CH–CO-Me), 8.15 (1H, d, *J* 15.8, C*H*=CH–COOH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.5 (Ar-C-*C*H_3), 27.9 (CO*C*H_3), 120.6 (CH=*C*H–

COOH), 127.9 (*C*H-Ar), 128.6 (*C*H-Ar), 129.9 (CH=*C*H–COMe), 131.7 (*C*H-Ar), 131.9 (*C*-Ar), 134.1 (*C*-Ar), 139.9 (*C*H=CH-CO-Me), 140.9 (*C*-Me), 143.9 (*C*H=CH–COOH), 171.1 (*C*OOH), 198.4 (*C*O-Me); *m/z* (NSI$^+$) 483 ([2M+Na]$^+$, 100%), 253 ([M+Na]$^+$, 75%); HRMS (NSI$^+$) $C_{14}H_{14}O_3Na$[M+Na]$^+$, found 253.0833, requires 253.0835 (–0.9 ppm).

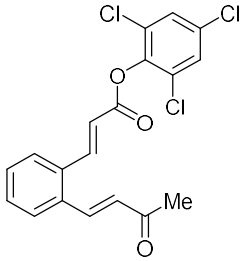
(*E*)-3-(4-Fluoro-2-((*E*)-3-Oxobut-1-en-1-yl)phenyl)acrylic (173)



Following General Procedure 4, *tert*-butyl (*E*)-3-(4-fluoro-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (424 mg, 1.46 mmol) gave the corresponding carboxylic acid (342 mg, quant.) as a yellow solid. mp 165–166 °C; ν_{max} (film) 3072–2525 br (carb. acid, O-H), 1682 (C=O), 1601 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.43 (3H, s, COC*H*$_3$), 6.34 (1H, d, *J* 15.8, CH=C*H*–COOH), 6.62 (1H, d, *J* 16.0, CH=C*H*-COMe), 7.15 (1H, td, *J* 8.2, 2.6, C*H*-Ar), 7.29 (1H, dd, *J* 9.4, 2.6, C*H*-Ar), 7.63 (1H, dd, *J* 8.6, 5.6, C*H*-Ar), 7.82 (1H, d, *J* 16.0, C*H*=CH–CO-Me), 8.08 (1H, d, *J* 15.8, C*H*=CH–COOH); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −109.0; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (CO*C*H$_3$), 114.4 (d, $^2J_{CF}$ = 22.6, C_{Ar}-F), 114.5 (*C*H-Ar), 117.8 (d, $^2J_{CF}$ = 22.1, C_{Ar}-F), 117.9 (*C*H-Ar), 120.6 (CH=*C*H–COOH), 130.2 (d, $^3J_{CF}$ = 8.7, C_{Ar}-F), 130.2 (*C*H-Ar), 131.4 (CH=*C*H–COMe), 136.9 (*C*-Ar), 137.0 (*C*-Ar), 138.4 (*C*H=CH-CO-Me), 142.5 (*C*H=CH–COOH), 164.9 (d, $^1J_{CF}$ = 252.5, C_{Ar}-F), 170.7 (*C*OOH), 197.8 (*C*O-Me); *m/z* (NSI$^+$) 467 ([2M–H]$^-$, 100%), 233 ([M–H]$^-$, 80%); HRMS (NSI$^+$) $C_{13}H_{10}O_3F_1$[M–H]$^-$, found 233.0617, requires 233.0619 (–1.1 ppm).

7.2.2.5 Data for trichlorophenyl (TCP) esters

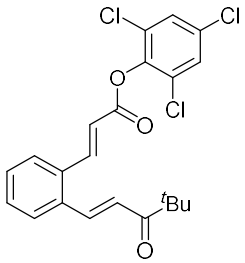
2,4,6-Trichlorophenyl (*E*)-3-(2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (115)



Following General Procedure 5, (*E*)-3-(2-((*E*)-3-Oxo-3-phenylprop-1-en-1-yl)phenyl)acrylic acid (1.36 g, 6.28 mmol), DCC (1.43 g, 6.91 mmol) and 2,4,6-trichlorophenol (TCP-OH) (1.28 g, 6.40 mmol) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, R_f 0.25) the title compound (2.04

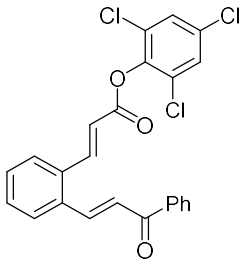
g, 82%) as a brown solid. mp 85–86 °C; ν_{max} (film) 3077 (alkenyl C-H), 2858 (alkylC-H), 1741 (C=O) 1672 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, COC*H*$_3$), 6.62 (1H, d, *J* 15.8, CH=C*H*–COTCP), 6.64 (1H, d, *J* 16.1, CH=C*H*-COMe), 7.41 (2H, s, C*H*-Ar$_{TCP}$), 7.44–7.50 (2H, m, C*H*-Ar), 7.60–7.64 (1H, m, C*H*-Ar), 7.68–7.74 (1H, m, C*H*-Ar), 7.90 (1H, d, *J* 16.1, C*H*=CH–CO-Me), 8.31 (1H, d, *J* 15.8, C*H*=CH–COTCP); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.0 (CO*C*H$_3$), 118.9 (CH=*C*H–COTCP), 128.0 (*C*H-Ar), 128.1 (*C*H-Ar), 128.8 (2×*C*H-TCP), 129.8 (2×*C*-TCP), 130.5 (CH=*C*H–COMe), 131.1 (2×*C*H-Ar), 132.2 (*C*-Ar), 133.7 (*C*-Ar), 135.0(*C*-TCP), 139.7(*C*H=CH-CO-Me), 143.1 (CO*C*-TCP), 145.0 (*C*H=CH–COTCP), 162.6 (*C*OTCP), 198.0 (*C*O-Me); *m/z* (NSI$^+$) 413 ([M+NH$_4$]$^+$, 100%); HRMS (NSI$^+$) $C_{19}H_{14}O_3{}^{35}Cl_3$ [M+H]$^+$, found 395.0005, requires 395.0003 (+0.5 ppm).

2,4,6-Trichlorophenyl (*E*)-3-(2-((*E*)-4,4-dimethyl-3-oxopent-1-en-1-yl)phenyl)acrylate (152)



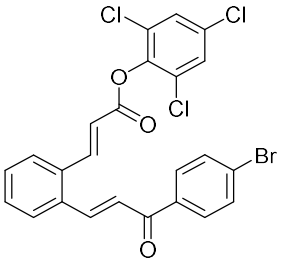
Following General Procedure 5, (*E*)-3-(2-((*E*)-4,4-dimethyl-3-oxopent-1-en-1-yl)phenyl)acrylic acid (0.36 g, 1.39 mmol), DCC (0.32 g, 1.53 mmol) and 2,4,6-trichlorophenol (TCP-OH) (0.28 g, 1.42 mmol) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, R_f 0.25) the title compound (509 mg, 84%) as a yellow solid. mp 113–115 °C; ν_{max} (film) 3120 (alkenyl C-H), 2967 (alkyl C-H), 1751 (C=O) 1676 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.23 (9H, s, C(C*H*$_3$)$_3$), 6.62 (1H, d, *J* 15.8, CH=C*H*–CO$_2$TCP), 6.99 (1H, d, *J* 15.5, CH=C*H*-CO*t*Bu), 7.41 (2H, s, C*H*-Ar$_{TCP}$), 7.42–7.53 (2H, m, C*H*-Ar), 7.58–7.65 (1H, m, C*H*-Ar), 7.70–7.72 (1H, m, C*H*-Ar), 8.01 (1H, d, *J* 15.5, C*H*=CH–CO^{t}Bu), 8.33 (1H, d, *J* 15.8, C*H*=CH–CO$_2$TCP); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 27.3 (C(*C*H$_3$)$_3$), 118.3 (CH=*C*H–CO$_2$TCP), 128.0 (*C*H-Ar), 128.7 (*C*H-Ar), 128.8 (2×*C*H-TCP), 129.9 (2×*C*-TCP), 130.1 (CH=*C*H–CO^{t}Bu), 130.9 (2×*C*H-Ar), 132.2 (*C*-Ar), 133.8 (*C*-Ar), 135.9 (*C*-TCP), 139.5 (*C*H=CH-CO^{t}Bu), 143.1 (CO$_2$*C*-TCP), 145.6 (*C*H=CH–CO$_2$TCP), 162.6 (*C*O$_2$TCP), 203.8 (*C*O^{t}Bu); *m/z* (NSI$^+$) 651 ([2M+Na]$^+$, 100%), 332 ([M+NH$_4$]$^+$, 65%); HRMS (NSI$^+$) $C_{22}H_{19}O_3{}^{35}Cl_3Na$ [M+Na]$^+$, found 459.0281, requires 459.0292 (–2.4 ppm).

(*E*)-2,4,6-Trichlorophenyl 3-(2-((*E*)-3-oxo-3-phenylprop-1-en-1-yl)phenyl)acrylate (153)



Following General Procedure 5, (*E*)-3-(2-((*E*)-3-Oxobut-1-en-1-yl)phenyl)acrylic acid (1.00 g, 3.60 mmol), DCC (816 mg, 3.96 mmol) and 2,4,6-trichlorophenol (TCP-OH) (732 mg, 3.67 mmol) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, Rf 0.25) the title compound (1.27 g, 77%) as a yellow solid. mp 64–67 °C; ν_{max} (film) 3068 (alkenyl C-H), 2843 (alkyl C-H), 1735 (C=O), 1672 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.64 (1H, d, *J* 15.8, CH=C*H*–COTCP), 7.41 (2H, s, C*H*-Ar_{TCP}), 7.43 (1H, d, *J* 15.5, CH=C*H*-CO-Ph), 7.47–7.53 (4H, m, C*H*-Ar), 7.58 (1H, m, C*H*-Ph), 7.73 (2H, m, C*H*-Ph), 8.03 (2H, m, C*H*-Ph), 8.17 (1H, d, *J* 15.6, C*H*=CH–COTCP), 8.39 (1H, d, *J* 15.8, C*H*=CH–CO-Ph),^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 118.7 (CH=*C*H–COTCP), 126.8 (CH=*C*H-CO-Ph), 128.1 (*C*H-Ar), 128.7 (*C*H-Ar), 128.8 (2×*C*H-TCP + 2×*C*H-Ph), 128.9 (2×*C*H-Ph), 129.9 (2×*C*-TCP), 130.4 (*C*H-Ar), 131.0 (*C*H-Ar), 132.2 (*C*-Ar), 133.3 (*C*H-Ph), 134.0 (*C*-Ar), 137.9 (*C*-Ph), 141.3 (*C*H=CH-CO-Ph), 143.1 (CO*C*-TCP), 145.4 (*C*H=CH–COTCP), 162.6 (*C*OTCP), 190.0 (*C*O-Ph); *m/z* (NSI$^+$) 458 ([M+H]$^+$, 15%); HRMS (NSI$^+$) $C_{24}H_{16}O_3{}^{35}Cl_3$ [M+H]$^+$, found 457.0155, requires 457.0160 (–1.0 ppm).

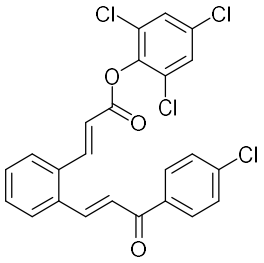
2,4,6-Trichlorophenyl (*E*)-3-(2-((*E*)-3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylate (154)



Following General Procedure 5, the corresponding acid (0.53 g, 1.48 mmol), DCC (0.34 g, 1.63 mmol) and 2,4,6-trichlorophenol (0.29 g, 1.50 mmol) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, R_f 0.25) the title compound (655 mg, 83%) as a pink solid. mp 65–66 °C; ν_{max} (film) 3076 (alkenyl C-H), 1739 (C=O) 1663 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.64 (1H, d, *J* 15.8,

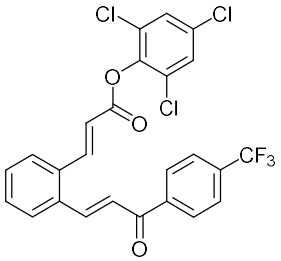
CH=C*H*–CO_2TCP), 7.37 (1H, d, *J* 15.5, CH=C*H*-$COPh_{Br}$), 7.42 (2H, s, C*H*-Ar_{TCP}), 7.47–7.54 (2H, m, C*H*-Ar), 7.63–7.64 (2H, m, C*H*-Ph_{Br}), 7.70–7.74 (2H, m, C*H*-Ar), 7.89–7.90 (2H, m, C*H*-Ph_{Br}), 8.17 (1H, d, *J* 15.5, C*H*=CH–$COPh_{Br}$), 8.38 (1H, d, *J* 15.8, C*H*=CH–CO_2TCP); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 118.8 (CH=*C*H–CO_2TCP), 126.2 (*C*H-Ar), 128.2 (*C*H-Ar), 128.4 (*C*-Ph_{Br}), 128.7 (2×*C*H-Ph_{Br}), 128.8 (2×*C*H-TCP), 129.9 (2×*C*-TCP), 130.3 (2×*C*H-Ph_{Br}), 130.6 (CH=*C*H-$COPh_{Br}$), 131.0 (2×*C*H-Ar), 132.2 (*C*-Ar), 134.1 (*C*-Ar), 135.4 (*C*-TCP), 136.6 (*C*H=CH-$COPh_{Br}$), 143.1 (CO_2*C*-TCP), 145.3 (*C*H=CH–CO_2TCP), 162.6 (*C*O_2TCP), 188.9 (*C*OPh_{Br}); *m/z* (NSI^+) 556 ($[M+Na]^+$, 65%); HRMS (NSI^+) $C_{24}H_{14}O_3{}^{79}Br^{35}Cl_3Na$ $[M+Na]^+$, found 556.9074, requires 556.9084 (−1.8 ppm).

2,4,6-Trichlorophenyl (*E*)-3-(2-((*E*)-3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylate (155)



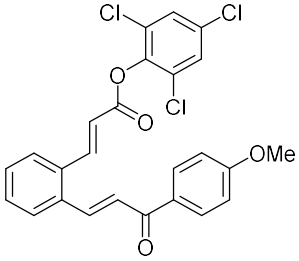
Following General Procedure 5, the corresponding acid (0.55 g, 1.77 mmol), DCC (0.40 g, 1.95 mmol) and 2,4,6-trichlorophenol (0.35 g, 1.81 mmol) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, R_f 0.25) the title compound (719 mg, 83%) as a pink solid. mp 106–108 °C; ν_{max} (film) 3082 (alkenyl C-H), 3020 (alkyl C-H), 1740 (C=O) 1667 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 6.64 (1H, d, *J* 15.8, CH=C*H*–CO_2TCP), 7.38 (1H, d, *J* 15.5, CH=C*H*-$COPh_{Cl}$), 7.41 (2H, s, C*H*-Ar_{TCP}), 7.46–7.48 (2H, m, C*H*-Ph_{Cl}), 7.49–7.54 (2H, m, C*H*-Ar), 7.68–7.75 (2H, m, C*H*-Ar), 7.96–7.98 (2H, m, C*H*-Ph_{Cl}), 8.17 (1H, d, *J* 15.5, C*H*=CH–$COPh_{Cl}$), 8.38 (1H, d, *J* 15.8, C*H*=CH–CO_2TCP); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 118.8 (CH=*C*H–CO_2TCP), 126.2 (*C*H-Ar), 128.2 (*C*H-Ar), 128.8 (2×*C*H-Ph_{Cl}), 129.2 (2×*C*H-TCP), 129.9 (2×*C*-TCP), 130.2 (2×*C*H-Ph_{Cl} + C*H*-Ar), 130.6 (CH=*C*H-$COPh_{Cl}$), 131.0 (2×*C*H-Ar), 132.2 (*C*-Ar), 134.0 (*C*-Ar), 135.4 (*C*-TCP), 136.2 (*C*-Ph_{Cl}), 139.7 (*C*-Ph_{Cl}), 141.8 (*C*H=CH-$COPh_{Cl}$), 143.1 (CO_2*C*-TCP), 145.3 (*C*H=CH–CO_2TCP), 162.6 (*C*O_2TCP), 188.7 (*C*OPh_{Cl}); *m/z* (NSI^+) 510 ($[M+NH_4]^+$, 90%); HRMS (NSI^+) $C_{24}H_{15}O_3{}^{35}Cl_4$ $[M+H]^+$, found 490.9763, requires 490.9770 (−1.4 ppm).

2,4,6-Trichlorophenyl (*E*)-3-(2-((*E*)-3-oxo-3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)phenyl)-acrylate (156)



Following General Procedure 5, the corresponding acid (0.64 g, 1.86 mmol), DCC (0.42 g, 2.05 mmol) and 2,4,6-trichlorophenol (0.38 g, 1.90 mmol) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, R_f 0.3) the title compound (698 mg, 72%) as a yellow foam. mp 54–55 °C; ν_{max} (film) 3078 (alkenyl C-H), 2815 (alkylC-H), 1742 (C=O) 1667 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.65 (1H, d, *J* 15.8, CH=C*H*–CO_2TCP), 7.40 (1H, d, *J* 15.5, CH=C*H*-$COPh_{CF3}$), 7.41 (2H, s, C*H*-Ar_{TCP}), 7.50–7.54 (2H, m, C*H*-Ar), 7.70–7.74 (2H, m, C*H*-Ar), 7.75–7.77 (2H, m, C*H*-Ph_{CF3}), 8.11–8.13 (2H, m, C*H*-Ph_{CF3}), 8.20 (1H, d, *J* 15.5, C*H*=CH–$COPh_{CF3}$), 8.38 (1H, d, *J* 15.8, C*H*=CH–CO_2TCP); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −63.1 (C*F*$_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 119.0 (CH=*C*H–CO_2TCP), 125.9 (CH=*C*H-$COPh_{CF3}$), 126.0 (*C*H-Ph_{CF3}), 126.1 (*C*H-Ph_{CF3}), 126.1 (q, $^3J_{CF}$ = 4.5, C_{Ar}-CF_3), 127.1 (q, $^1J_{CF}$ = 263.7, C_{Ar}-CF_3), 128.2 (*C*H-Ar), 128.7 (*C*H-Ar), 128.8 (2×*C*H-Ph_{CF3}), 129.0 (2×*C*H-TCP), 129.8 (2×*C*-TCP), 130.8 (*C*H-Ar), 130.9 (q, $^2J_{CF}$ = 36.8, C_{Ar}-CF_3), 131.1 (*C*H-Ar), 132.3 (*C*-Ar), 134.2 (*C*-Ar + *C*F_3), 135.2 (*C*-Ph_{CF3} + *C*-TCP), 142.5 (*C*H=CH-$COPh_{CF3}$), 143.1 (CO_2*C*-TCP + *C*-Ph_{CF3}), 145.2 (*C*H=CH–CO_2TCP), 162.5 (CO_2TCP), 189.1 (*C*OPh_{CF3}); *m/z* (NSI$^+$) 1073 ([2M+Na]$^+$, 100%), 1598 ([3M+Na]$^+$, 45%); HRMS (NSI$^+$) $C_{25}H_{18}O_3N_1{}^{35}Cl_3F_3$ [M+NH_4]$^+$, found 542.0289, requires 542.0299 (−1.8 ppm).

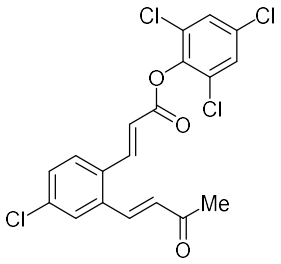
2,4,6-Trichlorophenyl (*E*)-3-(2-((*E*)-3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)phenyl)acrylate (157)



Following General Procedure 5, the corresponding acid (0.55 g, 1.80 mmol), DCC (0.41 g, 1.98 mmol) and 2,4,6-trichlorophenol (0.36 g, 1.84 mmol) afforded after SiO_2-chromatography (80:20

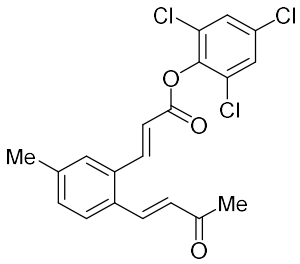
Hexane : EtOAc, R_f 0.25) the title compound (777 mg, 88%) as a yellow foam. mp 56–57 °C; ν_{max} (film) 3075 (alkenyl C-H), 2843 (alkyl C-H), 1742 (C=O) 1597 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.88 (O*C*H$_3$), 6.65 (1H, d, *J* 15.8, CH=C*H*–CO$_2$TCP), 6.97 (2H, m, C*H*-Ph$_{OMe}$), 7.41 (2H, s, C*H*-Ar$_{TCP}$), 7.43 (1H, d, *J* 15.5, CH=C*H*-COPh$_{OMe}$), 7.45–7.52 (2H, m, C*H*-Ar), 7.70–7.74 (2H, m, C*H*-Ar), 8.03–8.05 (2H, m, C*H*-Ph$_{OMe}$), 8.14 (1H, d, *J* 15.5, C*H*=CH–COPh$_{OMe}$), 8.40 (1H, d, *J* 15.8, C*H*=CH–CO$_2$TCP); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 55.6 (O*C*H$_3$), 114.1 (2×*C*H-Ph$_{OMe}$), 118.5 (CH=*C*H–CO$_2$TCP), 126.9 (*C*H-Ph$_{OMe}$), 128.1 (*C*H-Ph$_{OMe}$), 128.1 (*C*H-Ar), 128.7 (*C*H-Ar), 128.8 (2×*C*H-TCP), 129.9 (*C*-TCP), 130.2 (*C*H=CH–COPh$_{OMe}$), 130.9 (*C*H-Ar), 131.0 (*C*H-Ar), 131.1 (2×*C*H- Ph$_{OMe}$), 132.2 (2×*C*-TCP), 133.9 (*C*-Ar), 135.9 (*C*-TCP), 140.5 (*C*H=CH-COPh$_{OMe}$), 143.1 (CO$_2$*C*-TCP + *C*-Ph$_{OMe}$), 145.6 (*C*H=CH–CO$_2$TCP), 162.6 (*C*O$_2$TCP), 188.2 (*C*OPh$_{OMe}$); *m/z* (NSI$^+$) 510 ([M+Na]$^+$, 100%), 997 ([2M+Na]$^+$, 55%); HRMS (NSI$^+$) $C_{25}H_{17}O_4{}^{35}Cl_3Na$ [M+Na]$^+$, found 509.0072, requires 509.0085 (–2.5ppm).

2,4,6-Trichlorophenyl (*E*)-3-(4-chloro-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (174)



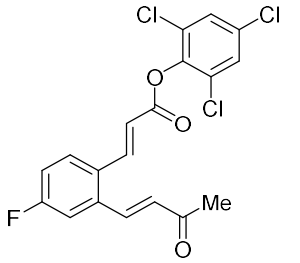
Following General Procedure 5, (*E*)-3-(4-chloro-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylic acid (730 mg, 2.80 mmol), DCC (635 mg, 3.08 mmol) and 2,4,6-trichlorophenol (TCP-OH) (564 mg, 2.86 mmol, 1.02 equiv) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, R_f 0.25) the title compound (1.04 g, 86%) as a yellow solid. mp 129–131 °C; ν_{max} (film) 3080 (alkenyl C-H), 2932 (alkyl C-H), 1746 (C=O) 1674 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, COC*H*$_3$), 6.61 (1H, d, *J* 15.8, CH=C*H*–COTCP), 6.65 (1H, d, *J* 16.0, CH=C*H*-COMe), 7.42 (2H, s, C*H*-Ar$_{TCP}$), 7.44 (2H, dd, *J* 8.4, 2.1, C*H*-Ar), 7.60 (1H, d, *J* 2.1, C*H*-Ar), 7.65 (1H, d, *J* 8.4, C*H*-Ar), 7.82 (1H, d, *J* 16.0, C*H*=CH–CO-Me), 8.22 (1H, d, *J* 15.8, C*H*=CH–COTCP); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.4 (CO*C*H$_3$), 119.2 (CH=*C*H–COTCP), 128.0 (*C*H-Ar), 128.9 (2×*C*H-TCP), 129.3 (*C*H-Ar), 129.8 (2×*C*-TCP), 130.5 (CH=*C*H–COMe), 131.8 (2×*C*H-Ar), 132.1 (*C*-Ar), 132.3 (*C*-Ar), 135.0 (*C*-TCP), 138.1 (*C*H=CH-CO-Me), 143.0 (CO*C*-TCP), 143.7 (*C*H=CH–COTCP), 162.4 (*C*OTCP), 197.5 (*C*O-Me); *m/z* (NSI$^+$) 453 ([M+Na]$^+$, 55%), 883 ([2M+Na]$^+$, 35%); HRMS (NSI$^+$) $C_{19}H_{16}O_3N_1{}^{35}Cl_4$ [M+NH$_4$]$^+$, found 445.9875, requires 445.9879 (–0.9 ppm).

2,4,6-Trichlorophenyl (*E*)-3-(5-methyl-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (175)



Following General Procedure 5, (*E*)-3-(5-methyl-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylic acid (858 mg, 3.73 mmol), DCC (924 mg, 3.08 mmol) and 2,4,6-trichlorophenol (TCP-OH) (751 mg, 3.80 mmol) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, R_f 0.25) the title compound (1.04 g, 68%) as a yellow solid. mp 129–131 °C; ν_{max} (film) 3069 (alkenyl C-H), 2928 (alkyl C-H), 1732 (C=O) 1667 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.40 (3H, s, COC*H*$_3$), 2.37 (3H, s, Ar-C*H*$_3$), 6.61 (1H, d, *J* 15.8, CH=C*H*–COTCP), 6.62 (1H, d, *J* 16.0, CH=C*H*-COMe), 7.29 (1H, d, *J* 9.5, C*H*-Ar), 7.42 (2H, s, C*H*-Ar$_{TCP}$), 7.51–7.54 (2H, m, C*H*-Ar), 7.87 (1H, d, *J* 16.0, C*H*=CH–CO-Me), 8.30 (1H, d, *J* 15.8, C*H*=CH–COTCP); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.4 (Ar-*C*H$_3$), 27.8 (CO*C*H$_3$), 118.5 (CH=*C*H–COTCP), 127.9 (*C*H-Ar), 128.5 (*C*H-Ar), 128.7 (2×*C*H-TCP), 129.7 (2×*C*-TCP), 130.1 (CH=*C*H–COMe), 132.0 (*C*H-Ar), 132.0 (*C*-Ar), 132.1 (*C*-Ar), 133.6 (*C*-TCP), 139.5 (*C*H=CH-CO-Me), 140.8 (Ar-*C*CH$_3$), 143.0 (CO*C*-TCP), 145.1 (*C*H=CH–COTCP), 162.5 (*C*OTCP), 198.0 (*C*O-Me); *m/z* (NSI$^+$) 841 ([2M+Na]$^+$, 100%), 432 ([M+Na]$^+$, 70%); HRMS (NSI$^+$) $C_{20}H_{19}O_3N_1{}^{35}Cl_3$ [M+NH$_4$]$^+$, found 426.0420, requires 426.0425 (−1.2 ppm).

2,4,6-Trichlorophenyl (*E*)-3-(4-fluoro-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylate (176)



Following General Procedure 5, (*E*)-3-(4-fluoro-2-((*E*)-3-oxobut-1-en-1-yl)phenyl)acrylic acid (341 mg, 1.46 mmol), DCC (331 mg, 1.61 mmol) and 2,4,6-trichlorophenol (TCP-OH) (294 mg, 1.49 mmol) afforded after SiO_2-chromatography (90:10 Hexane : EtOAc, R_f 0.25) the title compound (543 mg, 90%) as a white solid. mp 139–141 °C; ν_{max} (film) 3080 (alkenyl C-H), 2832 (alkyl C-H), 1744 (C=O) 1672 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, COC*H*$_3$), 6.57 (1H, d, *J* 15.8,

CH=C*H*–COTCP), 6.63 (1H, d, *J* 16.0, CH=C*H*-COMe), 7.18 (1H, td, *J* 8.2, 2.6, C*H*-Ar), 7.31 (1H, dd, *J* 9.4, 2.6, C*H*-Ar), 7.42 (2H, s, C*H*-Ar$_{TCP}$), 7.72 (1H, dd, *J* 8.7, 5.6, C*H*-Ar), 7.84 (1H, d, *J* 16.0, C*H*=CH–CO-Me), 8.24 (1H, d, *J* 15.8, C*H*=CH–COTCP); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −108.2; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (CO*C*H$_3$), 114.5 (*C*H-Ar), 114.6 (d, $^2J_{CF}$ = 22.6, C_{Ar}-F), 117.9 (*C*H-Ar), 117.9 (d, $^2J_{CF}$ = 22.1, C_{Ar}-F), 118.6 (CH=*C*H–COTCP), 128.8 (2×*C*H-TCP), 129.8 (2×*C*-TCP), 130.3 (*C*H-Ar), 130.3 (d, $^3J_{CF}$ = 8.8, C_{Ar}-F), 131.8 (CH=*C*H–COMe), 132.3 (*C*-Ar), 137.3 (*C*-Ar), 137.4 (*C*-TCP), 138.2 (*C*H=CH-CO-Me), 143.0 (CO*C*-TCP), 143.8 (*C*H=CH–COTCP), 162.5 (Ar*C*-F), 164.1 (d, $^1J_{CF}$ = 252.9, C_{Ar}-F), 165.1 (*C*OTCP), 197.5 (*C*O-Me); *m/z* (NSI$^+$) 849 ([2M+Na]$^+$, 100%), 436 ([M+Na]$^+$, 60%); HRMS (NSI$^+$) $C_{19}H_{16}O_3{}^{35}Cl_3F_1Na_1$ [M+Na]$^+$, found 434.9721, requires 434.9728 (−1.7 ppm).

7.2.2.6 Data for 1,3-diketones

1,3-*bis*(Furan-2-yl)propane-1,3-dione (118)

Following General Procedure 6, 2-acetylfuran (550 mg, 5.0 mmol), furoyl chloride (590 µL, 6.0 mmol) and LiHMDS (1.0 M in THF, 7.50 mL, 7.50 mmol) afforded after SiO_2-chromatography (80:20 Petroleum ether : Et_2O) to afford the corresponding diketone as a pale-yellow solid (395 mg, 39%). mp 69-71 °C {Lit.[5] 70.5–72.0 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.58 (2H, dd, *J* 3.5, 1.7, Ar(4)*H*), 6.65 (1H, s, =C*H*), 7.20 (2H, dd, *J* 3.5, 0.6, Ar(3)*H*), 7.61 (2H, dd, *J* 1.7, 0.6, Ar(5)*H*). Data in agreement with the literature.[6]

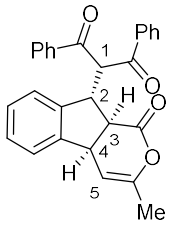
1,3-*bis*(4-Fluorophenyl)propane-1,3-dione (119)

Following General Procedure 6, 4-fluoroacetophenone (690 mg, 5.0 mmol), 4-fluorobenzoyl chloride (620 µL, 6.0 mmol) and LiHMDS (1.0 M in THF, 7.50 mL, 7.5 mmol) and purified by chromatography (90:10 Petroleum ether : Et_2O) to afford the corresponding diketone as a pink needle-like solid (780 mg, 60%), mp 108–110 °C {Lit.[7] 109 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.75 (1H, s, =C*H*), 7.16–7.19 (4H, m, Ar*H*), 7.99–8.02 (4H, m, Ar*H*). Data in agreement with the literature.[8]

7.2.3 Michael-Michael-Lactonisation with 1,3-dicarbonyls

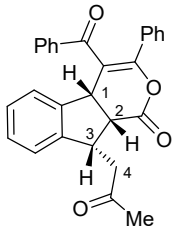
7.2.3.1 Data for indanes 116, 121-123, 125, 128-130, 159-164, 177-182

2-((4a*S*,9*S*,9a*R*)-3-Methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (116a)



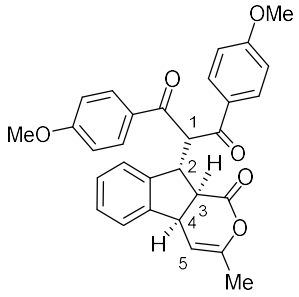
Following General Procedure 7, the corresponding TCP-ester (39.5 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (25.4 mg, 60%) as a white solid. mp 79–81 °C; $[\alpha]_D^{20}$ +16.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 18.2 min, t_R minor: 29.0 min, >99:1 er; ν_{max} (film) 2922 (C-H), 1751 (C=O), 1694 (C=O), 1667 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.87 (3H, s, COCH_3), 3.45 (1H, dd, *J* 9.0, 4.2, H–3), 4.07–4.12 (1H, m, H–4), 4.81–4.86 (1H, m, H–2), 5.17 (1H,d, *J* 4.9, H–5),5.72 (1H, d, *J* 6.1, H–1), 7.10–7.22 (4H, m, H–Ar), 7.37–7.43 (4H, m, H–Ph), 7.51–7.55 (2H, m, H–Ph), 7.89–7.91 (4H, m, H–Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CO-*C*H_3), 40.4 (CH-2), 45.5 (CH-4), 48.5 (CH-3), 59.4 (CH-1), 99.9 (CH-5), 123.7 (CH–Ar), 125.7 (CH-Ar), 127.5 (CH-Ph1), 128.2, (CH-Ar), 128.8 (2×CH-Ph2), 128.9 (2×CH-Ph2), 129.0 (2×CH-Ph1, Ar), 129.0 (2×CH-Ph1), 133.8 (CH-Ph2), 133.9 (CH-Ph1), 136.0 (CH-C=OO*C*), 136.7 (C-Ph2), 140.9 (C-Ph1), 143.7 (C1-Ar), 148.1 (C6-Ar), 170.0 (CH-*C*=OO), 195.0 (*C*=OPh2), 195.6 (*C*=OPh1); *m/z* (NSI$^+$) 867 ([2M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{28}H_{23}O_4$ [M+H]$^+$, found 423.1587, requires 423.1591 (–0.9 ppm).

(4a*R*,9*S*,9a*R*)-4-Benzoyl-9-(2-oxopropyl)-3-phenyl-9,9a-dihydroindeno[2,1-*c*]pyran-1(4aH)-one (116b)



The title compound was observed as a minor product in the inseparable product mixture (**a**:**b** 2:1) under different reaction conditions than described in General Procedure 7 (24 h, CH_2Cl_2 as a reaction solvent); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R major: 15.2 min, t_R minor: 20.1 min, >99:1 er; δ_H: 2.35 (3H, s, COC*H*$_3$), 3.23 (1H, dd, *J* 18.0, 5.9, H–4a), 3.60 (1H, dd, *J* 18.0, 9.8, H–4b), 3.95 (1H, t, *J* 7.3, H–2), 4.03–4.07 (1H, m, H–3), 4.74 (1H, d, *J* 7.9, H–1), 7.10–7.22 (4H, m, H–Ar), 7.37–7.43 (4H, m, H–Ph), 7.51–7.55 (2H, m, H–Ph), 7.71–7.73 (4H, m, H–Ph).

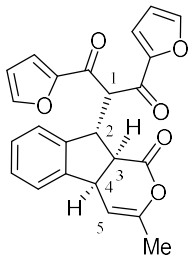
1,3-Bis(4-methoxyphenyl)-2-((4a*R*,9*R*,9a*S*)-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)propane-1,3-dione (121a)



Following General Procedure 7, the corresponding TCP-ester (39.5 mg, 0.1 mmol), 1,3-bis(4-methoxyphenyl)propane-1,3-dione (56.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (98:2 CH_2Cl_2 : EtOAc, R_f 0.20) afforded the title compound (28.0 mg, 58%) as a colorless foam. mp 86–87 °C; $[\alpha]_D^{20}$+39.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 1.5 mLmin^{-1}, 220 nm, 40 °C) t_R minor: 18.5 min, t_R major: 28.6 min, 98:2 er; ν_{max} (film) 3071 (C-H), 1751 (C=O), 1684 (C=O), 1599 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.89 (3H, s, COC*H*$_3$), 3.42 (1H, dd, *J* 8.8, 3.7, H–3), 3.85 (6H, s, 2×*p*-OC*H*$_3$), 4.06–4.15 (1H, m, H–4), 4.90 (1H, dd, *J* 6.2, 4.0, H–2), 5.21 (1H, d, *J* 5.1, H–5), 5.51 (1H, d, *J* 6.7, H–1), 6.84–.6.92 (4H, m, H–Ar), 7.11–7.26 (4H, m, H–Ph), 7.94 (4H, dd, *J* 8.8, 2.4, H–Ph), 7.89–7.91 (4H, m, H–Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CO-

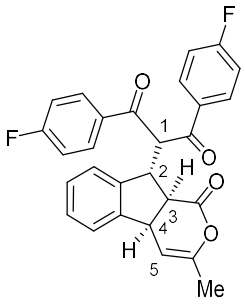
*C*H$_3$), 40.3 (CH-2), 45.7 (CH-4), 48.3 (CH-3), 55.6 (2×*p*-O*C*H$_3$) 60.0 (CH-1), 99.8 (CH-5), 114.2 (4×*C*H-Ph1+Ph2), 123.6 (*C*H-Ar), 125.9 (*C*H-Ar), 127.5 (*C*H-Ar), 128.1 (*C*H-Ar), 129.1 (*C*-Ph1), 129.8 (*C*-Ph2), 131.4 (4×*C*H-Ph1+Ph2), 141.5 (CH-C=OO*C*), 141.6 (*C*-Ar), 148.2 (*C*-Ar), 163.9 (*C*-Ph1), 164.1 (*C*-Ph2), 170.0 (CH-*C*=OO), 193.4 (*C*=OPh2), 194.1 (*C*=OPh1); *m/z* (NSI$^+$) 987 ([2M+Na]$^+$, 100%), 505 ([M+Na]$^+$, 95%); HRMS (NSI$^+$) $C_{30}H_{26}O_6Na$ [M+Na]$^+$, found 505.1620, requires 505.1622 (–0.3 ppm).

1,3-Di(furan-2-yl)-2-((4a*R*,9*R*,9a*S*)-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)propane-1,3-dione (122a)



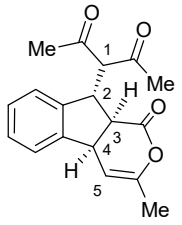
Following General Procedure 7, the corresponding TCP-ester (39.5 mg, 0.1 mmol), 1,3-di(furan-2-yl)propane-1,3-dione (40.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (98:2 CH_2Cl_2 : EtOAc, R_f 0.2) afforded the title compound (28.6 mg, 71%) as colorless crystalline solid. mp 186–187 °C; $[\alpha]_D^{20}$ +43.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 12.1 min, t_R major: 21.8 min, 98:2 er; ν_{max} (film) 3021 (C-H), 1751 (C=O), 1680 (C=O), 1649 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.87 (3H, s, COC*H*$_3$), 3.40 (1H, dd, *J* 8.8, 3.3, H–3), 4.11–4.17 (1H, m, H–4), 4.87 (1H, dd, *J* 7.3, 3.2, H–2), 5.21 (1H, d, *J* 7.2, H–1), 5.23 (1H, d, *J* 4.2, H–5), 6.51 (2H, dd, *J* 8.4, 2.1, H–Fur), 7.07–7.24 (4H, m, H–Ar), 7.29 (1H, d, *J* 3.5, H–Fur), 7.35 (1H, d, *J* 3.5, H–Fur), 7.53 (2H, d, *J* 6.2, H–Fur); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CO-*C*H$_3$), 40.3 (CH-2), 45.4 (CH-4), 47.6 (CH-3), 60.6 (CH-1), 99.7 (CH-5), 113.0 (2×*C*H-fur), 119.5 (2×*C*H-fur), 123.6 (*C*H-Ar), 125.9 (*C*H-Ar), 127.5 (*C*H-Ar), 128.3 (*C*H-Ar), 140.9 (CH-C=OO*C*), 143.6 (*C*-Ar), 147.3 (2×*C*-fur), 148.3 (*C*-Ar), 151.8 (*C*H-fur), 152.3 (*C*H-fur), 169.7 (CH-*C*=OO), 182.6 (*C*=O-fur), 183.1 (*C*=O-fur); *m/z* (NSI$^+$) 827 ([2M+Na]$^+$, 100%), 425 ([M+Na]$^+$, 65%); HRMS (NSI$^+$) $C_{24}H_{19}O_6$ [M+H]$^+$, found 403.1172, requires 403.1176 (–1.0 ppm).

1,3-Bis(4-fluorophenyl)-2-((4a*R*,9*R*,9a*S*)-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)propane-1,3-dione (123a)



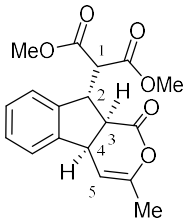
Following General Procedure 7, the corresponding TCP-ester (39.5 mg, 0.1 mmol), 1,3-bis(4-fluorophenyl)propane-1,3-dione (52.0 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.20) afforded the title compound (23.8 mg, 52%) as a light yellow crystalline solid. mp 113–114 °C; $[\alpha]_D^{20}$ +19.2 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 16.5 min, t_R minor: 28.2 min, 99:1 er; ν_{max} (film) 3071 (C-H), 1751 (C=O), 1684 (C=O), 1599 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.87 (3H, s, COCH_3), 3.39 (1H, dd, *J* 8.9, 4.1, H–3), 4.06–4.11 (1H, m, H–4), 4.84 (1H, dd, *J* 6.0, 4.4, H–2), 5.18 (1H, d, *J* 5.0, H–5), 5.56 (1H, d, *J* 6.3, H–1), 7.05–7.11 (4H, m, H–Ar), 7.11–7.13 (2H, m, H–PhF), 7.17–7.20 (2H, m, H–PhF), 7.91–7.96 (4H, m, H–PhF); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −103.5 (PhF1), −103.2 (PhF2); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CO-*C*H$_3$), 40.4 (CH-2), 45.5 (CH-4), 48.4 (CH-2), 59.9 (CH-1), 99.8 (CH-5), 116.2 (2×*C*H-PhF1), 116.3 (d, $^2J_{CF}$ = 27.5, C_{Ar}-F), 116.4 (2×*C*H-PhF2), 123.8 (*C*H-Ar), 125.6 (*C*H-Ar), 127.6 (*C*H-Ar), 128.4 (*C*H-Ar), 131.6 (2×*C*H-PhF1), 131.6 (d, $^3J_{CF}$ = 6.5, C_{Ar}-F), 131.7 (2×*C*H-PhF2), 132.3 (*C*-PhF1), 133.8 (*C*-PhF2), 140.7 (CH-C=OO*C*), 143.6 (*C*-Ar), 148.2 (*C*-Ar), 165.2 (*C*-PhF1), 166.2 (d, $^1J_{CF}$ = 252.0, C_{Ar}-F), 167.2 (*C*-PhF2), 169.9 (CH-*C*=OO), 193.3 (*C*=OPhF2), 193.9 (*C*=OPhF2); *m/z* (NSI$^+$) 939 ([2M+Na]$^+$, 100%), 481 ([M+Na]$^+$, 85%); HRMS (NSI$^+$) $C_{28}H_{20}O_4F_2Na$ [M+Na]$^+$, found 481.1213, requires 481.1222 (–1.8 ppm).

3-((4a*R*,9*R*,9a*S*)-3-Methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)pentane-2,4-dione (125a)



Following General Procedure 7, the corresponding TCP-ester (39.5 mg, 0.1 mmol), pentane-2,4-dione (21 μL mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (22.9 mg, 77%) as a colorless oil; $[\alpha]_D^{20}$ +5.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (97:3 hexane : IPA, flowrate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 11.9 min, t_R minor: 15.9 min, 63:37 er; ν_{max} (film) 3054 (C-H), 1725 (C=O), 1678 (C=O), 1652 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.89 (3H, s, CH=COC*H*$_3$), 2.14 (3H, s, COC*H*$_3$), 2.27 (3H, s, COC*H*$_3$), 3.04 (1H, dd, *J* 8.8, 2.5, H–3), 3.93 (1H, d, *J* 9.4, H–1), 4.05–4.07 (1H, m, H–4), 4.65 (1H, dd, *J* 9.4, 2.4, H–2), 5.30 (1H, d, *J* 5.1, H–5), 7.14–7.18 (3H, m, H–Ar), 7.23–7.24 (1H, m, H–Ar); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CH=CO-*C*H$_3$), 28.6 (CO*C*H$_3$), 31.8 (CO*C*H$_3$), 39.9 (CH–2), 45.3 (CH–4), 47.6 (CH–3), 72.0 (CH–1), 99.4 (CH–5), 123.9 (CH-Ar), 125.3 (CH-Ar), 127.9, (CH-Ar), 128.6 (CH-Ar), 140.6 (CH=*C*O-CH$_3$), 143.4 (C1-Ar), 148.5 (C6-Ar), 169.7 (CH-*C*=OO), 203.2 (*C*OMe), 203.8 (*C*OMe); *m/z* (NSI$^+$) 321 ([M+Na]$^+$, 30%); HRMS (NSI$^+$) $C_{18}H_{18}O_4Na$ [M+Na]$^+$, found 321.1107, requires 321.1097 (+3.0 ppm).

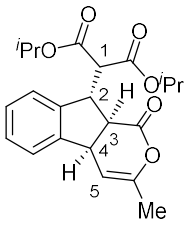
Dimethyl 2-((4a*S*,9*R*,9a*R*)-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)malonate (128a)



Following General Procedure 7, the corresponding TCP-ester (39.5 mg, 0.1 mmol), dimethylyl malonate (23 μL, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80 : 20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (33 mg, 58%) as a colorless oil. $[\alpha]_D^{20}$ +3.0 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis,

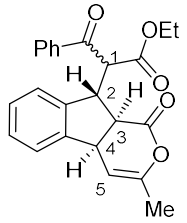
Chiralpak OJ-H (97:3 hexane : IPA, flowrate 1.0 mLmin^{-1}, 220 nm, 40 °C) t_R minor: 28.7 min, t_R major: 33.5 min, 73:27 er; ν_{max} (film) 3068 (C-H), 1733 (C=O), 1687 (C=O), 1663 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.88 (3H, s, COC*H*$_3$), 3.58 (1H, dd, *J* 9.0, 5.3, H–3), 3.70 (3H, s, COOC*H*$_3$), 3.73 (3H, s, COOC*H*$_3$), 3.88 (1H, d, *J* 6.3, H–1), 4.08–4.15 (1H, m, H–4), 4.42 (1H, t, *J* 5.8, H–2), 5.11 (1H, dd, *J* 4.4, 1.0, H–5), 7.17–7.22 (2H, m, H–Ar), 7.22–7.26 (2H, m, H–Ar); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.0 (CO-*C*H$_3$), 40.6 (CH-*C*H-CHCOO), 45.2 (*C*H-CH=CO), 47.9 (*C*H-C=OO), 52.8 (CO_2*C*H$_3$), 52.9 (CO_2*C*H$_3$), 54.2 (MeO$_2$C*C*HCO$_2$Me), 100.1 (*C*H=COC=O), 123.8 (CH-Ar), 125.1 (CH-Ar), 127.7, (CH-Ar), 128.6 (CH-Ar), 139.9 (CH-C=OO*C*), 143.7 (C1-Ar), 147.9 (C6-Ar), 168.2 (*C*O$_2$Me), 168.7 (*C*O$_2$Me), 169.8 (CH-*C*=OO); HRMS (NSI$^+$) $C_{18}H_{19}O_6$ [M+H]$^+$, found 331.1176, requires 331.1176 (–0.0 ppm).

Diisopropyl 2-((4a*R*,9*S*,9a*S*)-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)malonate (129a)



Following General Procedure 7, the corresponding TCP-ester (39.5 mg, 0.1 mmol), diisopropyl malonate (38 μL, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (90:10 Petroleum ether : EtOAc, R_f 0.3) afforded the title compound (20.1 mg, 52%) as a colorless oil; $[\alpha]_D^{20}$ +28.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak OJ-H (98:2 hexane : IPA, flowrate 0.5 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 15.3 min, t_R major: 16.3 min, 82:18 er; ν_{max} (film) 2982 (C-H), 1748 (C=O), 1724 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.09 (3H, d, *J* 6.3, ^{i}Pr-C*H*$_3$), 1.15 (3H, d, *J* 6.3, ^{i}Pr-C*H*$_3$), 1.18 (3H, d, *J* 6.3, ^{i}PrCH-C*H*$_3$), 1.24 (3H, d, *J* 6.3, ^{i}PrCH-C*H*$_3$), 1.88 (3H, s, COC*H*$_3$), 3.61 (1H, dd, *J* 9.0, 5.4, H–3), 3.80 (1H, d, *J* 5.6, H–1), 4.11 (1H, dd, *J* 8.3, 2.2, H–4), 4.40 (1H, t, *J* 5.5, H–2), 4.97 (1H, sept, *J* 6.2, ^{i}Pr-C*H*), 5.04 (1H, sept, *J* 6.2, ^{i}Pr-C*H*), 5.10 (1H, d, *J* 4.2, H–5), 7.16–7.24 (3H, m, H–Ar), 7.35 (1H, d, *J* 7.6, H–Ar); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.0 (CO-*C*H$_3$), 21.6 (2×^{i}PrCH-*C*H$_3$), 21.7 (2×^{i}PrCH-*C*H$_3$), 40.6 (CH-2), 45.4 (CH-4), 47.7 (CH-3), 54.8 (CH-1), 69.4 (^{i}Pr-*C*H), 69.5 (^{i}Pr-*C*H), 100.2 (CH-5), 123.6 (*C*H-Ar), 125.7 (*C*H-Ar), 127.5, (*C*H-Ar), 128.4 (*C*H-Ar), 140.1 (CH-C=OO*C*), 143.8 (*C*1-Ar), 147.8 (*C*6-Ar), 167.4 (*C*O$_2$^{i}Pr), 168.2 (*C*O$_2$^{i}Pr), 169.9 (CH-*C*=OO); *m/z* (NSI$^+$) 409 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{22}H_{26}O_6Na$[M+Na]$^+$, found 409.1624, requires 409.1622 (+0.6 ppm).

Ethyl 2-((4a*R*,9*S*,9a*S*)-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-3-oxo-3-phenylpropanoate (±130a)



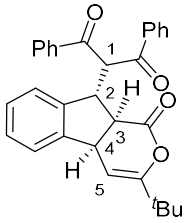
Following General Procedure 7, the corresponding TCP-ester (39.5 mg, 0.1 mmol), ethyl benzoylacetate (43 μL, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL)and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound as inseparable diastereomeric mixture (29.4 mg, 74%, dr 75:25) as a colorless oil; ν_{max} (film) 2945 (C-H), 1743 (C=O), 1687 (C=O), 1671 (C=O);

16a (major): ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.00 (3H, t, *J* 7.1, OCH_2CH_3), 1.87 (3H, s, $COCH_3$), 3.60 (1H, dd, *J* 8.9, 5.9, H–3), 4.03 (2H, qd, *J* 7.1, 2.2, OCH_2CH_3), 4.11–4.15 (1H, m, H–4), 4.57 (1H, t, *J* 5.1, H–2), 4.85 (1H, d, *J* 5.1, H–1), 5.07 (1H, d, *J* 3.7, H–5), 7.16–7.24 (4H, m, H–Ar), 7.44–7.48 (2H, m, H–Ph), 7.56–7.59 (1H, m, H–Ph), 7.97 (2H, d, *J* 7.4, H–Ph); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 13.9 (OCH_2CH_3), 19.0 ($CO\text{-}CH_3$), 40.6 (CH-2), 45.8 (CH-4), 47.8 (CH-3), 56.6 (CH-1), 61.8 (OCH_2CH_3) 99.7 (CH-5), 123.7 (CH–Ar), 125.8 (CH-Ar), 127.5 (CH-Ar), 128.4 (CH-Ar), 128.8 (2×CH-Ph), 128.9 (2×CH-Ph), 133.8 (CH-Ph), 140.2 (CH-C=OO*C*), 143.5 (C-Ph1), 143.8 (C1-Ar), 147.7 (C6-Ar), 169.6 (CO_2Et), 170.1 (CH-*C*=OO), 194.4 (*C*=OPh);

16a' (minor): ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.14 (3H, t, *J* 7.1, OCH_2CH_3), 1.90 (3H, s, $COCH_3$), 3.41 (1H, dd, *J* 8.8, 3.8, H–3), 4.03 (2H, qd, *J* 7.1, 2.2, OCH_2CH_3), 4.11–4.15 (1H, m, H–4), 4.67 (1H, d, *J* 8.3, H–1), 4.77 (1H, dd, *J* 8.3, 3.8, H–2), 5.21 (1H, d, *J* 4.9, H–5), 7.16–7.24 (4H, m, H–Ar), 7.44–7.48 (2H, m, H–Ph), 7.56–7.59 (1H, m, H–Ph), 7.97 (2H, d, *J* 7.4, H–Ph).

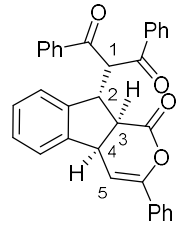
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.0 (OCH_2CH_3), 19.1 ($CO\text{-}CH_3$), 40.5 (CH-2), 45.5 (CH-4), 47.5 (CH-3), 57.3 (CH-1), 62.0 (OCH_2CH_3) 100.4 (CH-5), 123.7 (CH–Ar), 125.9 (CH-Ar), 127.6 (CH-Ar), 128.3 (CH-Ar), 128.6 (2×CH-Ph), 128.9 (2×CH-Ph), 133.8 (CH-Ph), 140.2 (CH-C=OO*C*), 141.0 (C-Ph1), 141.9 (C1-Ar), 143.8 (C6-Ar), 168.4 (CO_2Et), 168.6 (CH-*C*=OO), 193.6 (*C*=OPh); *m/z* (NSI^+) 413 ($[M+Na]^+$, 100%); HRMS (NSI^+) $C_{24}H_{22}O_5Na$ $[M+Na]^+$, found 413.1354, requires 413.1359 (–1.3 ppm).

2-((4a*R*,9*R*,9a*S*)-3-(*tert*-Butyl)-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (159a)



Following General Procedure 7, the corresponding TCP-ester (43.8 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (35.0 mg, 74%) as a yellow oil; $[\alpha]_D^{20}$ +20.4 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 10.1 min, t_R minor: 12.1 min, 97:3 er; ν_{max} (film) 2997 (C-H), 1749 (C=O), 1695 (C=O), 1597 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.10 (9H, s, (C*H*$_3$)$_3$), 3.44 (1H, dd, *J* 8.9, 4.5, H–3), 4.11 (1H, dd, *J* 8.9, 5.0, H–4), 4.79 (1H, t, *J* 5.1, H–2), 5.18 (1H, d, *J* 5.0, H–5), 5.74 (1H, d, *J* 5.9, H–1), 7.08–7.19 (4H, m, H–Ar), 7.37–7.43 (4H, m, H–Ph),7.50–7.54 (2H, m, H–Ph), 7.89–7.92 (4H, m, H–Ph); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 27.5 (C(*C*H$_3$)$_3$), 34.8 (*C*(CH$_3$)$_3$), 40.2 (CH-2), 45.6 (CH-4), 48.3 (CH-3), 59.1 (CH-1), 96.0 (CH-5), 123.7 (CH–Ar), 125.5 (CH-Ar), 127.5 (CH-Ar), 128.2, (CH-Ar), 128.8 (2×CH-Ph1), 128.9 (2×CH-Ph2), 129.0 (2×CH-Ph1), 129.0 (2×CH-Ph2), 133.9 (CH-Ph1), 133.7 (CH-Ph2), 136.0 (C-Ph1), 136.7 (C-Ph2), 141.1 (C1-Ar), 143.8 (C6-Ar), 158.8 (C=OO*C*(CH$_3$)$_3$), 170.2 (CH-*C*=OO), 195.1 (*C*=OPh2), 195.7 (*C*=OPh1); *m/z* (NSI^+) 487 ([M+Na]$^+$, 100%), 951 ([2M+Na]$^+$, 70%); HRMS (NSI^+) $C_{28}H_{23}O_4$ [M+H]$^+$, found 423.1587, requires 423.1591 (–0.9 ppm).

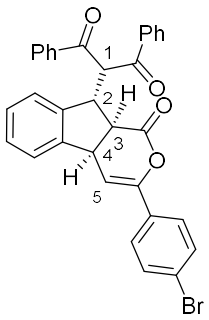
2-((4a*S*,9*S*,9a*R*)-1-Oxo-3-phenyl-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (160a)



Following General Procedure 7, the corresponding TCP-ester (45.8 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title

compound (34.4 mg, 71%) as a yellow solid. mp 85–87 °C; $[\alpha]_D^{20}$ +50.3 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R major: 26.9 min, t_R minor: 40.3 min, >99:1 er; ν_{max} (film) 3077 (C-H), 1740 (C=O), 1694 (C=O), 1665 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.60 (1H, dd, *J* 9.0, 4.0, H–3), 4.37 (1H, dd, *J* 8.9, 5.4, H–4), 4.92 (1H, dd, *J* 5.8, 4.1, H–2), 5.78 (1H, d, *J* 6.2, H–5), 5.97 (1H, d, *J* 5.3, H–1), 7.19–7.24 (3H, m, H–Ar), 7.33–7.35 (1H, m, H–Ar), 7.37–7.45 (7H, m, 2×CH-Ph1, 2×CH-Ph2, 3×CH-Ph3), 7.50–7.56 (2H, m, 1×CH-Ph1, 1×CH-Ph2), 7.58–7.62 (2H, m, CH-Ph3), 7.90–7.95 (4H, m, 2×CH-Ph1, 2×CH-Ph2); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 40.9 (CH-2), 45.6 (CH-4), 48.6 (CH-3), 59.4 (CH-1), 99.8 (CH-5), 123.8 (CH-Ar), 124.9 (2×CH-Ph3), 125.7 (CH-Ar), 127.2 (CH-Ph1), 128.3, (CH-Ar), 128.6 (2×CH-Ph2), 128.8 (2×CH-Ph2), 128.9 (2×CH-Ph1, Ar), 129.0 (2×CH-Ph3),129.1 (2×CH-Ph1), 129.3 (CH-Ph3), 132.4 (C-Ph3), 133.8 (CH-Ph2), 133.9 (CH-Ph1), 136.0(CH-C=OO*C*), 136.6 (C-Ph2), 141.0 (C-Ph1), 143.3 (C1-Ar), 148.8 (C6-Ar), 169.6 (CH-*C*=OO), 195.0 (*C*=OPh2), 195.5 (*C*=OPh1); *m/z* (NSI$^+$) 507 ([M+Na]$^+$, 65%), 485 ([M+H]$^+$, 35%); HRMS (NSI$^+$) $C_{33}H_{28}O_5N$ [M+O+NH_4]$^+$, found 518.1954, requires 518.1962 (–1.5 ppm).

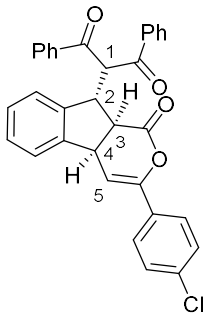
2-((4a*R*,9*R*,9a*S*)-3-(4-Bromophenyl)-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (161a)



Following General Procedure 7, the corresponding TCP-ester (53.7 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (36.6 mg, 65%) as a yellow oil; $[\alpha]_D^{20}$ +30.6 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 27.6 min, t_R minor: 33.3 min, 97:3 er; ν_{max} (film) 3077 (C-H), 1740 (C=O), 1694 (C=O), 1665 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.62 (1H, dd, *J* 9.0, 3.9, H–3), 4.36 (1H, dd, *J* 9.0, 5.3, H–4), 4.86–4.91 (1H, m, H–2), 5.76 (1H, d, *J* 6.0, H–5), 5.97 (1H, d, *J* 5.3, H–1), 7.19–7.20 (2H, m, H–Ar), 7.37–7.45 (6H, m, 2×H–Ph + 2×H–Ar + 2×H–Ph_{Br}), 7.47 (4H, s, H–Ph), 7.53–7.58 (2H, m, 2×H–Ph_{Br}), 7.89–7.94

(4H, m, H–Ph); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 40.9 (CH-2), 45.4 (CH-4), 48.7 (CH-3), 59.4 (CH-1), 100.3 (CH-5), 123.8 (CH-Ar), 125.7 (CH-Ar), 126.4 (2×CH-Ph_{Br}), 127.9 (CH-Ar), 128.4 (CH-Ar), 128.8 (2×CH-Ph2 + 2×CH-Ph1), 128.9 (2×CH-Ph2), 129.0 (2×CH-Ph1), 129.1 (2×CH-Ph_{Br}), 131.8 (2×CH-Ph_{Br}), 133.9 (C-Ph1), 134.0 (C-Ph2), 135.1 (CH-C=OO*C*), 136.0 (C-Ph2), 136.6 (C-Ph_{Br}), 141.0 (C-Ph1), 143.1 (C1-Ar), 145.2 (C6-Ar), 169.3 (CH-*C*=OO), 195.0 (*C*=OPh2), 195.5 (*C*=OPh1); *m/z* (NSI^+) 586 ($[M+Na]^+$, 90%); HRMS (NSI^+) $C_{33}H_{23}O_5{}^{79}BrNa$ $[M+Na]^+$, found 601.0606, requires 601.0621 (–2.5 ppm).

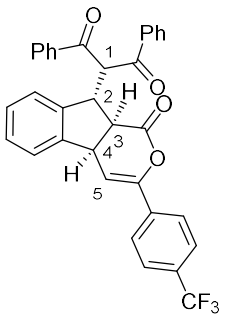
2-((4a*R*,9*R*,9a*S*)-3-(4-Chlorophenyl)-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (162a)



Following General Procedure 7, the corresponding TCP-ester (49.2 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (34.8 mg, 67%) as a yellow oil; $[\alpha]_D^{20}$ +55.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 25.7 min, t_R minor: 30.7 min, 96:4 er; ν_{max} (film) 2924 (C-H), 1759 (C=O), 1694 (C=O), 1595 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 3.62 (1H, dd, *J* 9.0, 4.0, H–3), 4.37 (1H, dd, *J* 9.0, 5.3, H–4), 4.89–4.91 (1H, m, H–2), 5.77 (1H, d, *J* 6.0, H–5), 5.95 (1H, d, *J* 5.3, H–1), 7.19–7.20 (2H, m, H–Ar), 7.31–7.33 (2H, m, H–Ar), 7.37–7.45 (6H, m, 4×H–Ph + 2×H–Ph_{Cl}), 7.53–7.56 (4H, m, 2×H–Ar + 2×H–Ph_{Cl}), 7.89–7.94 (4H, m, H–Ph); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 40.8 (CH-2), 45.4 (CH-4), 48.5 (CH-3), 59.3 (CH-1), 100.1 (CH-5), 123.7 (CH-Ar), 126.1 (2×CH-Ph_{Cl}), 127.2 (CH-Ar), 127.7 (CH-Ar), 128.3 (CH-Ar), 128.7 (2×CH-Ph2 + 2×CH-Ph1), 128.8 (2×CH-Ph2), 128.9 (2×CH-Ph1), 129.0 (2×CH-Ph_{Cl}), 129.0 (2×CH-Ph_{Cl}), 130.8 (C-Ph_{Cl}), 133.8 (C-Ph1 + C-Ph2), 135.1 (CH-C=OO*C*), 135.9 (C-Ph2), 136.5 (C-Ph_{Cl}), 140.9 (C-Ph1), 143.0 (C1-Ar), 147.8 (C6-Ar), 169.2 (CH-*C*=OO), 194.9

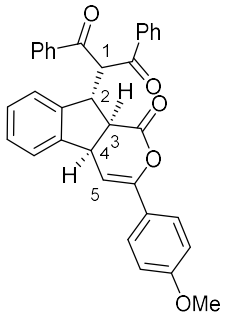
(*C*=OPh2), 195.4 (*C*=OPh1); *m/z* (NSI$^+$) 541 ([M+Na]$^+$, 70%); HRMS (NSI$^+$) $C_{33}H_{23}O_4{}^{35}Cl_1Na$ [M+Na]$^+$, found 541.1168, requires 541.1177 (–1.7 ppm).

2-((4a*R*,9*R*,9a*S*)-1-Oxo-3-(4-(trifluoromethyl)phenyl)-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (163a)



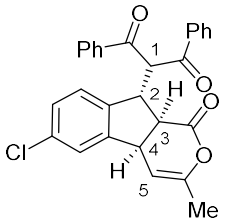
Following General Procedure 7, the corresponding TCP-ester (52.6 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (37.0 mg, 67%) as a yellow oil; $[\alpha]_D^{20}$ +19.8 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 18.9 min, t_R minor: 23.5 min, 97:3 er; ν_{max} (film) 2924 (C-H), 1751 (C=O), 1695 (C=O), 1668 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.67 (1H, dd, *J* 9.1, 3.9, H–3), 4.42 (1H, dd, *J* 9.0, 5.4, H–4), 4.90 (1H, dd, *J* 5.5, 4.1, H–2), 5.78 (1H, d, *J* 5.9, H–5), 6.08 (1H, d, *J* 5.4, H–1), 7.20–7.21 (2H, m, H–Ar), 7.37–7.46 (4H, m, H–Ph), 7.53–7.57 (2H, m, H–Ar), 7.60–7.62 (2H, m, H–Ph_{CF3}), 7.71–7.73 (2H, m, H–Ph_{CF3}), 7.89–7.94 (4H, m, H–Ph); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: –63.0 (CF_3); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 41.0 (CH-2), 45.4 (CH-4), 48.7 (CH-3), 59.3 (CH-1), 102.0 (CH-5), 123.8 (CH-Ar), 125.1 (2×CH-Ph_{CF3}), 125.7 (q, $^3J_{CF}$ = 3.7, C_{Ar}-CF_3), 125.7 (CH-Ar), 126.8 (q, $^1J_{CF}$ = 285.2, C_{Ar}-CF_3), 127.9 (CH-Ar), 128.5 (CH-Ar), 128.8 (2×CH-Ph2 + 2×CH-Ph1), 128.9 (2×CH-Ph2 + 2×CH-Ph_{CF3}), 129.0 (q, $^2J_{CF}$ = 40.9, C_{Ar}-CF_3), 129.1 (2×CH-Ph1), 129.1 (2×CH-Ph_{CF3}), 130.8 (C-Ph_{CF3}), 133.9 (CH-Ph1), 134.0 (CH-Ph2), 135.8 (CH-C=OO*C*), 136.0 (C-Ph2), 136.5 (C-Ph_{CF3}), 141.0 (C-Ph1), 142.9 (C1-Ar), 147.6 (C6-Ar), 169.2 (CH-*C*=OO), 195.0 (*C*=OPh2), 195.5 (*C*=OPh1); *m/z* (NSI$^+$) 575 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{32}H_{23}O_4F_3Na$ [M+Na]$^+$, found 575.1428, requires 575.1441 (–2.2 ppm).

2-((4a*R*,9*R*,9a*S*)-3-(4-Methoxyphenyl)-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (164a)



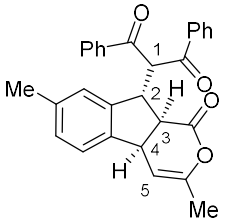
Following General Procedure 7, the corresponding TCP-ester (48.8 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (98:2 CH_2Cl_2 : EtOAc, R_f 0.2) afforded the title compound (35.4 mg, 69%) as a yellow oil; $[\alpha]_D^{20}$ +68.8 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 36.5 min, t_R minor: 43.1 min, >99:1 er; ν_{max} (film) 2932 (C-H), 1751 (C=O), 1694 (C=O), 1670 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.57 (1H, dd, *J* 8.9, 4.0, H–3), 3.81 (3H, s, OCH_3), 4.33 (1H, dd, *J* 8.9, 5.3, H–4), 4.91 (1H, dd, *J* 5.7, 4.0, H–2), 5.76 (1H, d, *J* 6.2, H–5), 5.82 (1H, d, *J* 5.7, H–1), 6.87 (2H, d, *J* 8.9, H–Ph$_{OMe}$), 7.10–7.13 (1H, m, H–Ar), 7.18–7.19 (2H, m, H–Ar), 7.23–7.25 (1H, m, H–Ar), 7.37–7.44 (4H, m, H–Ph), 7.51–7.55 (4H, m, 2×H–Ph$_{OMe}$ + 2×H–Ph), 7.91–7.94 (4H, m, H–Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 40.8 (CH-2), 45.7 (CH-4), 48.6 (CH-3), 55.5 (O*C*H$_3$), 59.5 (CH-1), 97.9 (CH-5), 113.9 (2×CH-Ph$_{OMe}$), 123.8 (CH-Ar), 125.0 (C-Ph$_{OMe}$), 125.7 (CH-Ar), 126.3 (2×CH-Ph$_{OMe}$), 127.7 (CH-Ar), 128.3 (CH-Ar), 128.8 (2×CH-Ph1), 128.9 (2×CH-Ph2), 129.0 (2×CH-Ph1), 129.1 (2×CH-Ph2), 133.8 (CH-Ph1), 133.9 (CH-Ph2), 135.8 (CH-C=OO*C*), 136.0 (C-Ph2), 136.7 (C-Ph$_{OMe}$), 141.0 (C-Ph1), 143.5 (C1-Ar), 148.6 (C6-Ar), 160.4 (Ph-*C*-OMe), 169.7 (CH-*C*=OO), 195.0 (*C*=OPh2), 195.6 (*C*=OPh1); *m/z* (NSI$^+$) 537 ([M+Na]$^+$, 100%), 1051 ([2M+Na]$^+$, 25%); HRMS (NSI$^+$) $C_{34}H_{26}O_5Na$ [M+Na]$^+$, found 537.1659, requires 537.1672 (–2.5 ppm).

2-((4a*R*,9*R*,9a*S*)-6-Chloro-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (177a)



Following General Procedure 7, the corresponding TCP-ester (43.0 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (30.6 mg, 67%) as a colorless oil; $[\alpha]_D^{20}$ +18.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R major: 18.7 min, t_R minor: 31.3 min, 99:1 er; ν_{max} (film) 2926 (C-H), 1749 (C=O), 1695 (C=O), 1668 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.88 (3H, s, COC*H*$_3$), 3.44 (1H, dd, *J* 9.0, 4.6, H–3), 4.07–4.13 (1H, m, H–4), 4.76 (1H, t, *J* 5.2, H–2), 5.12 (1H, d, *J* 4.0, H–5), 5.72 (1H, d, *J* 5.9, H–1), 7.06–7.18 (3H, m, H–Ar), 7.39–7.45 (4H, m, H–Ph), 7.51–7.55 (2H, m, H–Ph), 7.91–7.93 (4H, m, H–Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CO-*C*H$_3$), 40.4 (CH-2), 45.6 (CH-4), 48.0 (CH-3), 59.2 (CH-1), 99.3 (CH-5), 124.0 (CH-Ar), 127.0 (CH-Ar), 127.8 (CH-Ar), 128.8 (2×CH-Ph2), 128.9 (2×CH-Ph2), 129.1 (2×CH-Ph1), 129.2 (2×CH-Ph1), 134.0 (CH-Ph2), 133.9 (CH-Ph1), 134.0 (C-Cl), 135.8 (CH-C=OO*C*), 136.6 (C-Ph2), 139.4 (C-Ph1), 145.6 (C1-Ar), 148.5 (C6-Ar), 169.6 (CH-*C*=OO), 194.9 (*C*=OPh2), 195.5 (*C*=OPh1); *m/z* (NSI$^+$) 479 ([M+Na]$^+$, 100%), 935 ([2M+Na]$^+$, 65%); HRMS (NSI$^+$) $C_{28}H_{22}{}^{35}ClO_4$ [M+H]$^+$, found 457.1199, requires 457.1201 (–0.5 ppm).

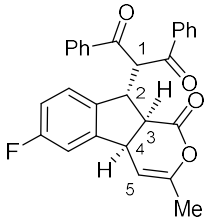
2-((4a*R*,9*R*,9a*S*)-3,7-Dimethyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (178a)



Following General Procedure 7, the corresponding TCP-ester (41.0 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title

compound (20.1 mg, 46%) as a yellow oil; $[\alpha]_D^{20}$ +17.2 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (98:2 hexane : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 22.8 min, t_R minor: 33.6 min, >99:1 er; ν_{max} (film) 2922 (C-H), 1749 (C=O), 1697 (C=O), 1668 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.85 (3H, s, COCH_3), 2.21 (3H, s, ArC-CH_3), 3.43 (1H, dd, *J* 9.0, 4.6, H–3), 4.04–4.09 (1H, m, H–4), 4.78–4.80 (1H, m, H–2), 5.16 (1H, d, *J* 4.6, H–5), 5.69 (1H, d, *J* 6.2, H–1), 6.95–7.02 (3H, m, H–Ar), 7.40 (4H, dt, *J* 15.3, 7.8, H–Ph), 7.53 (2H, dd, *J* 16.3, 7.6, H–Ph), 7.90 (4H, d, *J* 8.0, H–Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.0 (CO-*C*H$_3$), 21.4 (ArC-*C*H$_3$), 40.0 (CH-2), 45.6 (CH-4), 48.4 (CH-3), 59.4 (CH-1), 100.0 (CH-5), 123.4 (CH-Ar), 126.2 (CH-Ar), 128.8 (2×CH-Ph2), 128.9 (2×CH-Ph2), 129.0 (2×CH-Ph1), 129.0 (2×CH-Ph1), 129.1 (CH-Ar), 133.7 (CH-Ph2), 133.8 (CH-Ph1), 136.0 (C-Cl), 136.7 (CH-C=OO*C*), 137.3 (C-Ph2), 140.8 (C-Ph1), 141.1 (C1-Ar), 147.9 (C6-Ar), 170.1 (CH-*C*=OO), 195.1 (*C*=OPh2), 195.5 (*C*=OPh1); *m/z* (NSI$^+$) 459 ([M+Na]$^+$, 100%), 895 ([2M+Na]$^+$, 50%); HRMS (NSI$^+$) $C_{29}H_{24}O_4Na$ [M+Na]$^+$, found 459.1567, requires 459.1567 (0.0 ppm).

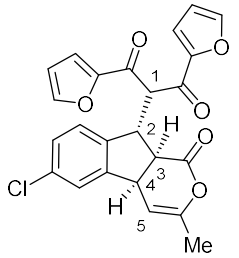
2-((4a*R*,9*R*,9a*S*)-6-Fluoro-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-diphenylpropane-1,3-dione (179a)



Following General Procedure 7, the corresponding TCP-ester (41.4 mg, 0.1 mmol), 1,3-dipheny-1,3-propanedione (44.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (24.2 mg, 55%) as a yellow oil; $[\alpha]_D^{20}$ +34.1 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R major: 18.6 min, t_R minor: 30.7 min, 98:2 er; ν_{max} (film) 2924 (C-H), 1745 (C=O), 1695 (C=O), 1663 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.88 (3H, s, COCH_3), 3.46 (1H, dd, *J* 8.9, 4.3, H–3), 4.07–4.09 (1H, m, H–4), 4.78 (1H, t, *J* 4.9, H–2), 5.12 (1H, d, *J* 4.4, H–5), 5.72 (1H, d, *J* 6.0, H–1), 6.78–6.81 (2H, m, H–Ar), 7.16–7.18 (1H, m, H–Ar), 7.38–7.44 (4H, m, H–Ph), 7.52–7.57 (2H, m, H–Ph), 7.90–7.92 (4H, m, H–Ph); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −114.3; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CO-*C*H$_3$), 40.4 (CH-2), 45.9 (CH-4), 47.8 (CH-3), 59.3 (CH-1), 99.2 (CH-5), 110.7 (CH-Ar), 110.8 (d, $^2J_{CF}$ = 22.6, C_{Ar}-F), 114.6 (CH-Ar), 114.6 (d, $^2J_{CF}$ = 22.5, C_{Ar}-F), 127.1 (CH-Ar), 128.8 (2×CH-Ph2), 128.9

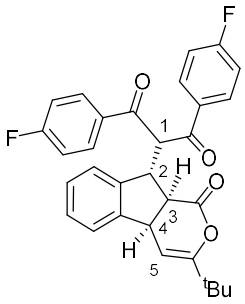
(2×CH-Ph2), 128.9 (d, $^{3}J_{CF}$ = 8.9, C_{Ar}-F), 129.1 (2×CH-Ph1), 129.1 (2×CH-Ph1), 133.9 (CH-Ph2), 134.0 (CH-Ph1), 135.9 (CH-C=OO*C*), 136.3 (C-Ph2), 136.6 (C-Ph1), 145.9 (C1-Ar), 148.6 (C6-Ar), 163.0 (d, $^{1}J_{CF}$ = 246.9, C_{Ar}-F), 169.6 (CH-*C*=OO), 195.0 (*C*=OPh2), 195.5 (*C*=OPh1); *m/z* (NSI^{+}) 463 ($[M+Na]^{+}$, 100%), 903 ($[2M+Na]^{+}$, 25%); HRMS (NSI^{+}) $C_{24}H_{28}O_{6}Cl$ $[M+H]^{+}$, found 463.1306, requires 463.01316 (–2.2 ppm).

2-((4a*R*,9*R*,9a*S*)-6-Chloro-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-di(furan-2-yl)propane-1,3-dione (180a)



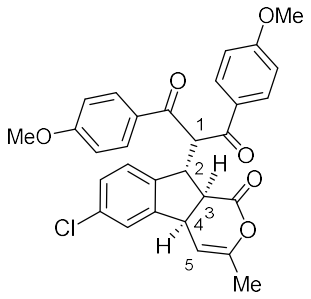
Following General Procedure 7, the corresponding TCP-ester (43.0 mg, 0.1 mmol), 1,3-di(furan-2-yl)propane-1,3-dione (40.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (98:2 CH_2Cl_2 : EtOAc, R_f 0.2) afforded the title compound (27.1 mg, 62%) as a yellow oil; $[\alpha]_D^{20}$ +60.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 11.5 min, t_R major: 18.9 min, 98:2 er; ν_{max} (film) 3136 (C-H), 1749 (C=O), 1684 (C=O), 1657 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.88 (3H, s, COCH_3), 3.40 (1H, dd, *J* 8.8, 3.5, H–3), 4.07–4.15 (1H, m, H–4), 4.80 (1H, dd, *J* 7.1, 3.5, H–2), 5.18 (1H, d, *J* 5.1, H–5), 5.21 (1H, d, *J* 7.1, H–1), 6.51 (2H, ddd, *J* 8.1, 3.6, 1.6, H–Fur), 7.05–7.12 (2H, m, H–Ar), 7.19–7.21 (1H, m, Ar-H), 7.30 (1H, d, *J* 3.6, H–Fur), 7.36 (1H, d, *J* 3.6, H–Fur), 7.54 (2H, dd, *J* 9.5, 0.8, H–Fur); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CO-*C*H_3), 40.2 (CH-2), 45.5 (CH-4), 47.1 (CH-3), 60.2 (CH-1), 99.0 (CH-5), 113.1 (2×*C*H-fur), 119.5 (*C*H-fur), 119.6 (*C*H-fur), 124.0 (*C*H-Ar), 127.2 (*C*H-Ar), 127.7 (*C*H-Ar), 134.1 (*C*-Cl), 139.3 (CH-C=OO*C*), 145.6 (*C*-Ar), 147.5 (2×*C*H-fur), 148.8 (*C*-Ar), 151.7 (*C*-fur), 152.3 (*C*-fur), 169.3 (CH-*C*=OO), 182.4 (*C*=O-fur), 182.9 (*C*=O-fur); *m/z* (NSI^{+}) 459 ($[M+Na]^{+}$, 100%), 895 ($[2M+Na]^{+}$, 45%); HRMS (NSI^{+}) $C_{24}H_{28}O_{6}{}^{35}Cl$ $[M+H]^{+}$, found 437.0782, requires 437.0786 (–1.0 ppm).

1,3-Bis(4-fluorophenyl)-2-((4a*R*,9*R*,9a*S*)-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)propane-1,3-dione (181a)



Following General Procedure 7, the corresponding TCP-ester (45.6 mg, 0.1 mmol), 1,3-bis(4-fluorophenyl)propane-1,3-dione (52.0 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80: 20 Petroleum ether : EtOAc, R_f 0.20) afforded the title compound (39.5 mg, 79%) as colorless needles; $[\alpha]_D^{20}$ +55.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 7.5 min, t_R minor: 9.5 min, >99:1 er; ν_{max} (film) 2926 (C-H), 1746 (C=O), 1694 (C=O), 1597 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.10 (9H, s, $CO(CH_3)_3$), 3.38 (1H, dd, *J* 8.9, 4.3, H–3), 4.09 (1H, dd, *J* 8.9, 5.0, H–4), 4.77–4.82 (1H, m, H–2), 5.19 (1H, d, *J* 5.1, H–5), 5.57 (1H, d, *J* 6.3, H–1), 7.04–7.12 (4H, m, H–Ar), 7.13–7.11 (2H, m, H–PhF), 7.18–7.21 (2H, m, H–PhF), 7.91–7.96 (4H, m, H–PhF); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −103.6 (PhF1), −103.2 (PhF2); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 27.5 ($CO(CH_3)_3$), 40.2 (CH-2), 45.6 (CH-4), 48.3 (CH-3), 59.7 (*C*H-1), 99.9 (CH-5), 116.1 (d, $^2J_{CF}$ = 22.0, C_{Ar}-F), 116.2 (2×*C*H-PhF1), 116.2 (d, $^2J_{CF}$ = 21.9, C_{Ar}-F), 116.4 (2×*C*H-PhF2), 123.8 (*C*H-Ar), 125.5 (*C*H-Ar), 127.6 (*C*H-Ar), 128.4 (*C*H-Ar), 131.5 (d, $^3J_{CF}$ = 8.1, C_{Ar}-F), 131.6 (2×*C*H-PhF1), 131.7 (2×*C*H-PhF2), 132.3 (*C*-PhF1), 133.0 (*C*-PhF2), 140.9 (CH-C=OO*C*), 143.8 (*C*-Ar), 148.4 (*C*-Ar), 159.0 (*C*-PhF1), 164.6 (*C*-PhF2), 166.0 (d, $^1J_{CF}$ = 249.8, C_{Ar}-F), 170.1 (CH-*C*=OO), 193.4 (*C*=OPhF2), 194.0 (*C*=OPhF2); *m/z* (NSI^+) 523 ($[M+Na]^+$, 100%), 1023 ($[2M+Na]^+$, 75%); HRMS (NSI^+) $C_{24}H_{28}O_6Cl$ $[M+Na]^+$, found 523.1676, requires 523.1691 (–2.9 ppm).

2-((4a*R*,9*R*,9a*S*)-6-Chloro-3-methyl-1-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*c*]pyran-9-yl)-1,3-bis(4-methoxyphenyl)propane-1,3-dione (182a)

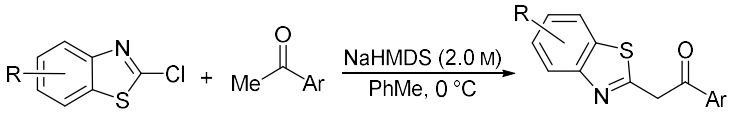


Following General Procedure 7, the corresponding TCP-ester (43.0 mg, 0.1 mmol), 1,3-bis(4-fluorophenyl)propane-1,3-dione (56.8 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.15) afforded the title compound (33.6 mg, 65%) as white needles. mp 145−146 °C; $[\alpha]_D^{20}$ +10.2 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 17.5 min, t_R major: 25.3 min, 97:3 er; ν_{max} (film) 2938 (C-H), 1734 (C=O), 1676 (C=O), 1655 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.87 (3H, s, COC*H*$_3$), 3.38 (1H, dd, *J* 8.8, 4.1, H–3), 3.83 (3H, s, *p*-OC*H*$_3$), 3.84 (3H, s, *p*-OC*H*$_3$), 4.06–4.09 (1H, m, H–4), 4.80 (1H, dd, *J* 6.1, 4.1, H–2), 5.13 (1H, d, *J* 4.7, H–5), 5.48 (1H, d, *J* 6.6, H–1), 6.86–.6.89 (3H, m, H–Ph), 7.06–7.09 (2H, m, H–Ar), 7.11–7.15 (1H, m, H–Ar), 7.93 (4H, dd, *J* 8.8, 5.4, H–Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.1 (CO-*C*H$_3$), 40.2 (CH-2), 45.8 (CH-4), 47.9 (CH-3), 55.7 (2×*p*-O*C*H$_3$), 59.7 (CH-1), 99.2 (CH-5), 114.3 (4×*C*H-Ph1 + Ph2), 123.9 (*C*H-Ar), 127.2 (*C*H-Ar), 127.7 (*C*H-Ar), 128.9 (*C*-Ph1), 129.6 (*C*-Ph2), 131.4 (4×*C*H-Ph1 + Ph2), 133.9 (*C*-Cl), 139.9 (CH-C=OO*C*), 145.6 (*C*-Ar), 148.6 (*C*-Ar), 164.1 (*C*-Ph1), 164.2 (*C*-Ph2), 169.6 (CH-*C*=OO), 193.3 (*C*=OPh2), 193.9 (*C*=OPh1); *m/z* (NSI$^+$) 517 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{30}H_{26}{}^{35}Cl_1O_6Na$ [M+H]$^+$, found 517.1401, requires 517.1412 (–2.2 ppm).

7.3 Experimental for Chapter 3

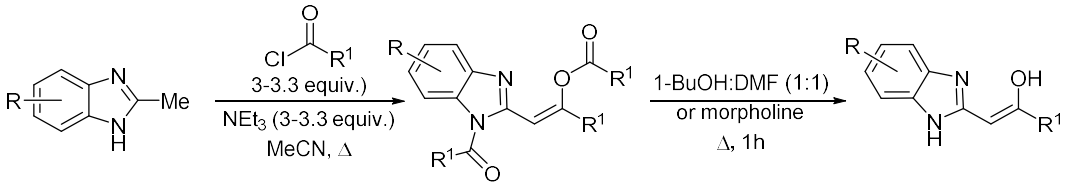
7.3.1 General procedures

General Procedure 8: ***Preparation of Acyl Benzothiazoles***



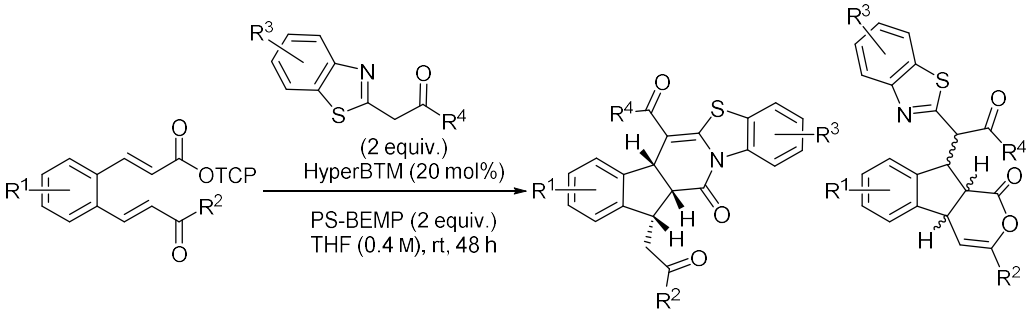
To a degassed solution of chlorobenzoxazole (1 equiv.) and carbonyl nucleophile (3 equiv.) in anhydrous toluene (0.25–0.35 M) was added NaHMDS (3 equiv., 2 M solution in toluene or THF) dropwise at 0 °C, and the solution stirred for 5 h at 0 °C followed by room temperature for 16 h. Excess NaHMDS was quenched by dropwise addition of saturated aqueous NH_4Cl (50 mL) at 0 °C. The organic layer was separated, then the aqueous layer extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified as specified to afford the product.

General Procedure 9: *Preparation of Acyl Benzimidazoles*



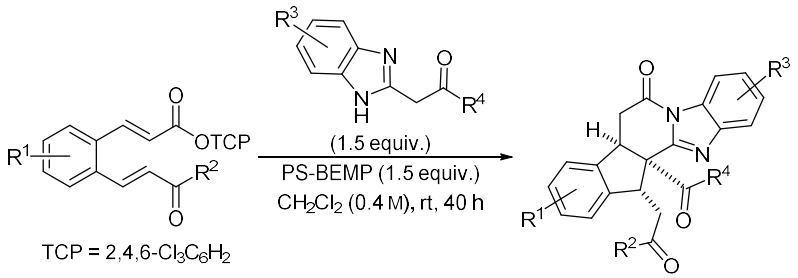
A mixture of 2-methyl-benzimidazole (1 equiv.), triethylamine (3–3.3 equiv.), acetonitrile (1 M), and aroyl chloride (3.0–3.3 equiv.) was heated at reflux for 18 h. The cooled reaction mixture was filtered and the precipitate was washed on the filter with 1:1 2-propanol–water, water, and then 2-propanol. After drying, the triacylation product was dissolved in a 1:1 1-butanol–dimethyl formamide mixture and heated at reflux for 1 h. The precipitate was washed with cold 2-propanol and then hexane to give an analytically pure product. If the triacylation product could not be isolated as a solid, the reaction mixture was carefully diluted by adding water (2 mL) and morpholine (6 equiv.). Heating was then continued for an additional 15 min. The cooled mass was filtered and washed with cold 2-propanol and then hexane to give an analytically pure product.

General Procedure 10: *Michael-Lactamisation-Michael Reaction with Acyl Benzothiazoles*



To a solution of the corresponding tricholorophenol-activated ester (1 equiv.) in anhydrous THF (0.4 M), was added isothiourea HyperBTM (20 mol%) and polymer-bound 2-*tert*-butylimino-2-diethylamino-1,3,dimethylperhydro,1,3,2,diazaphosphorine (PS-BEMP) (2 equiv.) followed by addition of a the appropriate acyl benzothiazole (2 equiv.). The reaction mixture was stirred for 48 h at room temperature. The crude mixture was filtered to remove the base and concentrated *in vacuo*. The residue was purified by flash silica column chromatography using mixtures of petroleum ether and ethyl acetate as eluents giving the products of approximatly 95% purity. Analytically pure compounds can be obtained after a second purification by flash silica column chromatography using dichloromethane as eluent.

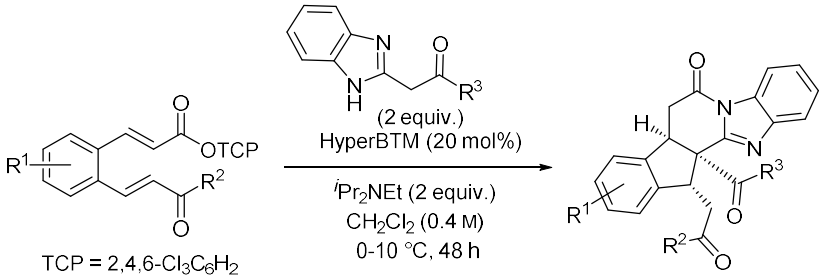
General Procedure 11: *Racemic Michael-Lactamisation-Michael Reaction with Acyl Benzimidazoles*



To a solution of the corresponding tricholorophenol-activated ester (1 equiv.) in anhydrous CH_2Cl_2 (0.4 M), was added polymer-bound 2-*tert*-butylimino-2-diethylamino-1,3,dimethylperhydro-1,3,2,diazaphosphorine (PS-BEMP) (1.5 equiv.) followed by addition of a benzimidazole (1.5 equiv.). The reaction mixture was stirred for 40 h at room temperature. The crude mixture was filtered to remove the base and concentrated *in vacuo*. The residue was purified by flash silica column chromatography using mixtures of petroleum ether and ethyl acetate as eluents giving the products of

approximatly 95% purity. Analytically pure compounds can be obtained after a second purification by flash silica column chromatography using dichloromethane as eluent.

General Procedure 12: *Asymmetric Michael-Lactamisation-Michael Reaction with Acyl Benzimidazoles*



To a solution of the corresponding tricholorophenol-activated ester (1 equiv.) in anhydrous CH_2Cl_2 (0.4 M), was added benzimidazole (2 equiv.), isothiourea HyperBTM **1** (20 mol%) followed by addition of $^{i}Pr_2NEt$ (2 equiv.) at 0 °C. The reaction mixture was warmed to 10 °C and stirred at this temperature for 48 h. The reaction mixture was quenched with 0.1 M HCl and extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash silica column chromatography using mixtures of petroleum ether and ethyl acetate as eluents giving the products of approximatly 95% purity. Analytically pure compounds can be obtained after a second purification by flash silica column chromatography using dichloromethane as eluent.

7.3.2 Preparation of starting materials

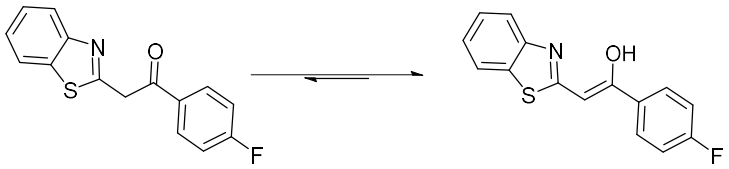
7.3.2.1 Data for acyl benzothiazoles

2-Phenacylbenzothiazole (67)

Following General Procedure 8, 2-chlorobenzothiazole (2.62 mL, 20.0 mmol), acetophenone (6.99 mL, 60.0 mmol) in anhydrous, degassed toluene (60 mL) and NaHMDS (30 mL, 2.0 M in THF, 12.0 mmol) afforded the title compound after trituration with cold hexane as a yellow solid (3.38 g, 67%). mp 115–117 °C {Lit.[9] 113–114 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.85 (2H, s, *keto*-C*H*$_2$COAr), 6.38 (1H, s, *enol*-C*H*COHAr), 7.31 (1H, t, *J* 7.6, *enol*benzothiazoleC(6)*H*), 7.39 (1H, t, *J* 7.5, *enol*-benzothiazoleC(6)*H*), 7.42–7.52 (6H, m, Ar*H*), 7.51 (1H, t, *J* 7.7, *enol*-benzothiazoleC(5)*H*), 7.62

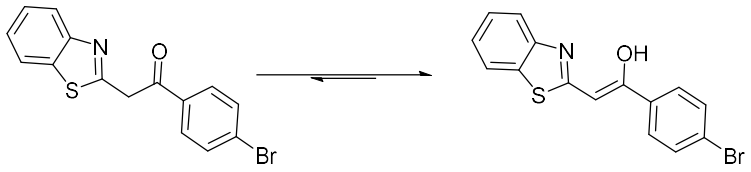
(1H, t, *J* 7.4, *keto*-benzothiazoleC(5)*H*), 7.79 (1H, d, *J* 7.9, *enol*benzothiazoleC(4)*H*), 7.82 (1H, d, *J* 8.2, *enol*-benzothiazoleC(7)*H*)), 7.88 (3H, m, *keto*-benzothiazole C(4)*H*, *enol*-phenacyl C(2')*H*), 8.02 (1H, d, *J* 8.0, *keto*-benzothiazole C(7)*H*), 8.10 (2H, d, *J* 7.5 *keto*phenacyl C(2')*H*). Data in agreement with the literature.[9]

2-(Benzo[d]thiazol-2-yl)-1-(4-fluorophenyl)ethan-1-one (208)



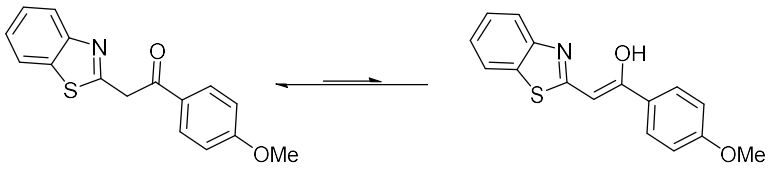
Following General Procedure 8, 2-chlorobenzothiazole (0.65 mL, 5.0 mmol), 1-(4-fluorophenyl)ethan-1-one (1.80 mL, 15.0 mmol) in anhydrous, degassed toluene (15 mL) and NaHMDS (7.50 mL, 2 M in THF, 12.0 mmol) afforded the title compound after trituration with cold hexane as a yellow solid (3.38 g, 67%). mp 122–123 °C; ν_{max} (film) 3049 (alkenyl C-H), 1614 (C=O), 1581 (C=C, aromatic), 1475 (C=C, heteroaromatic), 1138 (C-N); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.80 (2H, s, *keto*-CH_2COAr), 6.31 (1H, s, *enol*-C*H*COHAr), 7.13 (2H, t, *J* 8.7, ArH_{enol}), 7.17 (2H, t, *J* 8.7, ArH_{keto}), 7.29–7.31 (1H, m, ArH_{enol}), 7.38–7.41 (1H, m, ArH_{keto}), 7.44–7.46 (1H, m, ArH_{enol}), 7.44–7.46 (1H, m, ArH_{enol}), 7.46–7.49 (1H, m, ArH_{keto}), 7.79 (2H, t, *J* 8.8, *enol*-benzothiazole C*H*), 7.86–7.89 (1H, m, *enol*-benzothiazole C*H*), 7.87–7.89 (2H, m, *keto*-benzothiazole C*H*), 8.01 (1H, d, *J* 8.0, *keto*-benzothiazole C*H*), 8.12–8.15 (2H, m, *keto/enol*-benzothiazole C*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −110.0 (*enol*), −103.5 (*keto*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 44.1 (*keto*-*C*H_2-C=O), 90.6 (*enol*-*C*H=COH), 115.7 (d, $^{2}J_{CF}$ = 21.8, *enol*-C_{Ar}-F), 116.2 (d, $^{2}J_{CF}$ = 21.0, *keto*-C_{Ar}-F), 115.7 (*enol*-Ar*C*H), 115.8 (*enol*-Ar*C*H), 116.1 (*keto*-Ar*C*H), 116.3 (*keto*-Ar*C*H), 119.9 (*enol*-benzothiazole*C*H), 121.6 (*enol*-benzothiazole*C*H), 121.7 (*keto*-benzothiazole*C*H), 123.0 (benzothiazole*C*), 123.1 (*keto*-benzothiazole*C*H), 124.3 (*enol*-benzothiazole*C*H), 125.3 (*keto*-benzothiazole*C*H), 126.2 (*keto*-benzothiazole*C*H), 126.7 (*enol*-benzothiazole*C*H), 127.0 (benzothiazole*C*), 128.2 (d, $^{3}J_{CF}$ = 8.4, C_{Ar}-F), 128.2 (2×*enol*-Ar*C*H), 131.3 (Ar*C*), 131.6 (*keto*-Ar*C*H), 131.7 (*keto*-Ar*C*H), 150.1 (benzothiazole*C*), 165.2 (*enol*-*C*=N), 165.4 (*enol*-Ar*C*-F), 166.4 (d, $^{1}J_{CF}$ = 248.7, C_{Ar}-F), 167.3 (*keto*-*C*=N), 167.3 (*keto*-Ar*C*-F), 168.1 (*enol*-CH=*C*OH), 192.7 (*keto*-C=O); *m/z* (NSI$^+$) 272 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{15}H_{11}F_1N_1O_1S_1$ [M+H]$^+$, found 272.0542, requires 272.0540 (+0.8 ppm).

2-(Benzo[d]thiazol-2-yl)-1-(4-bromophenyl)ethan-1-one (209)



Following General Procedure 8, 2-chlorobenzothiazole (0.65 mL, 5.0 mmol), 1-(4-bromophenyl)ethan-1-one (1.80 mL, 15.0 mmol) in anhydrous, degassed toluene (15 mL) and NaHMDS (7.50 mL, 2.0 M in THF, 12.0 mmol) afforded the title compound after trituration with cold hexane as a yellow solid (3.38 g, 67%). mp 122–123 °C; ν_{max} (film) 3049 (alkenyl C-H), 1614 (C=O), 1581 (C=C, aromatic), 1475 (C=C, heteroaromatic), 1138 (C-N); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.80 (2H, s, *keto*-CH_2COAr), 6.31 (1H, s, *enol*-C*H*COHAr), 7.13 (2H, t, *J* 8.7, ArH_{enol}), 7.17 (2H, t, *J* 8.7, ArH_{keto}), 7.29–7.31 (1H, m, ArH_{enol}), 7.38–7.41 (1H, m, ArH_{keto}), 7.44–7.46 (1H, m, ArH_{enol}), 7.44–7.46 (1H, m, ArH_{enol}), 7.46–7.49 (1H, m, ArH_{keto}), 7.79 (2H, t, *J* 8.8, *enol*-benzothiazole C*H*), 7.86–7.89 (1H, m, *enol*-benzothiazole C*H*), 7.87–7.89 (2H, m, *keto*-benzothiazole C*H*), 8.01 (1H, d, *J* 8.0, *keto*-benzothiazole C*H*), 8.12–8.15 (2H, m, *keto/enol*-benzothiazole C*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 44.1 (*keto*-CH_2-C=O), 90.6 (*enol*-C*H*=COH), 115.7 (*enol*-ArC*H*), 115.8 (*enol*-ArC*H*), 116.1 (*keto*-ArC*H*), 116.3 (*keto*-ArC*H*), 119.9 (*enol*-benzothiazole*C*H), 121.6 (*enol*-benzothiazole*C*H), 121.7 (*keto*-benzothiazole*C*H), 123.0 (benzothiazole*C*), 123.1 (*keto*-benzothiazole*C*H), 124.3 (*enol*-benzothiazole*C*H), 125.3 (*keto*-benzothiazole*C*H), 126.2 (*keto*-benzothiazole*C*H), 126.7 (*enol*-benzothiazole*C*H), 127.0 (benzothiazole*C*), 128.2 (2×*enol*-ArC*H*), 131.3 (Ar*C*), 131.6 (*keto*-ArC*H*), 131.7 (*keto*-ArC*H*), 150.1 (benzothiazole*C*), 165.2 (*enol*-*C*=N), 165.4 (*enol*-Ar*C*-F), 167.3 (*keto*-*C*=N), 168.1 (*keto*-Ar*C*-F), 180.4 (*enol*-CH=*C*OH), 192.7 (*keto*-C=O); *m/z* (NSI$^+$) 333 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{15}H_{11}O_1N_1{}^{79}Br_1S_1$ [M+H]$^+$, found 331.9744, requires 331.9739 (+1.4 ppm).

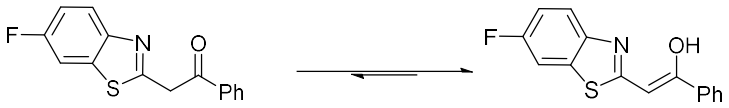
2-(Benzo[d]thiazol-2-yl)-1-(4-methoxyphenyl)ethan-1-one (210)



Following General Procedure 8, 2-chlorobenzothiazole (0.65 mL, 5.0 mmol), 1-(4-methoxyphenyl)ethan-1-one (2.25 g, 15.0 mmol) in anhydrous, degassed toluene (15 mL) and

NaHMDS (7.50 mL, 2.0 M in THF, 12.0 mmol) afforded the title compound after trituration with cold hexane as a yellow solid (0.44 g, 31%). mp 104–106 °C; ν_{max} (film) 3057 (alkenyl C-H), 1603 (C=O), 1574 (C=C, aromatic), 1472 (C=C, heteroaromatic), 1177 (C-N); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.87 (3H, s, *enol*-CH_3), 3.88 (3H, s, *keto*-CH_3), 4.78 (2H, s, *keto*-CH_2COAr), 6.29 (1H, s, *enol*-C*H*COHAr), 6.93–6.95 (2H, m, ArH_{enol}), 6.96–6.98 (2H, m, ArH_{keto}), 7.36–7.39 (2H, m, *enol*-benzothiazole C*H*), 7.43–7.45 (1H, m, *enol*-benzothiazole C*H*), 7.45–7.48 (2H, m, *keto*-benzothiazole C*H*), 7.76–7.78 (2H, m, ArH_{enol}), 7.83–7.87 (1H, m, *keto*-benzothiazole C*H*), 7.87–7.88 (1H, m, *keto*-benzothiazole C*H*), 7.93–7.95 (1H, m, *enol*-benzothiazole C*H*), 8.01 (1H, d, *J* 8.0, *keto*-benzothiazole C*H*), 8.07–8.09 (2H, m, ArH_{keto}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 43.9 (*keto*-CH_2-C=O), 55.6 (*enol*-CH_3), 55.7 (*keto*-CH_3), 89.7 (*enol*-C*H*=COH), 114.0 (2×*enol*-Ar*C*H), 114.2 (2×*keto*-Ar*C*H),) 119.7 (*enol*-benzothiazole*C*H), 121.5 (*enol*-benzothiazole*C*H), 121.7 (*keto*-benzothiazole*C*H), 123.0 (*keto*-benzothiazole*C*H), 123.2 (benzothiazole*C*), 124.1 (*enol*-benzothiazole*C*H), 125.2 (*keto*-benzothiazole*C*H), 126.1 (*keto*-benzothiazole*C*H), 126.6 (*enol*-benzothiazole*C*H), 126.7 (benzothiazole*C*), 127.8 (2×*enol*-Ar*C*H), 131.2 (Ar*C*), 131.3 (2×*keto*-Ar*C*H), 151.2 (*enol*-benzothiazole*C*), 152.7 (*keto*-benzothiazole*C*), 161.5 (*enol*-*C*=N), 164.0 (*keto*-*C*=N), 164.1 (*keto*-Ar*C*-OMe), 168.1 (*enol*-Ar*C*-OMe), 168.2 (*enol*-CH=*C*OH), 192.6 (*keto*-C=O); *m/z* (NSI$^+$) 284 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{16}H_{14}O_2N_1S_1$ [M+H]$^+$, found 284.0739, requires 284.0740 (–0.3 ppm).

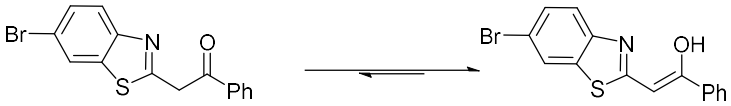
2-(6-Fluorobenzo[d]thiazol-2-yl)-1-phenylethan-1-one (211)



Following General Procedure 8, 6-fluoro-2-chlorobenzothiazole (938 mg, 5.0 mmol), acetophenone (1.70 mL, 15.0 mmol) in anhydrous, degassed toluene (15 mL) and NaHMDS (7.50 mL, 2.0 M in THF, 12.0 mmol) afforded the title compound after trituration with cold hexane as a yellow solid (1.02 g, 75%). mp 128–129 °C; ν_{max} (film) 3065 (alkenyl C-H), 1614 (C=O), 1564 (C=C, aromatic), 1452 (C=C, heteroaromatic), 1134 (C-N); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.82 (2H, s, *keto*-CH_2COAr), 6.34 (1H, s, *enol*-C*H*COHAr), 7.17–7.23 (2H, m, *enol*/*keto*-benzothiazole C*H*), 7.44–7.46 (3H, m, ArH_{enol}), 7.49–7.53 (3H, m, ArH_{keto}), 7.55–7.57 (1H, m, *keto*-benzothiazole C*H*), 7.61–7.64 (1H, m, *enol*-benzothiazole C*H*), 7.77–7.80 (1H, m, ArH_{enol}), 7.86–7.88 (2H, m, *enol/keto*-benzothiazole C*H*), 7.93–7.96 (1H, m, ArH_{enol}), 8.07–8.09 (2H, m, ArH_{keto}); ^{19}F NMR (282 MHz,

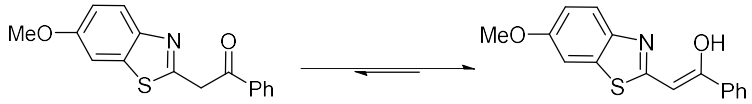
$CDCl_3$) δ_F: −117.1 (*keto*), −116.2 (*enol*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 43.8 (*keto*-*C*H_2-C=O), 91.2 (*enol*-*C*H=COH), 107.9 (d, $^2J_{CF}$ = 27.1, *keto*-C_{Ar}-F), 108.0 (d, $^2J_{CF}$ = 27.1, *enol*-C_{Ar}-F), 108.0 (*keto*-benzothiazole*C*H) , 108.1 (*enol*-benzothiazole*C*H), 114.8 (*keto*-benzothiazole*C*H), 114.8 (d, $^2J_{CF}$ = 20.8, *keto*-C_{Ar}-F), 115.0 (d, $^2J_{CF}$ = 20.9, *enol*-C_{Ar}-F), 115.1 (*enol*-benzothiazole*C*H), 121.3 (*keto*-benzothiazole*C*H), 124.0 (*enol*-benzothiazole*C*H), 126.0 (2×*enol*-Ar*C*H), 128.7 (2×*enol*-Ar*C*H), 128.8 (d, $^3J_{CF}$ = 9.5, C_{Ar}-F), 128.8 (2×*keto*-Ar*C*H), 129.1 (2×*keto*-Ar*C*H), 130.5 (*enol*-Ar*C*H), 134.1 (*keto*-Ar*C*H), 134.5 (benzothiazole*C*), 148.0 (benzothiazole*C*), 160.9 (*enol*-*C*=N), 162.1 (d, $^1J_{CF}$ = 303.9, C_{Ar}-F), 163.2 (*keto*-*C*=N), 180.4 (*enol*-CH=*C*OH), 192.7 (*keto*-C=O); *m/z* (NSI^+) 272 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{15}H_{11}F_1N_1O_1S_1$ $[M+H]^+$, found 272.0543, requires 272.0540 (+1.1ppm).

2-(6-Bromobenzo[d]thiazol-2-yl)-1-phenylethan-1-one (212)



Following General Procedure 8, 6-bromo-2-chlorobenzothiazole (1.24 g, 5.0 mmol), acetophenone (1.70 mL, 15.0 mmol) in anhydrous, degassed toluene (15 mL) and NaHMDS (7.50 mL, 2.0 M in THF, 12.0 mmol) afforded the title compound after trituration with cold hexane as a yellowish solid (562 mg, 34%). mp 165–166 °C; ν_{max} (film) 3078 (alkenyl C-H), 1609 (C=O), 1595 (C=N), 1473 (C=C, heteroaromatic), 1134 (C-N); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 4.82 (2H, s, *keto*-CH_2COAr), 6.36 (1H, s, *enol*-*CH*COHAr), 7.43–7.47 (3H, m, ArH_{enol}), 7.50–7.54 (1H, m, *enol*-benzothiazole C*H*), 7.54–7.58 (2H, m, ArH_{keto}), 7.62–7.65 (1H, m, *keto*-benzothiazole C*H*), 7.70 (1H, d, *J* 8.6, ArH_{keto}), 7.85–7.88 (2H, m, ArH_{enol}), 7.93 (1H, d, *J* 1.8, *enol*-benzothiazole C*H*), 8.03 (1H, d, *J* 1.8, *keto*-benzothiazole C*H*), 8.07–8.09 (2H, m, ArH_{keto}); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 43.8 (*keto*-*C*H_2-C=O), 91.1 (*enol*-*C*H=COH), 117.5 (*C*-Br), 121.5 (*enol*-benzothiazole*C*H) , 124.1 (*enol*-benzothiazole*C*H), 124.1 (*enol*-benzothiazole*C*H) , 124.3 (*enol*-benzothiazole*C*H), 126.1 (2×*enol*-Ar*C*H), 126.4 (*C*-Ar), 128.8 (2×*enol*-Ar*C*H), 129.1 (2×*keto*-Ar*C*H), 130.0 (2×*keto*-Ar*C*H), 130.7 (*enol*-Ar*C*H), 134.2 (*keto*-Ar*C*H), 138.8 (benzothiazole*C*), 148.0 (benzothiazole*C*), 160.9 (*enol*-*C*=N), 165.0 (*keto*-*C*=N), 180.4 (*enol*-CH=*C*OH), 192.7 (*keto*-C=O); *m/z* (NSI^+) 333 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{15}H_{11}{}^{79}Br_1N_1O_1S_1$ $[M+H]^+$, found 331.9743, requires 331.9739 (+1.1ppm).

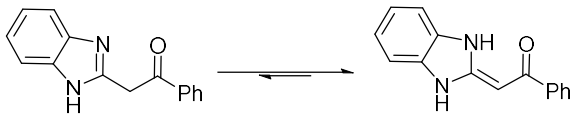
2-(6-Methoxybenzo[d]thiazol-2-yl)-1-phenylethan-1-one (213)



Following General Procedure 8, 6-methoxy-2-chlorobenzothiazole (998 mg, 5.0 mmol), acetophenone (1.70 mL, 15.0 mmol) in anhydrous, degassed toluene (15 mL) and NaHMDS (7.50 mL, 2.0 M in THF, 12.0 mmol) afforded the title compound after trituration with cold hexane as a yellow solid (878 mg, 62%). mp 156–157 °C; ν_{max} (film) 1599 (C=O), 1456 (C=C, heteroaromatic), 1134 (C-N), 824 (C=C, aromatic); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.87 (3H, s, *keto*-OCH_3), 3.88 (3H, s, *enol*-OCH_3), 4.79 (2H, s, *keto*-CH_2COAr), 6.32 (1H, s, *enol*-C*H*COHAr), 7.05−7.08 (2H, m, *enol*/*keto*-benzothiazole C*H*), 7.30 (2H, dd, *J* 18.3, 2.5, *enol*-benzothiazole C*H*), 7.43–7.45 (3H, m, ArH_{enol}), 7.49–7.52 (2H, m, *keto*-benzothiazole C*H*), 7.60–7.63 (1H, m, ArH_{keto}), 7.74 (1H, d, *J* 8.9, ArH_{keto}), 7.85−7.87 (2H, m, ArH_{enol}), 7.99 (1H, d, *J* 9.1, ArH_{keto}), 8.07−8.09 (2H, m, ArH_{keto}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 43.9 (*keto*-*C*H_2-C=O), 56.0 (*keto*, *enol*-O*C*H_3), 91.3 (*enol*-*C*H=COH), 104.1 (*keto*-benzothiazole*C*H), 104.6 (*enol*-benzothiazole*C*H), 115.5 (*enol*-benzothiazole*C*H), 115.6 (*keto*-benzothiazole*C*H), 121.1 (*keto*-benzothiazole*C*H), 123.5 (*enol*-benzothiazole*C*H), 125.9 (2×*enol*-Ar*C*H), 126.4 (*C*-Ar), 128.7 (2×*enol*-Ar*C*H), 128.9 (2×*keto*-Ar*C*H), 129.0 (2×*keto*-Ar*C*H), 130.2 (*enol*-Ar*C*), 134.0 (*enol*-Ar*C*H), 134.8 (*keto*-Ar*C*H), 136.0 (*keto*-benzothiazole*C*), 137.4 (*keto*-benzothiazole*C*), 145.7 (*enol*-benzothiazole*C*), 147.4 (*keto*-benzothiazole*C*), 157.2 (*enol*-*C*-OMe), 157.8 (*keto*-*C*-OMe), 157.8 (*keto*-*C*-OMe), 160.9 (*enol*-*C*=N), 163.5 (*keto*-*C*=N), 166.3 (*enol*-*C*OH), 194.5 (*keto*-C=O); *m/z* (NSI$^+$) 284 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{16}H_{14}O_2N_1S_1$ [M+H]$^+$, found 284.0740, requires 284.0740 (+0.1ppm)

7.3.2.2 Data for acyl benzimidazoles

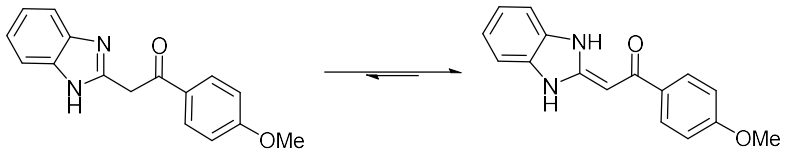
2-Phenacylbenzimidazole (228)



Following the General Procedure 9, 2-methylbenzimidazole (0.66 g, 5.0 mmol), benzoyl chloride (1.92 mL, 16.5 mmol)) and NEt_3 (2.29 mL, 16.5 mmol) in HPLC grade acetonitrile (5 mL) gave the *ester* as a yellow solid. Heating the ester at reflux in 1-BuOH:DMF (5 mL) for 1 h afforded the title compound after filtration as a yellow solid as a 4:1 mixture of enamino:keto tautomers (531 mg, 45%). mp 176–178 °C {Lit.[10] 178–179 °C}; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 4.69 (2H, s, *keto*-

C*H*$_2$CO), 6.11 (1H, s, *enamino*-C*H*CO), 7.12–7.21 (4H, m, benzimidazoleC(5)*H* and benzimidazoleC(6)*H*), 7.38–7.60 (9H, m, Ar*H*), 7.62–7.72 (1H, m, *keto*-phenylC(4)*H*), 7.83–7.92 (2H, m, 2×*enamino*-phenylC(2)*H*), 8.04–8.13 (2H, m, 2×*keto*-phenylC(2)*H*), 12.27 (1H, s, *enamino*-N*H*), 12.31 (1H, s, *keto*-N*H*). Data in agreement with the literature.[10]

2-(4-Methoxy)phenacylbenzimidazole (S1)



Following the General Procedure 9, 2-methylbenzimidazole (0.66 g, 5.0 mmol), 4-methoxybenzoyl chloride (2.56 g, 15.0 mmol) and NEt_3 (2.10 mL, 15.0 mmol) in HPLC grade acetonitrile (5 mL) and subsequent hydrolysis in morpholine (2.9 mL) afforded the title compound after filtration as a yellow solid as a 1.1:1 mixture of enamino:keto tautomers (866 mg, 65%). mp 205–207 °C {Lit.[10] 208–209 °C}; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 3.81 (3H, *enamino*-OC*H*$_3$), 3.85 (3H, *keto*-OC*H*$_3$), 4.59 (2H, s, *keto*-C*H*$_2$CO), 6.00 (1H, s, *enamino*-C*H*CO), 7.01 (2H, d, *J* 8.9, *enamino*-H-Ar$_{OMe}$), 7.08 (2H, d, *J* 8.9, *enamino*-H-Ar$_{OMe}$), 7.14–7.16 (4H, m, benzimidazoleC(5)*H* and benzimidazoleC(6)*H*), 7.36 (1H, dd, *J* 5.9, 3.2, *enamino*-benzimidazoleC(4)*H*), 7.45–7.46 (1H, m, *keto*-benzimidazoleC(4)*H*), 7.53 (2H, dd, *J* 5.8, 3.2, *enamino/keto*-benzimidazoleC(7)*H*), 7.80 (2H, d, *J* 8.9, *keto*-H-Ar$_{OMe}$), 8.07 (2H, d, *J* 8.9, *keto*-H-Ar$_{OMe}$), 12.17 (1H, s, *keto*-N*H*), 12.32 (1H, s, *enamino*-N*H*). Data in agreement with the literature.[10]

2-(4-Nitro)phenacylbenzimidazole (S2)

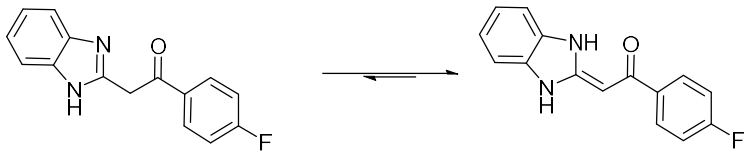
Following the General Procedure 9, 2-methylbenzimidazole (0.66 g, 5.0 mmol), 4-nitrobenzoyl chloride (2.78 g, 15.0 mmol) and NEt_3 (2.10 mL, 15.0 mmol) in HPLC grade acetonitrile (5 mL) and subsequent hydrolysis in 1-BuOH:DMF (8 mL) afforded the title compound after filtration as a red solid as a 1.1:1 mixture of enamino:keto tautomers (947 mg, 67%). mp 270–272 °C {Lit.[10] 266–268 °C}; ^{1}H NMR (500 MHz, DMSO-d$_6$) δ_H: 3.81 (3H, *enamino*-OC*H*$_3$), 3.85 (3H, *keto*-OC*H*$_3$), 4.59 (2H, s, *keto*-C*H*$_2$CO), 6.00 (1H, s, *enamino*-C*H*CO), 7.01 (2H, d, *J* 8.9, *enamino*-H-Ar$_{OMe}$), 7.08 (2H, d, *J* 8.9, *enamino*-H-Ar$_{OMe}$), 7.14–7.16 (4H, m, benzimidazoleC(5)*H* and benzimidazoleC(6)*H*), 7.36 (1H,

dd, *J* 5.9, 3.2, *enamino*-benzimidazoleC(4)*H*), 7.45–7.46 (1H, m, *keto*-benzimidazoleC(4)*H*), 7.53 (2H, dd, *J* 5.8, 3.2, *enamino/keto*-benzimidazoleC(7)*H*), 7.80 (2H, d, *J* 8.9, *keto*-H-Ar_{OMe}), 8.07 (2H, d, *J* 8.9, *keto*-H-Ar_{OMe}), 12.17 (1H, s, *keto*-N*H*), 12.32 (1H, s, *enamino*-N*H*). Data in agreement with the literature.[10]

2-(4-Trifluoromethyl)phenacylbenzimidazole (S3)

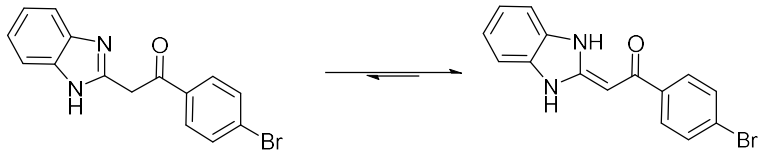
Following the General Procedure 9, 2-methylbenzimidazole (0.66 g, 5.0 mmol), 4-trifluoromethylbenzoyl chloride (2.23 mL, 15.0 mmol) and NEt_3 (2.10 mL, 15.0 mmol) in HPLC grade acetonitrile (5 mL) and subsequent hydrolysis in 1-BuOH:DMF (8 mL) afforded the title compound after filtration as a yellow solid as a 25:1 mixture of enamino:keto tautomers (1.708 g, 69%). mp 240–241 °C; ν_{max} (film) 3009 (N-H), 2758 (C-H), 1616 (C=O), 1327 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 4.75 (2H, s, *keto*-CH_2CO), 6.09 (1H, s, *enamino*-C*H*CO), 7.17–7.20 (2H, m, *enamino*-benzimidazoleC(5)*H* and benzimidazoleC(6)*H*), 7.37–7.40 (1H, m, benzimidazoleC(4)*H*), 7.57–7.59 (1H, m, *enamino*-benzimidazoleC(7)*H*), 7.81 (2H, d, *J* 8.4, *enamino*-H-Ar_{CF3}), 7.95 (2H, d, *J* 8.4, *keto*-H-Ar_{CF3}), 8.05 (2H, d, *J* 8.4, *enamino*-H-Ar_{CF3}), 8.27 (2H, d, *J* 8.4, *keto*-H-Ar_{CF3}), 12.33 (1H, s, *enamino*-N*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: –61.0 (CF_3); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 79.2 (*enamino*-C*H*), 110.5 (C*H*-azaAr), 113.9 (C*H*-azaAr), 122.2 (*C*H-azaAr), 122.6 (*C*H-azaAr), 123.2 (*C*F_3), 125.3 (2×CH-Ar_{CF3}), 125.3 (q, $^3J_{CF}$ = 3.8, C_{Ar}-CF_3), 126.5 (2×CH-Ar_{CF3}), 126.9 (q, $^1J_{CF}$ = 282.5, C_{Ar}-CF_3), 129.4 (*C*-azaAr), 129.5 (q, $^2J_{CF}$ = 32.4, C_{Ar}-CF_3), 129.6 (*C*-azaAr), 142.2 (C-Ar_{CF3}), 153.2 (N=*C*(C)-N), 171.0 (*C*=OAr_F); *m/z* (NSI$^+$) 305 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{16}H_{12}N_2O_1F_3$ [M+H]$^+$, found 305.0898, requires 305.0896 (+0.6 ppm).

2-(4-Fluoro)phenacylbenzimidazole (S4)



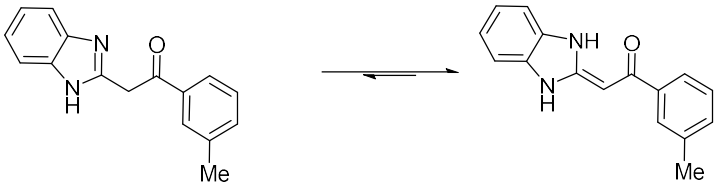
Following the General Procedure 9, 2-methylbenzimidazole (0.66 g, 5.0 mmol), 4-fluorobenzoyl chloride (1.77 mL, 15.0 mmol) and NEt_3 (2.10 mL, 15.0 mmol) in HPLC grade acetonitrile (5 mL) and subsequent hydrolysis in 1-BuOH:DMF (8 mL) afforded the title compound after filtration as a yellow solid as a 4:1 mixture of enamino:keto tautomers (1.708 g, 69%). mp 204–205 °C; ν_{max} (film) 3057 (N-H), 2758 (C-H), 1616 (C=O), 1491 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 4.67 (2H, s, *keto*-CH_2CO), 5.99 (1H, s, *enamino*-C*H*CO), 7.14–7.17 (2H, m, *enamino/keto*-benzimidazoleC(5)*H* and benzimidazoleC(6)*H*), 7.25–7.29 (2H, *enamino*-H-Ar_F), 7.36–7.38 (1H, m, benzimidazoleC(4)*H*), 7.40–7.42 (2H, *keto*-H-Ar_F), 7.54–7.55 (1H, m, *enamino*-benzimidazoleC(7)*H*), 7.89–7.92 (2H, *enamino*-H-Ar_F), 8.16–8.19 (2H, m, *keto*-H-Ar_F), 12.21 (1H, s, *enamino*-N*H*), 12.33 (1H, s, *keto*-N*H*); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −111.8 (*enamino*), −105.3 (*keto*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 39.2 (*C*H$_2$), 78.5 (*enamino*-C*H*), 110.4 (C*H*-azaAr), 113.9 (C*H*-azaAr), 115.1 (C*H*-Ar_F), 115.3 (C*H*-Ar_F), 116.0 (d, $^2J_{CF}$ = 21.5, C_{Ph}-F), 122.0 (*C*H-azaAr), 122.3 (*C*H-azaAr), 128.0 (C*H*-Ar_F), 128.1 (C*H*-Ar_F), 131.6 (d, $^3J_{CF}$ = 9.8, C_{Ph}-F), 134.5 (*C*-azaAr), 134.6 (d, $^4J_{CF}$ = 2.8, C_{Ph}-F), 134.6 (*C*-azaAr), 153.5 (N=*C*(C)-N), 162.0 (NH-*C*-NH), 163.0 (d, $^1J_{CF}$ = 246.3, C_{Ph}-F), 164.0 (*C*-F), 170.8 (*C*=OAr_F); *m/z* (NSI$^+$) 255 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{15}H_{12}F_1N_2O_1$ [M+H]$^+$, found 255.0930, requires 255.0928 (+0.7 ppm).

2-(4-Bromo)phenacylbenzimidazole (S5)



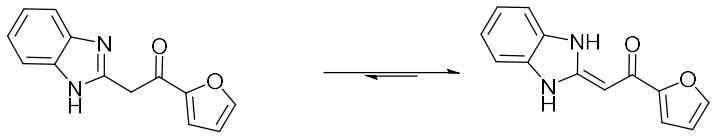
Following the General Procedure 9, 2-methylbenzimidazole (0.66 g, 5.0 mmol), 4-bromobenzoyl chloride (3.29 g, 15.0 mmol) and NEt_3 (2.10 mL, 15.0 mmol) in HPLC grade acetonitrile (5 mL) and subsequent hydrolysis in 1-BuOH:DMF (8 mL) afforded the title compound after filtration as a yellow solid as a 8:1 mixture of enamino:keto tautomers (864 mg, 55%). mp 238–240 °C {Lit.[10] 244–246 °C}; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 4.66 (2H, s, *keto*-CH_2CO), 6.03 (1H, s, *enamino*-C*H*CO), 7.15–7.18 (2H, m, benzimidazoleC(5)*H* and benzimidazoleC(6)*H*), 7.35–7.39 (1H, m, *enamino*-benzimidazoleC(4)*H*), 7.54–7.58 (1H, m, *keto*-benzimidazoleC(4)*H*), 7.53 (2H, dd, *J* 5.8, 3.2, *enamino/keto*-benzimidazoleC(7)*H*), 7.63–7.66 (2H, m, *enamino*-H-Ar_{Br}), 7.75–7.77 (2H, m, *J* 8.9, *keto*-H-Ar_{Br}), 7.79–7.81 (2H, m, *enamino*-H-Ar_{Br}), 8.00–8.02 (2H, m, *keto*-H-Ar_{Br}), 12.25 (1H, s, *enamino*-N*H*), 12.34 (1H, s, *keto*-N*H*). Data in agreement with the literature.[10]

2-(3-Methyl)phenacylbenzimidazole (S6)



Following the General Procedure 9, 2-methylbenzimidazole (0.66 g, 5.0 mmol), 3-methylbenzoyl chloride (1.98 mL, 15.0 mmol) and NEt_3 (2.10 mL, 15.0 mmol) in HPLC grade acetonitrile (5 mL) and subsequent hydrolysis with morpholine (1.7 mL) afforded the title compound after filtration as a yellow solid as a 3.5:1 mixture of enamino:keto tautomers (0.744 g, 59%). mp 142–143 °C; ν_{max} (film) 3053 (N-H), 2778 (C-H), 1684 (C=O), 1506 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.38 (3H, s, *enamino*-CH_3), 2.39 (3H, s, *keto*-CH_3), 4.66 (2H, s, *keto*-CH_2CO), 6.09 (1H, s, *enamino*-C*H*CO), 7.15–7.17 (2H, m, *enamino/keto*-benzimidazoleC(5)*H* and benzimidazoleC(6)*H*), 7.27 (2H, d, *J* 8.1, *enamino*-H-Ar_{Me}), 7.37 (2H, d, *J* 8.1, *keto*-H-Ar_{Me}), 7.46–7.52 (1H, m, *enamino/keto*-benzimidazoleC(4) (7)*H*), 7.98 (2H, d, *J* 8.1, *keto*-H-Ar_{Me}), 12.32 (1H, s, *enamino*-N*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.0 (*enamino*-*C*H_3), 21.2 (*keto*-*C*H_3), 46.1 (*C*H_2), 80.0 (*enamino*-*C*H), 122.0 (*C*H-azaAr), 125.5 (*C*H-Ar_{Me}), 128.6 (*C*H-azaAr), 129.0 (*C*H-Ar_{Me}), 129.4 (*C*H-azaAr), 133.5 (C-Ar_{Me}), 134.3 (*C*-azaAr), 139.4 (*C*-azaAr), 144.2 (*C*-Me), 149.0 (N=*C*-N), 153.7 (NH-*C*-NH), 169.1 (*enamino*-*C*=OAr_{Me}), 194.7 (*keto*-*C*=OAr_{Me}); *m/z* (NSI$^+$) 251 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{16}H_{15}N_2O_1$ [M+H]$^+$, found 251.1181, requires 251.1179 (+0.8 ppm).

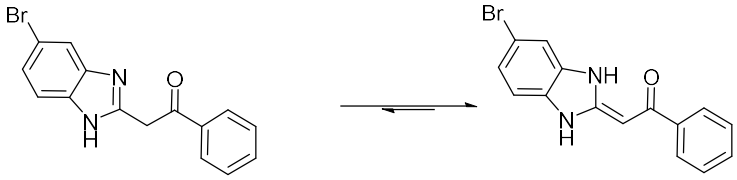
2-(Furan-2-yl)phenacylbenzimidazole (S7)



Following the General Procedure 9, 2-methylbenzimidazole (0.66 g, 5.0 mmol), 2-furoyl chloride (1.60 mL, 16.5 mmol) and NEt_3 (2.30 mL, 16.5 mmol) in HPLC grade acetonitrile (5 mL) and subsequent hydrolysis with morpholine (1.7 mL) afforded the title compound after filtration as a yellow solid as a 3:1 mixture of enamino:keto tautomers (0.306 g, 27%). mp 182–183 °C; ν_{max} (film) 3053 (N-H), 2585 (C-H), 1614 (C=O), 1574 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 4.46 (2H, s, *keto*-CH_2CO), 5.78 (1H, s, *enamino*-C*H*CO), 6.55 (1H, dd, *J* 3.4, 1.7, *enamino*-H–Fur), 6.77 (1H, dd, *J* 3.6, 1.8, *keto*-H–Fur), 6.87 (1H, dd, *J* 3.4, 0.7, *enamino*-H–Fur), 7.12–7.16 (2H, m,

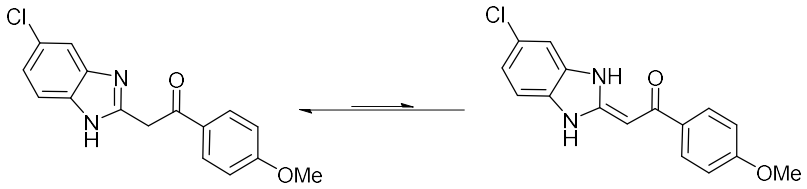
enamino/keto-benzimidazoleC(5)*H* and benzimidazoleC(6)*H*), 7.46–7.54 (2H, m, *enamino/keto*-benzimidazoleC(4)(7)*H*), 7.65 (1H, d, *J* 3.3, *keto*-H-Fur), 7.74–7.75 (1H, m, *enamino*-H–Fur), 8.06 (1H, d, *J* 2.1, *keto*-H-Fur), 12.13 (1H, s, *keto*-N*H*); 12.38 (1H, s, *enamino*-N*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 39.1 (*C*H_2), 76.1 (*enamino*-*C*H), 109.9 (*enamino*-*C*H-Fur), 111.8 (*enamino*-*C*H-Fur), 113.1 (*C*H-azaAr), 120.0 (*C*H-azaAr), 122.0 (*C*H-azaAr), 122.3 (*C*H-azaAr), 131.0 (*C*-azaAr), 134.0 (*C*-azaAr), 148.3 (N=*C*-N), 153.1 (*enamino*-*C*H-Fur), 166.1 (NH-*C*-NH), 183.0 (*C*=OFur); *m/z* (NSI^+) 227 ($[M+H]^+$, 100%; 249 $[M+Na]^+$, 30%); HRMS (NSI^+) $C_{13}H_{11}N_2O_2$ $[M+H]^+$, found 227.0815, requires 227.0815 (–0.0 ppm).

2-Phenacyl-(5-bromo)benzimidazole (S8)



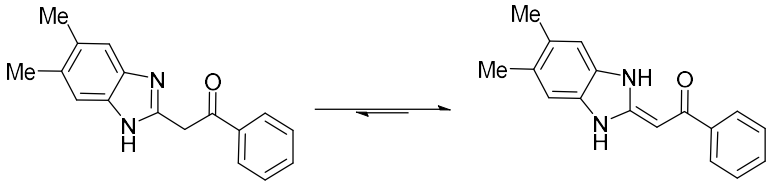
Following the General Procedure 9, 2-methyl-(5-bromo)benzimidazole (0.53 g, 3.0 mmol), benzoyl chloride (1.05 mL, 9.0 mmol) and NEt_3 (1.26 mL, 9.0 mmol) in HPLC grade acetonitrile (4 mL) and subsequent hydrolysis with morpholine (1.7 mL) afforded the title compound after filtration as a yellow solid as a 2.9:1 mixture of enamino:keto tautomers (165 mg, 21%). mp 171–172 °C; ν_{max} (film) 3088 (N-H), 2675 (C-H), 1593 (C=O), 1396 (C_{Ar}-C_{Ar}); ^1H NMR (500 MHz, DMSO-d_6) δ_H: 4.70 (2H, s, *keto*-CH_2CO), 6.15 (1H, s, *enamino*-C*H*CO), 7.31 (1H, dd, *J* 8.4, 2.0, *enamino*-benzimidazoleC(7)*H*), 7.40 (1H, dd, *J* 6.7, 3.3, *keto*-benzimidazoleC(6)*H*), 7.45–7.49 (4H, m, 3×H-Ph and *enamino*-benzimidazoleC(4)*H*), 7.57 (1H, t, *J* 7.7, *enamino*-benzimidazoleC(7)*H*), 7.69 (1H, t, *J* 7.4, *keto*-benzimidazoleC(4)*H*), 7.74–7.76 (1H, m, *keto*-benzimidazoleC(7)*H*), 7.85–7.86 (2H, m, *enamino*-H-Ph), 8.07–8.09 (2H, m, *keto*-H-Ph), 12.49 (1H, s, *keto*-N*H*), 12.55 (1H, s, *enamino*-N*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 39.6 (*C*H_2), 81.5 (*enamino*-*C*H), 114.0 (*enamino*-*C*H-azaAr), 124.8 (*enamino*-*C*H-azaAr), 125.5 (*keto*-*C*-Cl), 125.6 (2×*enamino*-*C*H-Ph), 128.4 (*enamino*-*C*-Cl), 128.5 (2×*keto*-*C*H-Ph), 128.6 (3×*enamino*-*C*H-Ph), 128.9 (2×*keto*-*C*H-Ph), 130.0 (*keto*-*C*H-Ph), 131.0 (*keto*-*C*-azaAr), 133.0 (*keto*-*C*-azaAr), 133.8 (*keto*-*C*H-azaAr), 135.9 (*keto*-*C*-Ph), 136.3 (*enamino*-*C*-Ph), 154.5 (N=*C*-N), 168.4 (*enamino*-*C*=OAr_{Me}), 195.0 (*keto*-*C*=OAr_{Me}); *m/z* (NSI^+) 315 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{15}H_{12}{}^{79}Br_1N_2O_1$ $[M+H]^+$, found 315.0132, requires 315.0128 (+1.4 ppm).

2-(4-Methoxy)phenacyl-(5-chloro)benzimidazole (S9)



Following the General Procedure 9, 2-methyl-(5-chloro)benzimidazole (0.50 g, 3.0 mmol), 4-methoxybenzoyl chloride (1.54 g, 9.0 mmol) and NEt_3 (1.26 mL, 9.0 mmol) in HPLC grade acetonitrile (4 mL) and subsequent hydrolysis with morpholine (1.7 mL) afforded the title compound after filtration as a yellow solid as a 1:1.4 mixture of enamino:keto tautomers (520 mg, 58%). mp 159–160 °C; ν_{max} (film) 3302 (N-H), 2691 (C-H), 1591 (C=O), 1495 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.81 (3H, s, *enamino*-OCH_3), 3.85 (3H, s, *keto*-OCH_3), 4.62 (2H, s, *keto*-CH_2CO), 6.06 (1H, s, *enamino*-C*H*CO), 7.02 (2H, d, *J* 8.9, *enamino*-C*H*-Ar_{OMe}), 7.08 (2H, d, *J* 8.9, *keto*-C*H*-Ar_{OMe}), 7.15–7.18 (2H, m, *enamino/keto*-benzimidazoleC(7)*H*), 7.38–7.49 (2H, m, *enamino*-benzimidazoleC(4)(6)*H*), 7.53–7.61 (2H, m, *keto*-benzimidazoleC(4)(6)*H*), 7.81 (2H, d, *J* 8.9, *enamino*-C*H*-Ar_{OMe}), 8.06 (2H, d, *J* 8.9, *keto*-C*H*-Ar_{OMe}), 12.37 (1H, s, *keto*-N*H*), 12.49 (1H, s, *enamino*-N*H*), 12.54 (1H, s, *enamino*-N*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 39.3 (CH_2), 55.3 (*enamino*-OCH_3), 55.6 (*keto*-OCH_3), 80.4 (*enamino*-*C*H), 110.3 (*keto*-*C*H-azaAr), 111.6 (*enamino*-*C*H-azaAr), 113.9 (*enamino*-*C*H-Ar_{OMe}), 114.1 (*enamino*-*C*H-Ar_{OMe}), 114.6 (*enamino*-*C*H-azaAr), 116.1 (*keto*-*C*H-azaAr), 121.9 (*keto*-*C*H-azaAr), 126.1 (*C*-Ar_{OMe}), 128.6 (*enamino*-*C*-Cl), 128.9 (*keto*-*C*-Cl), 132.3 (*keto*-*C*H-azaAr), 132.8 (*keto*-*C*-azaAr), 133.0 (*keto*-*C*-azaAr), 137.0 (*enamino*-*C*-azaAr), 139.1 (*enamino*-*C*-azaAr), 155.1 (N=*C*-N), 160.8 (*enamino*-*C*-OMe), 163.5 (*keto*-*C*-OMe) 167.8 (NH-*C*-NH), 167.9 (*enamino*-*C*=OAr_{OMe}), 193.3 (*keto*-*C*=OAr_{OMe}); *m/z* (NSI^+) 301 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{16}H_{14}{}^{35}Cl_1N_2O_2$ $[M+H]^+$, found 301.0741, requires 301.0738 (+0.9 ppm).

2-Phenacyl-(5,6-dimethyl)benzimidazole (S10)

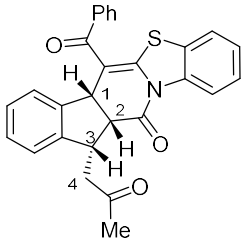


Following the General Procedure 9, 2-methyl-(5,6-dimethyl)benzimidazole (0.48 g, 3.0 mmol), benzoyl chloride (1.05 mL, 9.0 mmol) and NEt_3 (1.26 mL, 9.0 mmol) in HPLC grade acetonitrile (4 mL) and subsequent hydrolysis with morpholine (1.7 mL) afforded the title compound after filtration as a yellow solid as a 5:1 mixture of enamino:keto tautomers (622 mg, 78%). mp 190–191 °C; ν_{max} (film) 3034 (N-H), 2590 (C-H), 1575 (C=O), 1396 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 2.29 (6H, 2×CH_3), 4.67 (2H, s, *keto*-CH_2CO), 6.02 (1H, s, *enamino*-C*H*CO), 7.25 (2H, s, *enamino*-benzimidazoleC(4)(7)*H*), 7.30 (2H, s, *keto*-benzimidazoleC(4)(7)*H*), 7.40–7.47 (3H, m, *enamino*-*H*-Ph), 7.55–7.58 (3H, m, *keto*-*H*-Ph), 7.81–7.84 (2H, m, *enamino*-H-Ph), 8.07–8.08 (2H, m, *keto*-H-Ph), 12.18 (1H, s, *enamino*-N*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.9 (*enamino*-CH_3), 20.0 (*keto*-CH_3), 80.0 (*enamino*-*C*H), 125.5 (2×*C*H-Ph), 128.4 (2×*C*H-Ph), 128.5 (*C*H-azaAr), 128.9 (*C*H-azaAr), 129.6 (*C*H-Ph), 130.5 (2×*C*-CH_3), 137.5 (*C*-Ph), 152.9 (N=*C*-N), 169.4 (NH-*C*-NH), 169.4 (*C*=OPh); *m/z* (NSI$^+$) 271 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{17}H_{17}N_2O_1$ [M+H]$^+$, found 265.1336, requires 265.1335 (+0.2 ppm).

7.3.3 Michael-lactamisation-Michael using acyl benzothiazoles

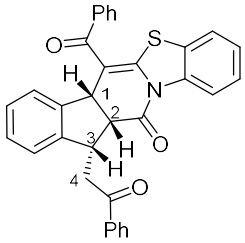
7.3.3.1 Data for indanes 204-207, 214-219

(6a*R*,11*S*,11a*R*)-6-Benzoyl-11-(2-oxopropyl)-11,11a-dihydrobenzo[4,5]thiazolo[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (204b)



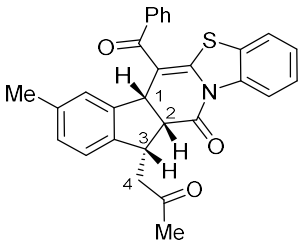
Following General Procedure 10, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-phenacylbenzothiazole (50.6 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (23.9 mg, 53%) as a yellow solid. mp 186–188 °C; $[\alpha]_D^{20}$ +83.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (95:5 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 18.4 min, t_R major: 31.4 min, 94:6 er; ν_{max} (film) 2920 (C-H), 1711 (C=O), 1609 (C=O), 1481 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.42 (3H, s, COC*H*$_3$), 3.21 (1H, dd, *J* 18.1, 5.4, H–4a), 3.61 (1H, dd, *J* 18.1, 5.4, H–4b), 3.96 (1H, t, *J* 6.5, H–2), 4.01–4.03 (1H, m, H–3), 4.67 (1H, d, *J* 6.5, H–1), 7.09–7.22 (5H, m, H–Ph), 7.25–7.28 (1H, m, H-azaAr), 7.43–7.51 (4H, m, H–Ar), 7.69–7.71 (2H, m, H-azaAr), 8.31 (1H, d, *J* 6.8, H-azaAr); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 30.5 (CO-*C*H$_3$), 42.0 (*C*H$_2$), 42.7 (*C*H-3), 43.0 (*C*H-2), 50.1 (*C*H-1), 104.6 (O=C-*C*=C), 118.5 (*C*H-azaAr), 121.8 (*C*H-azaAr), 122.1 (*C*H-azaAr), 123.2 (*C*H-Ar), 125.9 (*C*H-Ar), 126.7 (*C*H-azaAr), 127.4 (2×*C*H-Ph), 127.6 (*C*H-Ar), 127.7 (*C*-azaAr), 127.8 (*C*H-Ar), 128.6 (2×*C*H-Ph), 130.5 (*C*H-Ph), 136.2 (*C*-Ph), 139.4 (*C*-azaAr), 143.3 (*C*1-Ar), 143.6 (*C*6-Ar), 155.4 (O=C-C=*C*), 169.8 (CH-*C*=ON), 191.3 (*C*=OPh), 208.2 (*C*=OCH$_3$); *m/z* (NSI$^+$) 452 ([M+H]$^+$, 100%), 490 ([M+K]$^+$, 70%); HRMS (NSI$^+$) $C_{28}H_{22}O_3N_1S_1$ [M+H]$^+$, found 452.1309, requires 452.1315 (–1.3 ppm).

(6a*R*,11*S*,11a*R*)-6-Benzoyl-11-(2-oxo-2-phenylethyl)-11,11a-dihydrobenzo[4,5]thiazolo[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (205b)



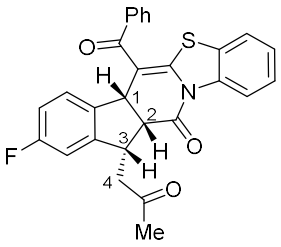
Following General Procedure 10, the corresponding TCP-ester (45.8 mg, 0.1 mmol), 2-phenacylbenzothiazole (50.6 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (90:10 Petroleum ether : EtOAc, R_f 0.3) afforded the title compound (42.6 mg, 83%) as a yellow solid. mp 262–264 °C; $[\alpha]_D^{20}$ +183.5 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 40 °C) t_R major: 38.2 min, t_R minor: 43.3 min, 97:3 er; ν_{max} (film) 2926 (C-H), 1715 (C=O), 1684 (C=O), 1487 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.71 (1H, dd, *J* 17.3, 4.5, H–4a), 4.07 (1H, t, *J* 6.2, H–2), 4.20–4.26 (1H, m, H–3), 4.29 (1H, dd, *J* 17.3, 8.4, H–4b), 4.74 (1H, d, *J* 6.2, H–1), 7.12–7.24 (6H, m, 5×H–Ph + H-azaAr), 7.25–7.28 (1H, m, H-azaAr), 7.43–7.51 (4H, m, H–Ar), 7.69–7.71 (2H, m, H-azaAr), 8.31 (1H, d, *J* 6.8, H-azaAr); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 30.5 (CO-*C*H$_3$), 42.0 (*C*H$_2$), 42.7 (*C*H-3), 43.0 (*C*H-2), 50.1 (*C*H-1), 104.6 (O=C-*C*=C), 118.5 (*C*H-aAr), 121.8 (*C*H-aAr), 122.1 (*C*H-azaAr), 123.2 (*C*H-Ar), 125.9 (*C*H-Ar), 126.7 (*C*H-azaAr), 127.4 (2×*C*H-Ph), 127.6 (*C*H-Ar), 127.7 (*C*-aAr), 127.8 (*C*H-Ar), 128.6 (2×*C*H-Ph), 130.5 (*C*H-Ph), 136.2 (*C*-Ph), 139.4 (*C*-azaAr), 143.3 (*C*1-Ar), 143.6 (*C*6-Ar), 155.4 (O=C-C=*C*), 169.8 (CH-*C*=ON), 191.3 (*C*=OPh), 208.2 (*C*=OCH$_3$); *m/z* (NSI$^+$) 514 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{33}H_{24}O_3N_1S_1$ [M+H]$^+$, found 514.1458, requires 514.1471 (–2.6 ppm).

(6a*R*,11*S*,11a*R*)-6-Benzoyl-8-methyl-11-(2-oxopropyl)-11,11a-dihydrobenzo[4,5]thiazolo[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (206b)



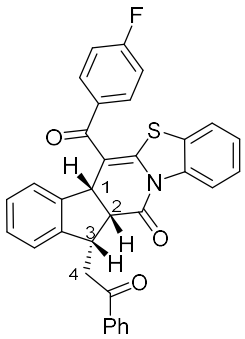
Following General Procedure 10, the corresponding TCP-ester (41.0 mg, 0.1 mmol), 2-phenacylbenzothiazole (50.6 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (36.8 mg, 79%) as a yellow solid. mp 255–257 °C; $[\alpha]_D^{20}$ +96.7 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 20.6 min, t_R minor: 37.6 min, 82:18 er; ν_{max} (film) 3017 (C-H), 1717 (C=O), 1614 (C=O), 1593 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.27 (3H, s, ArC-CH_3), 2.43 (3H, s, COCH_3), 3.20 (1H, dd, *J* 18.1, 5.4, H–4a), 3.60 (1H, dd, *J* 18.1, 5.4, H–4b), 3.93 (1H, t, *J* 6.7, H–2), 4.00 (1H, dd, *J* 10.4, 5.4, H–3) 4.67 (1H, d, *J* 6.7, H–1), 6.91 (1H, s, H–Ar), 7.00–7.04 (2H, m, H–Ar), 7.36–7.39 (1H, m, H-azaAr), 7.45–7.54 (5H, m, H-Ph), 7.72–7.74 (2H, m, H-azaAr), 8.34 (1H, d, *J* 6.8, H-azaAr); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 21.4 (ArC-*C*H_3), 30.5 (CO-*C*H_3), 42.1 (*C*H_2), 42.4 (*C*H-3), 42.9 (*C*H-2), 50.2 (*C*H-1), 104.7 (O=C-*C*=C), 118.5 (*C*H-aAr), 121.8 (2×*C*H-aAr), 123.4 (*C*H-Ar), 125.9 (*C*H-Ar), 126.7 (*C*H-azaAr), 127.4 (2×*C*H-Ph), 128.5 (*C*H-Ar), 127.7 (*C*-aAr), 128.6 (2×*C*H-Ph), 130.5 (*C*H-Ph), 136.2 (*C*-Ph), 137.5 (Ar*C*-CH_3), 139.4 (*C*-azaAr), 140.6 (*C*1-Ar), 143.4 (*C*6-Ar), 155.4 (O=C-C=*C*), 169.9 (CH-*C*=ON), 191.3 (*C*=OPh), 208.3 (*C*=OCH_3); *m/z* (NSI^+) 504 ($[M+K]^+$, 100%), 466 ($[M+H]^+$, 72%); HRMS (NSI^+) $C_{29}H_{23}O_3N_1Na_1S_1$ $[M+Na]^+$, found 488.1278, requires 488.1291 (–2.6 ppm).

(6a*R*,11*S*,11a*R*)-6-Benzoyl-9-fluoro-11-(2-oxopropyl)-11,11a-dihydrobenzo[4,5]thiazolo[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (207b)



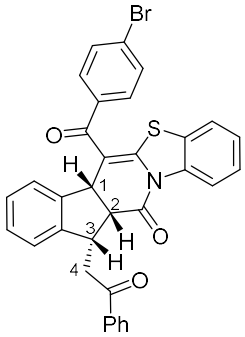
Following General Procedure 10, the corresponding TCP-ester (41.4 mg, 0.1 mmol), 2-phenacylbenzothiazole (50.6 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (19.7 mg, 42%) as a yellow solid. mp 234–236 °C; $[\alpha]_D^{20}$ +97.8 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (95:5 hexane : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 23.4 min, t_R major: 29.4 min, 92:8 er; ν_{max} (film) 2924 (C-H), 1717 (C=O), 1613 (C=O), 1483 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, COCH_3), 3.14 (1H, dd, *J* 18.2, 5.6, H–4a), 3.62 (1H, dd, *J* 18.1, 10.2, H–4b), 3.94 (1H, t, *J* 6.5, H–2), 3.99–4.02 (1H, m, H–3), 4.62 (1H, d, *J* 6.5, H–1), 6.80–6.84 (2H, m, H–Ar_F), 7.00–7.02 (1H, m, H–Ar_F), 7.28–7.30 (2H, m, H-azaAr), 7.44–7.48 (3H, m, H–Ph), 7.50–7.52 (1H, m, H-azaAr), 7.67–7.68 (2H, m, H–Ph), 8.32–8.34 (1H, m, H-azaAr); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −114.3; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 30.4 (CO-*C*H_3), 42.0 (*C*H_2), 42.5 (*C*H-3), 42.8 (*C*H-2), 50.5 (*C*H-1), 104.5 (O=C-*C*=C), 110.0 (d, $^2J_{CF}$ = 23.3, C_{Ar}-F), 110.1 (*C*H-Ar_F), 114.4 (*C*H-Ar_F), 114.5 (d, $^2J_{CF}$ = 22.6, C_{Ar}-F), 118.6 (*C*H-azaAr), 122.0 (*C*H-azaAr), 124.4 (*C*H-Ar_F), 124.4 (d, $^3J_{CF}$ = 8.9, C_{Ar}-F), 126.1 (*C*H-azaAr), 126.9 (*C*H-azaAr), 127.4 (2×*C*H-Ph), 128.7 (2×*C*H-Ph), 127.8 (*C*-azaAr), 130.7 (*C*H-Ph), 136.2 (*C*-Ph), 139.4 (*C*-azaAr), 146.0 (*C*1-Ar), 146.1 (*C*6-Ar), 155.6 (O=C-C=*C*), 162.0 (*C*-F), 163.0 (d, $^1J_{CF}$ = 245.9, C_{Ar}-F), 169.7 (CH-*C*=ON), 191.2 (*C*=OPh), 207.9 (*C*=OCH_3); *m/z* (NSI^+) 508 ($[M+K]^+$, 100%); HRMS (NSI^+) $C_{28}H_{20}O_3N_1F_1Na_1S_1$ $[M+Na]^+$, found 492.1030, requires 492.1040 (–2.1 ppm).

(6a*R*,11*S*,11a*R*)-6-(4-Fluorobenzoyl)-11-(2-oxo-2-phenylethyl)-11,11a-dihydrobenzo[4,5]thiazolo-[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (214b)



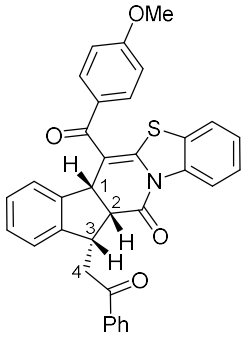
Following General Procedure 10, the corresponding TCP-ester (45.8 mg, 0.1 mmol), 2-(4-fluoro) phenacyl benzothiazole (54.2 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.25) afforded the title compound (35.6 mg, 67%) as a yellow solid. mp 259–261 °C; $[\alpha]_D^{20}$ +94.0 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (95:5 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 23.8 min, t_R minor: 37.1 min, 95:5 er; ν_{max} (film) 2920 (C-H), 1728 (C=O), 1678 (C=O), 1477 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.73 (1H, dd, *J* 17.0, 4.4, H–4a), 4.07 (1H, t, *J* 6.2, H–2), 4.23–4.30 (1H, m, H–3), 4.31 (1H, dd, *J* 17.0, 9.7, H–4b), 4.71 (1H, d, *J* 6.8, H–1), 7.10–7.17 (4H, m, Ar*H*), 7.18–7.24 (4H, m, 2×H–Ph + 2×H–Ph_F), 7.48–7.50 (1H, m, H-azaAr), 7.54–7.57 (2H, m, H-azaAr), 7.62–7.65 (1H, m, H-azaAr), 7.72–7.78 (2H, m, H–Ph_F), 8.15–8.17 (2H, m, H–Ph) 8.25–8.27 (1H, m, H-azaAr); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −109.0; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 37.6 (*C*H_2), 43.1 (*C*H-3), 43.3 (*C*H-2), 50.8 (*C*H-1), 104.5 (O=C-*C*=C), 115.7 (*C*H-Ph_F), 115.8 (d, $^2J_{CF}$ = 21.7, C_{Ph}-F), 115.9 (*C*H-Ph_F), 118.6 (*C*H-azaAr), 121.9 (*C*H-azaAr), 122.5 (*C*H-azaAr), 123.3 (*C*H-Ar), 126.0 (*C*H-Ar), 126.9 (*C*H-azaAr), 127.7 (*C*-azaAr), 127.8 (*C*H-Ar), 128.1 (*C*H-Ar), 128.4 (2×*C*H-Ph), 128.8 (2×*C*H-Ph), 129.9 (*C*H-Ph_F), 130.0 (d, $^3J_{CF}$ = 8.6, C_{Ph}-F), 130.0 (*C*H-Ph_F), 133.3 (*C*H-Ph), 135.7 (*C*-Ph_F), 136.3 (*C*-Ph), 137.3 (*C*-azaAr), 143.3 (*C*1-Ar), 144.1 (*C*6-Ar), 156.0 (N-*C*=C), 164.1 (d, $^1J_{CF}$ = 251.3, C_{Ph}-F), 165.1 (Ph-*C*-F) 169.8 (CH-*C*=ON), 189.8 (*C*=OPh_F), 199.5 (*C*=OPh); *m/z* (NSI$^+$) 532 ([M+H]$^+$, 100%), 554 ([M+Na]$^+$, 15%) HRMS (NSI$^+$) $C_{33}H_{23}O_3N_1F_1S_1$ [M+H]$^+$, found 532.1369, requires 532.1377 (−1.5 ppm).

(6a*R*,11*S*,11a*R*)-6-(4-Bromobenzoyl)-11-(2-oxo-2-phenylethyl)-11,11a-dihydrobenzo[4,5]thiazolo-[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (215b)



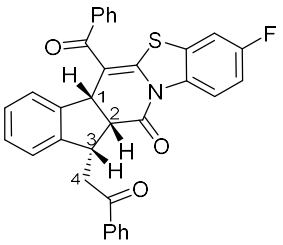
Following General Procedure 10, the corresponding TCP-ester (45.8 mg, 0.1 mmol), 2-(4-bromo) phenacyl benzothiazole (66.4 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.25) afforded the title compound (31.4 mg, 53%) as a yellow solid. mp 241–243 °C; $[\alpha]_D^{20}$ +137.5 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (95:5 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R major: 26.6 min, t_R minor: 39.8 min, 92:8 er; ν_{max} (film) 2924 (C-H), 1714 (C=O), 1682 (C=O), 1481 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.72 (1H, dd, *J* 17.5, 4.7, H–4a), 4.08 (1H, t, *J* 6.3, H–2), 4.20–4.30 (1H, m, H–3), 4.31 (1H, dd, *J* 17.5, 9.7, H–4b), 4.67 (1H, d, *J* 6.7, H–1), 7.22–7.24 (4H, m, Ar*H*), 7.48–7.50 (1H, m, H-azaAr), 7.54–7.64 (8H, m, 3×H–Ph + 2×H–Ph_{Br} + 3×H-azaAr), 8.15–8.17 (2H, m, H–Ph) 8.25–8.27 (1H, m, H-azaAr); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 37.6 (CH_2), 43.1 (*C*H-3), 43.2 (*C*H-2), 50.7 (*C*H-1), 104.3 (O=C-*C*=C), 118.6 (*C*H-azaAr), 121.9 (*C*H-azaAr), 122.5 (*C*H-azaAr), 123.2 (*C*H-Ar), 125.2 (*C*-Br), 126.0 (*C*H-Ar), 126.9 (*C*H-azaAr), 127.6 (*C*-azaAr), 127.8 (*C*H-Ar), 128.1 (*C*H-Ar), 128.4 (2×*C*H-Ph), 128.8 (2×*C*H-Ph), 129.2 (2×*C*H-Ph_{Br}), 131.9 (2×*C*H-Ph_{Br}), 133.3 (*C*H-Ph), 136.3 (*C*-Ph), 137.3 (*C*-Ph_{Br}), 138.3 (*C*-azaAr), 143.2 (*C*1-Ar), 144.0 (*C*6-Ar), 156.2 (N-*C*=C), 169.8 (CH-*C*=ON), 189.9 (*C*=OPh_{Br}), 199.4 (*C*=OPh); *m/z* (NSI$^+$) 1185 ([2M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{33}H_{23}O_3N_1{}^{79}Br_1S_1$ [M+H]$^+$, found 592.0571, requires 592.0577 (–0.9 ppm).

(6a*R*,11*S*,11a*R*)-6-(4-Methoxybenzoyl)-11-(2-oxo-2-phenylethyl)-11,11a-dihydrobenzo[4,5]-thiazolo[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (216b)



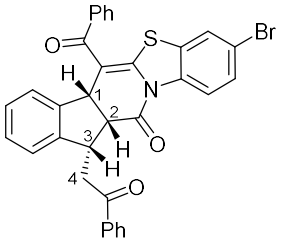
Following General Procedure 10, the corresponding TCP-ester (45.8 mg, 0.1 mmol), 2-(4-methoxy) phenacyl benzothiazole (56.6 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20→70:30 Petroleum ether : EtOAc, R_f 0.20) afforded the title compound (27.7 mg, 51%) as a yellow solid. mp 225–227 °C; $[\alpha]_D^{20}$ +129.0 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane : IPA, flow rate 0.5 mLmin^{-1}, 220 nm, 40 °C) t_R major: 53.3 min, t_R minor: 60.7 min, 95:5 er; ν_{max} (film) 2928 (C-H), 1709 (C=O), 1686 (C=O), 1483 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.70–3.75 (1H, m, H–4a), 4.05 (1H, t, *J* 6.4, H–2), 4.25–4.28 (1H, m, H–3), 4.31 (1H, dd, *J* 17.8, 9.4, H–4b), 4.80 (1H, d, *J* 6.8, H–1), 6.95 (1H, d, *J* 8.8, 2×H–Ph_{OMe}), 7.13–7.18 (2H, m, H–Ph), 7.20–7.25 (4H, m, Ar*H*), 7.46–7.48 (1H, m, H-azaAr), 7.53–7.56 (2H, H-azaAr), 7.62–7.63 (1H, m, H–Ph), 7.76 (1H, d, *J* 8.8, 2×H–Ph_{OMe}), 8.11–8.19 (2H, m, H–Ph) 8.20–8.29 (1H, m, H-azaAr); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 37.7 (*C*H_2), 43.1 (*C*H-3), 43.5 (*C*H-2), 50.8 (*C*H-1), 55.5 (O-CH_3), 105.0 (O=C-*C*=C), 113.9 (2×*C*H–Ph_{OMe}), 118.5 (*C*H-azaAr), 121.8 (*C*H-azaAr), 122.5 (*C*H-azaAr), 123.5 (*C*H-Ar), 125.9 (*C*H-Ar), 126.7 (*C*H-azaAr), 127.7 (*C*H-Ar), 128.0 (*C*H-Ar), 128.4 (2×*C*H-Ph), 128.8 (2×*C*H-Ph), 129.8 (2×*C*H-Ph_{OMe}), 130.1 (*C*-azaAr), 131.9 (*C*-Ph_{OMe}), 133.3 (*C*H-Ph), 136.4 (*C*-Ph), 137.3 (*C*-azaAr), 143.5 (*C*1-Ar), 144.1 (*C*6-Ar), 155.1 (N-*C*=C), 161.7 (*C*-Ph_{OMe}), 169.9 (CH-*C*=ON), 190.2 (*C*=OPh_{OMe}), 199.5 (*C*=OPh); *m/z* (NSI$^+$) 544 ([M+H]$^+$, 98%), 566 ([M+Na]$^+$, 30%); HRMS (NSI$^+$) $C_{34}H_{25}O_4N_1Na_1S_1$ [M+Na]$^+$, found 566.1385, requires 566.1397 (–2.0 ppm).

(6a*R*,11*S*,11a*R*)-6-Benzoyl-3-fluoro-11-(2-oxo-2-phenylethyl)-11,11a-dihydrobenzo[4,5]thiazolo-[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (217b)



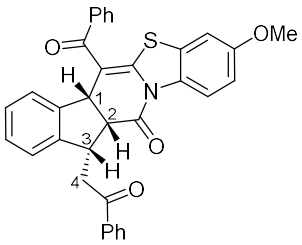
Following General Procedure 10, the corresponding TCP-ester (45.8 mg, 0.1 mmol), 2-phenacyl(6-fluoro)benzothiazole (54.2 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.25) afforded the title compound (31.9 mg, 60%) as a yellow solid. mp 238–240 °C; $[\alpha]_D^{20}$ +137.2 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 hexane : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 45.7 min, t_R minor: 50.2 min, 96:4 er; ν_{max} (film) 2924 (C-H), 1712 (C=O), 1684 (C=O), 1487 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.71 (1H, dd, *J* 16.5, 3.7, H–4a), 4.08 (1H, t, *J* 6.2, H–2), 4.22–4.27 (1H, m, H–3), 4.29 (1H, dd, *J* 16.7, 9.6, H–4b), 4.75 (1H, d, *J* 6.2, H–1), 6.88–6.92 (1H, m, H-azaAr), 7.11–7.13 (1H, m, H-azaAr), 7.17–7.25 (4H, m, H–Ar), 7.45–7.47 (3H, m, H–Ph), 7.53–7.56 (2H, m, H–Ph), 7.62–7.63 (1H, m, H–Ph), 7.72–7.74 (2H, m, H–Ph), 8.15 (2H, d, *J* 7.4, H–Ph), 8.22 (1H, dd, *J* 9.2, 4.6, H-azaAr); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −115.2; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 37.6 (*C*H_2), 43.1 (*C*H-3), 43.3 (*C*H-2), 50.5 (*C*H-1), 105.1 (O=C-*C*=C), 108.9 (d, $^2J_{CF}$ = 26.5, C_{Ar}-F), 109.0 (*C*H-azaAr$_F$), 113.8 (d, $^2J_{CF}$ = 23.1, C_{Ar}-F), 113.9 (*C*H-azaAr$_F$), 119.8 (*C*H-azaAr$_F$), 122.4 (*C*H-Ar), 123.4 (*C*H-Ar), 127.4 (2×*C*H-Ph), 127.8 (*C*H-Ar), 128.0 (*C*H-Ar), 128.3 (2×*C*H-Ph), 128.7 (2×*C*H-Ph), 128.8 (2×*C*H-Ph), 129.9 (*C*-azaAr), 129.9 (d, $^3J_{CF}$ = 9.1, C_{Ar}-F), 132.6 (*C*-azaAr), 133.3 (*C*H-Ph), 137.2 (*C*-Ph), 139.3 (*C*-Ph), 143.3 (*C*1-Ar), 143.9 (*C*6-Ar), 155.4 (O=C-C=*C*), 159.4 (*C*-F), 160.4 (d, $^1J_{CF}$ = 247.3, C_{Ar}-F), 169.7 (CH-*C*=ON), 191.4 (*C*=OPh), 199.4 (CH_2*C*=OPh); *m/z* (NSI$^+$) 532 ([M+H]$^+$, 100%), 554 ([M+Na]$^+$, 85%); HRMS (NSI$^+$) $C_{33}H_{23}O_3N_1F_1S_1$ [M+H]$^+$, found 566.1366, requires 532.1377 (–2.1 ppm).

(6a*R*,11*S*,11a*R*)-6-Benzoyl-3-bromo-11-(2-oxo-2-phenylethyl)-11,11a-dihydrobenzo[4,5]thiazolo-[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (218b)



Following General Procedure 10, the corresponding TCP-ester (45.8 mg, 0.1 mmol), 2-phenacyl(6-bromo)benzothiazole (66.4 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.25) afforded the title compound (27.8 mg, 47%) as a yellow solid. mp 262–264 °C; $[\alpha]_D^{20}$ +105.7 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (85:15 hexane : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 36.9 min, t_R minor: 43.6 min, 93:7 er; ν_{max} (film) 2872 (C-H), 1715 (C=O), 1686 (C=O), 1501 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.71 (1H, dd, *J* 16.9, 4.3, H–4a), 4.08 (1H, t, *J* 6.7, H–2), 4.21–4.25 (1H, m, H–3), 4.27 (1H, dd, *J* 16.9, 9.4, H–4b), 4.75 (1H, d, *J* 6.8, H–1), 7.11–7.25 (4H, m, H–Ar), 7.30 (1H, dd, *J* 8.9, 2.1, H-azaAr$_{Br}$), 7.45–7.47 (3H, m, H–Ph), 7.53–7.57 (3H, m, H–Ph), 7.62–7.65 (1H, m, H-azaAr$_{Br}$), 7.72–7.74 (2H, m, H–Ph), 8.10–8.12 (1H, H-azaAr$_{Br}$), 8.14–8.15 (2H, H–Ph; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 37.6 (*C*H$_2$), 43.1 (*C*H-3), 43.2 (*C*H-2), 50.7 (*C*H-1), 105.1 (O=C-*C*=C), 119.0 (*C*-Br), 119.7 (*C*H-azaAr$_{Br}$), 122.5 (*C*H-Ar), 123.4 (*C*H-Ar), 124.5 (*C*H-Ar), 127.6 (2×*C*H-Ph), 127.8 (*C*H-Ar), 128.1 (*C*H-azaAr$_{Br}$), 128.3 (2×*C*H-Ph), 128.7 (2×*C*H-Ph), 128.8 (2×*C*H-Ph), 129.8 (*C*H-azaAr$_{Br}$), 130.2 (*C*-azaAr), 130.9 (*C*H-Ph), 133.4 (*C*H-Ph), 135.5 (*C*-azaAr$_{Br}$), 137.2 (*C*-Ph), 139.3 (*C*-Ph), 143.2 (*C*1-Ar), 143.9 (*C*6-Ar), 154.9 (O=C-C=*C*), 169.8 (CH-*C*=ON), 191.5 (*C*=OPh), 199.4 (CH$_2$*C*=OPh); *m/z* (NSI$^+$) 1185 ([2M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{33}H_{23}O_3N_1{}^{79}Br_1S_1$ [M+H]$^+$, found 592.0570, requires 592.0577 (–1.1 ppm).

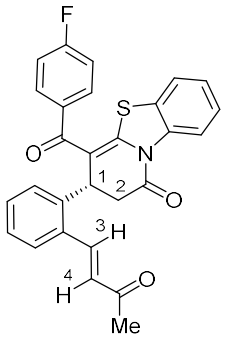
(6a*R*,11*S*,11a*R*)-6-Benzoyl-3-methoxy-11-(2-oxo-2-phenylethyl)-11,11a-dihydrobenzo[4,5]thiazolo-[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (219b)



Following General Procedure 10, the corresponding TCP-ester (45.8 mg, 0.1 mmol), 2-phenacyl(6-methoxy)benzothiazole (56.6 mg, 0.2 mmol) and PS-BEMP (2.0 mmol/g loading, 90.0 mg, 0.2 mmol) in THF (0.25 mL) and subsequent chromatography (80:20–70:30 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (11.3 mg, 20%) as a yellow solid. mp 240–241 °C; $[\alpha]_D^{20}$ +161.2 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (93:7 hexane : IPA, flow rate 1.0 mLmin^{-1}, 254 nm, 40 °C) t_R minor: 33.1 min, t_R major: 46.6 min, 91:9 (recryst. 98:2) er; ν_{max} (film) 2934 (C-H), 1707 (C=O), 1684 (C=O), 1485 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.70 (1H, dd, *J* 17.5, 4.9, H–4a), 3.79 (3H, s, OCH_3), 4.05 (1H, t, *J* 6.4, H–2), 4.20–4.28 (1H, m, H–3), 4.30 (1H, dd, *J* 17.5, 9.1, H–4b), 4.73 (1H, d, *J* 6.8, H–1), 6.74 (1H, dd, *J* 9.2, 2.6, H-azaAr$_{OMe}$), 6.98 (1H, d, *J* 2.6, H-azaAr$_{OMe}$), 7.12–7.24 (4H, m, H–Ar), 7.44–7.46 (3H, m, H–Ph), 7.53–7.56 (3H, m, H–Ph), 7.61–7.64 (1H, m, H-azaAr$_{OMe}$), 7.72–7.74 (2H, m, H–Ph), 8.15–8.16 (2H, H–Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 37.7 (*C*H$_2$), 43.1 (*C*H-3), 43.3 (*C*H-2), 50.5 (*C*H-1), 55.8 (O*C*H$_3$), 104.6 (O=C-*C*=C), 106.2 (*C*H-azaAr$_{OMe}$), 113.2 (*C*H-azaAr$_{OMe}$), 119.4 (*C*H-azaAr$_{OMe}$), 122.4 (*C*H-Ar), 123.4 (*C*H-Ar), 127.5 (2×*C*H-Ph), 127.7 (*C*H-Ar), 127.9 (*C*H-Ar), 128.4 (2×*C*H-Ph), 128.7 (2×*C*H-Ph), 128.8 (2×*C*H-Ph), 129.3 (*C*-azaAr$_{OMe}$), 130.2 (*C*-azaAr$_{OMe}$), 130.6 (*C*H-Ph), 133.3 (*C*H-Ph), 137.3 (*C*-Ph), 139.6 (*C*-Ph), 143.5 (*C*1-Ar), 144.0 (*C*6-Ar), 155.9 (O=C-C=*C*), 157.7 (*C*-OMe), 169.5 (CH-*C*=ON), 191.2 (*C*=OPh), 199.5 (CH$_2$*C*=OPh); *m/z* (NSI$^+$) 1185 ([M+H]$^+$, 40%); HRMS (NSI$^+$) $C_{34}H_{26}O_4N_1S_1$ [M+H]$^+$, found 544.1566, requires 544.1577 (+2.0 ppm).

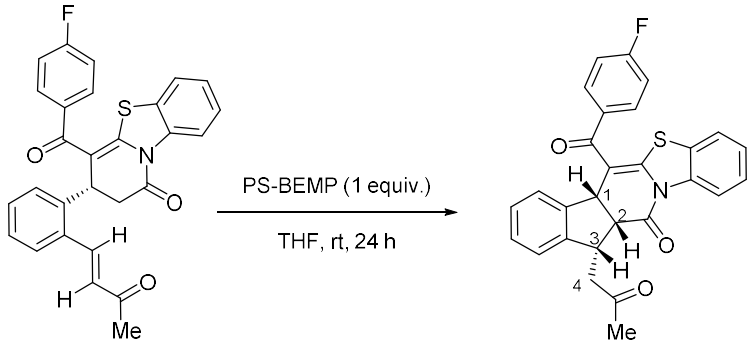
7.3.3.2 Formation of pre-cyclised dihydropyridone 226

(*R*,*E*)-4-(4-Fluorobenzoyl)-3-(2-(3-oxobut-1-en-1-yl)phenyl)-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridin-1-one (226)



Following General Procedure 10, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-fluoro)phenacylbenzothiazole (54.2 mg, 0.2 mmol) and PS-BEMP (70.0 mg, 0.15 mmol) in THF (0.25 mL) and subsequent chromatography (70:30 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (36.2 mg, 77%) as a yellow solid. mp 98–101 °C; $[\alpha]_D^{20}$ +117.4 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak AS-H (95:5 hexane : IPA, flow rate 1.5 mLmin^{-1}, 220 nm, 40 °C) t_R major: 23.3 min, t_R minor: 31.5 min, 88:12 er; ν_{max} (film) 2926 (C-H), 1726 (C=O), 1599 (C=O), 1481 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.33 (OCH_3), 2.85 (1H, dd, *J* 15.8, 2.3, H–2a), 3.28 (1H, dd, *J* 15.8, 7.4, H–2b), 4.61 (1H, dd, *J* 7.4, 2.3, H–2), 6.65 (1H, d, *J* 15.6, H–4), 6.91–6.93 (2H, m, H–Ph_F), 7.13–7.18 (4H, m, Ar*H*), 7.29–7.32 (2H, m, H–Ph_F), 7.36–7.39 (2H, m, H-azaAr), 7.55 (1H, d, *J* 15.6, H–3), 7.62–7.64 (1H, m, H-azaAr), 8.44–8.46 (1H, m, H-azaAr); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −109.1; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 29.2 (O*C*H$_3$), 35.4 (*C*H-1), 40.7 (*C*H$_2$), 107.1 (O=C-*C*=C), 115.4 (*C*H-Ph_F), 115.5 (*C*H-Ph_F), 115.5 (d, $^2J_{CF}$ = 21.7, C_{Ph}-F), 117.6 (*C*H-azaAr), 122.2 (*C*H-azaAr), 126.2 (*C*H-azaAr), 127.0 (*C*H-Ar), 127.4 (*C*H-azaAr), 127.7 (*C*-azaAr), 128.5 (2×*C*H-Ar), 128.5 (d, $^4J_{CF}$ = 4.0, C_{Ph}-F), 129.1 (*C*H-Ar), 129.1 (*C*H-Ph_F), 129.1 (d, $^3J_{CF}$ = 8.6, C_{Ph}-F), 129.7 (*C*H-Ph_F), 131.3 (*C*-4), 132.8 (*C*-azaAr), 135.5 (*C*1-Ar), 135.5 (*C*6-Ar), 136.0 (C-Ph_F), 139.8 (*C*-azaAr), 157.3 (N-*C*=C), 163.9 (d, $^1J_{CF}$ = 251.2, C_{Ph}-F), 164.9 (Ph-*C*-F), 167.3 (CH-*C*=ON), 190.0 (*C*=OPh_F), 197.4 (*C*=OMe); *m/z* (NSI$^+$) 470 ([M+H]$^+$, 70%); HRMS (NSI$^+$) $C_{28}H_{21}O_3N_1F_1S_1$ [M+H]$^+$, found 470.1212, requires 470.1221 (−1.8 ppm).

(6a*R*,11*S*,11a*R*)-6-(4-Fluorobenzoyl)-11-(2-oxopropyl)-11,11a-dihydrobenzo[4,5]thiazolo[3,2-*a*]indeno[1,2-*d*]pyridin-12(6a*H*)-one (227)



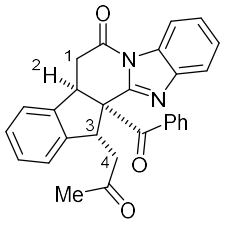
226 **227**

Pre-cyclisation intermediate **226** (36.2 mg, 0.08 mmol, 1.0 equiv) and PS-BEMP (2.0 mmol/g loading, 40 mg, 1.0 equiv) in THF were stirred 24 h at rt. Subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.25) afforded the title compound (31.0 mg, 86%) as a yellow solid. mp 190–192 °C; $[\alpha]_D^{20}$ +128.0 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R major: 25.9 min, t_R minor: 43.1 min, 92:8 er; ν_{max} (film) 2923 (C-H), 1735 (C=O), 1677 (C=O), 1452 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.45 (OC*H*$_3$), 3.24 (1H, dd, *J* 18.1, 5.5, H–4a), 3.65 (1H, dd, *J* 18.1, 10.5,, H–4b), 3.97 (1H, t, *J* 6.5,, H–2), 4.00–4.20 (1H, m, H–3), 4.66 (1H, d, *J* 6.8, H–1), 7.09–7.20 (6H, m, 4×Ar*H* + 2×H–Ph$_F$), 7.24–7.32 (2H, H-azaAr), 7.53–7.54 (1H, m, H-azaAr), 7.74–7.77 (2H, m, H–Ph$_F$), 8.33–8.35 (1H, m, H-azaAr); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −109.0; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 30.6 (O*C*H$_3$), 42.1 (*C*H$_2$), 42.9 (*C*H-3), 43.2 (*C*H-2), 50.2 (*C*H-1), 104.5 (O=C-*C*=C), 115.8 (d, $^2J_{CF}$ = 21.8, C_{Ph}-F), 115.7 (*C*H-Ph$_F$), 115.9 (*C*H-Ph$_F$), 118.6 (*C*H-azaAr), 122.0 (*C*H-azaAr), 122.3 (*C*H-azaAr), 123.2 (*C*H-Ar), 126.1 (*C*H-Ar), 126.9 (*C*H-azaAr), 127.1 (*C*-azaAr), 127.8 (*C*H-Ar), 128.1 (*C*H-Ar), 129.9 (d, $^3J_{CF}$ = 8.5, C_{Ph}-F), 129.9 (*C*H-Ph$_F$), 130.0 (*C*H-Ph$_F$), 136.2 (*C*-Ph$_F$), 138.8 (*C*-azaAr), 140.6 (*C*1-Ar), 143.7 (*C*6-Ar), 157.8 (N-*C*=C), 164.5 (d, $^1J_{CF}$ = 249.7, C_{Ph}-F), 169.8 (CH-*C*=ON), 188.1 (*C*=OPh$_F$), 208.3 (*C*=OMe); *m/z* (NSI$^+$) 492 ([M+H]$^+$, 100 %); HRMS (NSI$^+$) $C_{28}H_{20}O_3N_1F_1S_1Na$ [M+Na]$^+$, found 492.1031, requires 492.1021 (−1.9 ppm).

7.3.4 Michael-lactamisation-Michael using acyl benzimidazoles

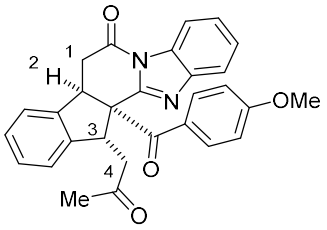
7.3.4.1 Data for racemic indanes (±) 229-244

12a-Benzoyl-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±229)



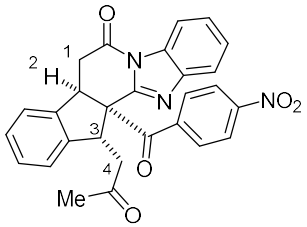
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-phenacylbenzimidazole (35.5 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (39.1 mg, 90%) as a pink solid. mp 195–196 °C; ν_{max} (film) 2924 (C-H), 1721 (C=O), 1668 (C=O), 1450 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.99 (3H, s, COC*H*$_3$), 2.74–2.76 (2H, m, H–1a,b), 3.48 (1H, dd, *J* 18.3, 2.4, H–4a), 3.76 (1H, dd, *J* 18.3, 5.8, H–4b), 4.61 (1H, dd, *J* 5.8, 2.4, H–3), 5.42 (1H, dd, *J* 8.2, 5.8, H–2), 7.11–7.22 (4H, m, H–Ar), 7.25–7.28 (2H, m, H-azaAr), 7.45–7.48 (2H, m, H-Ph), 7.54 (1H, t, *J* 7.3, H-Ph), 7.65 (1H, dd, *J* 5.9, 3.2, H-azaAr), 8.12 (1H, dd, *J* 5.9, 3.2, H-azaAr), 8.54 (2H, d, *J* 7.3, H-Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.0 (CO-*C*H$_3$), 33.3 (*C*H$_2$-4), 44.0 (*C*H$_2$-1), 44.3 (*C*H-3), 49.0 (*C*H-2), 65.6 (C_{quat}), 115.8 (*C*H-aAr), 120.0 (*C*H-aAr), 122.7 (*C*H-Ar), 125.3 (*C*H-Ar), 125.8 (*C*H-azaAr), 126.3 (*C*H-azaAr), 128.2 (*C*H-Ar), 128.6 (*C*H-Ar), 128.6 (2×*C*H-Ph), 130.8 (2×*C*H-Ph), 131.6 (*C*-aAr), 133.9 (*C*H-Ph), 135.1 (*C*-Ph), 139.1 (*C*-azaAr), 142.3 (*C*1-Ar), 143.9 (*C*6-Ar), 152.8 (N=*C*(C)-N), 167.3 (CH-*C*=ON), 196.3 (*C*=OPh), 205.7 (*C*=OCH$_3$); *m/z* (NSI$^+$) 435 ([M+H]$^+$, 100%), 891 ([2M+Na]$^+$, 30%); HRMS (NSI$^+$) $C_{28}H_{23}O_3N_2$ [M+H]$^+$, found 435.1696, requires 435.1703 (–1.7 ppm).

12a-(4-Methoxybenzoyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±230)



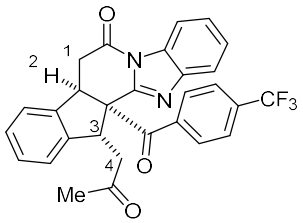
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-methoxy)phenacylbenzimidazole (39.9 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in THF (0.5 mL) and subsequent chromatography (80:20 − 70:30 Petroleum ether : EtOAc, R_f 0.15) afforded the title compound (40.2 mg, 87%) as a pale pink solid. mp 139–141 °C; ν_{max} (film) 2930 (C-H), 1721 (C=O), 1655 (C=O), 1452 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.99 (3H, s, COC*H*$_3$), 2.70–2.77 (2H, m, H–1a,b), 3.48 (1H, dd, *J* 18.3, 2.8, H–4a), 3.80 (1H, dd, *J* 18.3, 5.9, H–4b), 4.60 (1H, dd, *J* 5.9, 2.8, H–3), 5.41 (1H, t, *J* 7.1, H–2), 6.94 (2H, d, *J* 9.1, H-Ar$_{OMe}$), 7.07–7.17 (2H, m, H-azaAr), 7.20–7.27 (4H, m, H-Ar), 7.64–7.66 (1H, m, H-azaAr), 8.11–8.12 (1H, m, H-azaAr), 8.62 (2H, d, *J* 9.0, H-Ar$_{OMe}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.1 (CO-*C*H$_3$), 33.3 (*C*H$_2$-4), 43.9 (*C*H$_2$-1), 44.2 (*C*H-3), 49.0 (*C*H-2), 55.6 (O*C*H$_3$), 65.6 (C_{quat}), 113.8 (2×*C*H-Ar$_{OMe}$), 115.7 (*C*H-azaAr), 119.9 (*C*H-azaAr), 122.6 (*C*H-azaAr), 125.2 (*C*H-azaAr), 125.7 (*C*H-Ar), 126.0 (*C*H-Ar), 127.9 (*C*-Ar$_{OMe}$), 128.1 (*C*H-Ar), 128.5 (*C*H-Ar), 131.6 (*C*-azaAr), 133.5 (2×*C*H-Ar$_{OMe}$), 139.2 (*C*-azaAr), 142.2 (*C*1-Ar), 144.0 (*C*6-Ar), 153.2 (N=*C*(C)-N), 164.0 (*C*-OMe), 167.5 (CH-*C*=ON), 194.2 (*C*=OAr$_{OMe}$), 205.8 (*C*=OCH$_3$); *m/z* (NSI$^+$) 465 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{29}H_{25}O_4N_2$ [M+H]$^+$, found 465.1805, requires 465.1809 (–0.8 ppm).

12a-(4-Nitrobenzoyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±231)



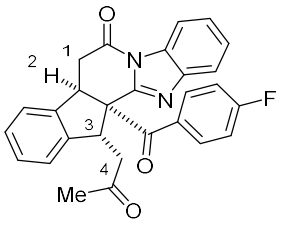
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-methoxy)phenacylbenzimidazole (42.2 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in THF (0.5 mL) and subsequent chromatography (80:20 – 70:30 Petroleum ether : EtOAc, R_f 0.15) afforded the title compound (28.7 mg, 60%) as an orange crystalline solid. mp 99–101 °C; ν_{max} (film) 2926 (C-H), 1721 (C=O), 1676 (C=O), 1528 (N-O), 1452 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.05 (3H, s, COC*H*$_3$), 2.73 (1H, dd, *J* 17.3, 3.8, H–1a), 2.82 (1H, dd, *J* 17.3, 10.1, H–1b), 3.55 (1H, dd, *J* 18.3, 2.7, H–4a), 3.68 (1H, dd, *J* 18.3, 5.9, H–4b), 4.67 (1H, dd, *J* 5.9, 2.7, H–3), 5.45 (1H, dd, *J* 10.1, 4.0, H–2), 7.17–7.29 (4H, m, H-Ar), 7.32–7.34 (2H, m, H-azaAr), 7.68–7.69 (1H, m, H-azaAr), 8.14–8.15 (1H, m, H-azaAr), 8.31 (2H, d, *J* 8.8, H-Ar$_{NO2}$), 8.72 (2H, d, *J* 8.8, H-Ar$_{NO2}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.1 (CO-*C*H$_3$), 33.1 (*C*H$_2$-4), 44.1 (*C*H$_2$-1), 44.3 (*C*H-3), 49.4 (*C*H-2), 65.6 (C_{quat}), 115.7 (*C*H-azaAr), 120.0 (*C*H-azaAr), 122.8 (*C*H-azaAr), 123.5 (2×*C*H-Ar$_{NO2}$), 125.6 (*C*H-azaAr), 125.8 (*C*H-Ar), 126.1 (*C*H-Ar), 128.4 (*C*H-Ar), 128.9 (*C*H-Ar), 131.5 (*C*-azaAr), 131.9 (2×*C*H-Ar$_{NO2}$), 138.6 (*C*-azaAr), 140.0 (*C*-Ar$_{NO2}$), 142.1 (*C*1-Ar), 143.5 (*C*6-Ar), 150.4 (*C*-NO_2), 152.0 (N=*C*(C)-N), 166.8 (CH-*C*=ON), 195.8 (*C*=OAr$_{NO2}$), 205.4 (*C*=OCH_3); *m/z* (NSI$^+$) 480 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{28}H_{22}O_5N_3$ [M+H]$^+$, found 480.1551, requires 480.1554 (–0.6 ppm).

12a-(4-(Trifluoromethyl)benzoyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±232)



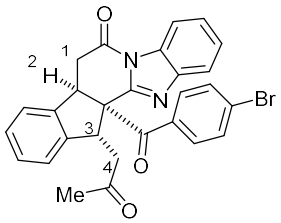
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-(trifluoromethyl)phenacylbenzimidazole (46.0 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in THF (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (24.4 mg, 49 %) as a pink solid. mp 71–72 °C; ν_{max} (film) 2928 (C-H), 1722 (C=O), 1674 (C=O), 1452 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.04 (3H, s, COCH_3), 2.71 (1H, dd, *J* 17.3, 3.7 Hz H–1a), 2.81 (1H, dd, *J* 17.3, 10.5, H–1b), 3.53 (1H, dd, *J* 18.3, 3.0, H–4a), 3.72 (1H, dd, *J* 18.3, 5.7, H–4b), 4.60 (1H, dd, *J* 5.7, 3.0, H–3), 5.45 (1H, dd, *J* 10.5, 3.7, H–2), 7.16–7.29 (4H, m, H-Ar), 7.31–7.33 (2H, m, H-azaAr), 7.67–7.69 (1H, m, H-azaAr), 7.75 (2H, d, *J* 8.4, H-Ar_{CF3}), 8.14–8.16 (1H, m, H-azaAr), 8.68 (2H, d, *J* 8.3, H-Ar_{CF3}); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −63.3 (CF_3); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.1 (CO-CH$_3$), 33.2 (CH$_2$-4), 44.0 (CH$_2$-1), 44.3 (CH-3), 49.2 (CH-2), 65.6 (C_{quat}), 115.8 (CH-azaAr), 120.0 (CH-azaAr), 122.7 (CH-azaAr), 125.5 (CH-azaAr), 125.5 (CH-Ar_{CF3}), 125.6 (CH-Ar_{CF3}), 125.6 (q, $^4J_{CF}$ = 3.6, C_{Ar}-CF_3), 125.9 (CH-Ar), 126.0 (CH-Ar), 127.2 (q, $^1J_{CF}$ = 294.7, C_{Ar}-CF_3), 128.3 (CH-Ar), 128.8 (CH-Ar), 131.3 (q, $^2J_{CF}$ = 40.3, C_{Ar}-CF_3), 131.2 (2×CH-Ar_{CF3}), 131.5 (*C*-azaAr), 137.9 (*C*-Ar_{CF3}), 138.8 (*C*-azaAr), 142.1 (*C*1-Ar), 143.6 (*C*6-Ar), 152.3 (N=*C*(C)-N), 167.0 (CH-*C*=ON), 195.8 (*C*=OAr_{CF3}), 205.5 (*C*=OCH_3); *m/z* (NSI$^+$) 503 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{29}H_{22}O_3N_2F_3$ [M+H]$^+$, found 503.1567, requires 503.1577 (–2.0 ppm).

12a-(4-Fluorobenzoyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±233)



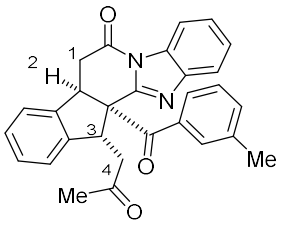
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-fluoro)phenacylbenzimidazole (38.1 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in THF (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (36.9 mg, 82%) as a colorless crystalline solid. mp 211–212 °C; ν_{max} (film) 2926 (C-H), 1722 (C=O), 1666 (C=O), 1452 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.99 (3H, s, COC*H*$_3$), 2.67 (1H, dd, *J* 17.2, 3.6, H–1a), 2.74 (1H, dd, *J* 17.2, 10.6, H–1b), 3.49 (1H, dd, *J* 18.3, 2.8, H–4a), 3.75 (1H, dd, *J* 18.3, 5.8, H–4b), 4.61 (1H, dd, *J* 5.8, 2.8, H–3), 5.40 (1H, dd, *J* 10.6, 3.6, H–2), 7.10–7.18 (4H, m, H–Ar), 7.21–7.24 (2H, m, H-azaAr), 7.27–7.29 (2H, m, H-Ar$_F$), 7.65 (1H, dd, *J* 6.1, 3.2, H-azaAr), 8.12 (1H, dd, *J* 6.2, 3.2, H-azaAr), 8.66 (2H, dd, *J* 9.0, 5.4, H-Ar$_F$); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −103.2; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.0 (CO-*C*H$_3$), 33.3 (*C*H$_2$-4), 43.8 (*C*H$_2$-1), 44.1 (*C*H-3), 49.0 (*C*H-2), 65.5 (*C*$_{quat}$), 115.7 (d, $^2J_{CF}$ = 21.7, C$_{Ph}$-F), 115.7 (*C*H-azaAr), 119.8 (*C*H-azaAr), 122.5 (*C*H-Ar), 125.3 (*C*H-Ar$_F$), 125.7 (*C*H-azaAr), 125.8 (*C*H-azaAr), 128.1 (*C*H-Ar), 128.5 (*C*H-Ar), 131.3 (d, $^4J_{CF}$ = 3.0, C$_{Ph}$-F), 131.4 (*C*-azaAr), 133.7 (d, $^3J_{CF}$ = 9.3, C$_{Ph}$-F), 138.8 (*C*-azaAr), 142.0 (*C*1-Ar), 143.7 (*C*6-Ar), 152.6 (N=*C*(C)-N), 166.0 (d, $^1J_{CF}$ = 257.0, C$_{Ph}$-F), 167.1 (CH-*C*=ON), 194.5 (*C*=OAr$_F$), 205.4 (*C*=OCH$_3$); *m/z* (NSI$^+$) 453 ([M+H]$^+$); HRMS (NSI$^+$) $C_{28}H_{22}O_3N_2F$ [M+H]$^+$, found 453.1607, requires 453.1609 (–0.4 ppm)

12a-(4-Bromobenzoyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±234)



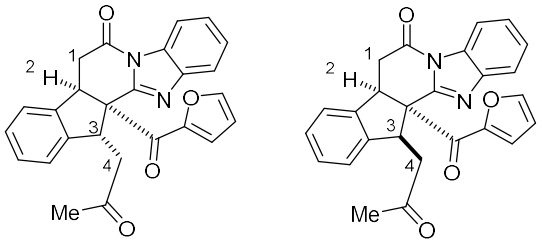
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-bromo)phenacylbenzimidazole (47.3 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in THF (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (37.8 mg, 74%) as a yellow solid. mp 95–96 °C; ν_{max} (film) 2924 (C-H), 1721 (C=O), 1667 (C=O), 1451 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.00 (3H, s, COCH_3), 2.67 (1H, dd, *J* 17.3, 3.4, H–1a), 2.75 (1H, dd, *J* 17.1, 10.7, H–1b), 3.49 (1H, dd, *J* 18.3, 2.6, H–4a), 3.72 (1H, dd, *J* 18.3, 5.8, H–4b), 4.59–4.60 (1H, m, H–3), 5.39 (1H, dd, *J* 10.6, 3.2, H–2), 7.11–7.26 (4H, m, H-Ar), 7.27–7.29 (2H, m, H-azaAr), 7.61 (2H, d, *J* 8.7, H-Ar_{Br}), 7.62–7.66 (1H, m, H-azaAr), 8.10–8.12 (1H, m, H-azaAr), 8.46 (2H, d, *J* 8.6, H-Ar_{Br}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.1 (CO-*C*H_3), 33.2 (*C*H_2-4), 43.9 (*C*H_2-1), 44.2 (*C*H-3), 49.1 (*C*H-2), 65.6 (C_{quat}), 115.8 (*C*H-azaAr), 120.0 (*C*H-azaAr), 122.7 (*C*H-azaAr), 125.4 (*C*H-azaAr), 125.9 (2×*C*H-Ar), 128.3 (*C*H-Ar), 128.7 (*C*H-Ar), 129.5 (*C*-Br), 131.5 (*C*-azaAr), 131.9 (2×*C*H-Ar_{Br}), 132.4 (2×*C*H-Ar_{Br}), 133.7 (*C*-Ar_{Br}), 138.9 (*C*-azaAr), 142.1 (*C*1-Ar), 143.7 (*C*6-Ar), 152.5 (N=*C*(C)-N), 167.2 (CH-*C*=ON), 195.3 (*C*=OAr_{NO2}), 205.5 (*C*=OCH_3); *m/z* (NSI$^+$) 513 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{28}H_{22}O_3N_2{}^{79}Br_1$ [M+H]$^+$, found 513.0807, requires 513.0850 (–0.3 ppm).

12a-(3-Methylbenzoyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±235)



Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-methoxy)phenacylbenzimidazole (37.5 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (28.3 mg, 63%) as a off-white solid. mp 51–52 °C; ν_{max} (film) 2920 (C-H), 1717 (C=O), 1663 (C=O), 1450 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.00 (3H, s, COCH_3), 2.40 (3H, s, Ar-CH_3), 2.72–2.79 (2H, m, H–1a,b), 3.48 (1H, dd, *J* 18.3, 3.0, H–4a), 3.74 (1H, dd, *J* 18.3, 5.9, H–4b), 4.61 (1H, dd, *J* 5.9, 3.0, H–3), 5.43 (1H, dd, *J* 8.3, 5.9, H–2), 7.10–7.24 (4H, m, H–Ar), 7.22–7.28 (2H, m, 1×H-azaAr + 1×H-Ar_{Me}), 7.34–7.36 (2H, m, H-Ar_{Me}), 7.64 (1H, dd, *J* 6.4, 2.9, H-azaAr), 8.12 (1H, dd, *J* 6.4, 2.9, H-azaAr), 8.24 (1H, s, H-Ar_{Me}), 8.40–8.42 (1H, m, H-azaAr); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.5 (Ar-*C*H$_3$), 31.0 (CO-*C*H$_3$), 33.3 (*C*H$_2$-4), 44.0 (*C*H$_2$-1), 44.4 (*C*H-3), 49.0 (*C*H-2), 65.7 (C_{quat}), 115.7 (*C*H-azaAr), 119.9 (*C*H-azaAr), 122.6 (*C*H-Ar), 125.3 (*C*H-Ar), 125.7 (*C*H-azaAr), 125.9 (*C*H-azaAr), 128.0 (*C*H-Ar), 128.1 (*C*H-Ar), 128.4 (*C*H-Ar_{Me}), 128.5 (*C*H-Ar_{Me}), 131.1 (*C*H-Ar_{Me}), 131.5 (*C*-azaAr), 134.6 (*C*H-Ar_{Me}), 135.2 (C-Ar_{Me}), 138.4 (*C*-azaAr), 139.1 (C_{Ar}-CH_3), 142.3 (*C*1-Ar), 144.0 (*C*6-Ar), 145.0 (C_{Ar}-Me), 152.9 (N=*C*(C)-N), 167.3 (CH-*C*=ON), 196.4 (*C*=OAr_{Me}), 205.7 (*C*=OCH_3); *m/z* (NSI$^+$) 471 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{29}H_{24}O_3N_2Na$[M+Na]$^+$, found 471.1683, requires 471.1679 (+0.8 ppm).

12a-(Furan-2-carbonyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±236)

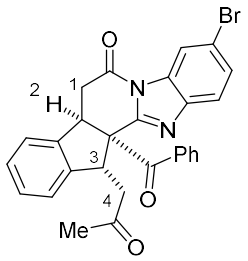


Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-furoylbenzimidazole (45.2 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (70:30 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (28.4 mg, 68%) as a diastereomeric mixture (2.5:1 dr). The major diastereomer was separated from the minor one: brown solid was obtained (15.1 mg, 36%).

major: mp 69–70 °C; ν_{max} (film) 2924 (C-H), 1722 (C=O), 1655 (C=O), 1452 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.06 (3H, s, COC*H*$_3$), 2.85–2.86 (2H, m, H–1a,b), 3.44 (1H, dd, *J* 18.1, 3.9, H–4a), 3.66 (1H, dd, *J* 18.1, 5.8, H–4b), 4.55 (1H, dd, *J* 5.8, 3.9, H–3), 5.19 (1H, dd, *J* 7.7, 6.1, H–2), 6.55 (1H, dd, *J* 3.7, 1.7, H–Fur), 7.10–7.24 (4H, m, H–Ar), 7.30–7.32 (2H, m, H-azaAr), 7.58 (1H, dd, *J* 1.7, 0.7, H-Fur), 7.66–7.68 (1H, m, H-azaAr), 8.15–8.17 (2H, m, H-azaAr + H-Fur); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.0 (CO-*C*H$_3$), 33.7 (*C*H$_2$-4), 43.4 (*C*H-3), 43.8 (*C*H$_2$-1), 48.6 (*C*H-2), 63.5 (C_{quat}), 112.8 (*C*H-Fur), 115.8 (*C*H-azaAr), 120.0 (*C*H-azaAr), 122.9 (*C*H-Ar), 123.2 (*C*H-Fur), 125.4 (*C*H-Ar), 125.7 (*C*H-azaAr), 125.8 (*C*H-azaAr), 128.1 (*C*H-Ar), 128.6 (*C*H-Ar), 131.6 (*C*-azaAr), 139.1 (*C*-azaAr), 142.4 (*C*1-Ar), 144.0 (*C*6-Ar), 147.8 (*C*H-Fur), 150.8 (*C*-Fur), 152.7 (N=*C*(C)-N), 167.2 (CH-*C*=ON), 183.7 (*C*=OFur), 205.9 (*C*=OCH$_3$); *m/z* (NSI$^+$) 425 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{26}H_{21}O_4N_2$[M+H]$^+$, found 425.1491, requires 425.1496 (–1.1 ppm).

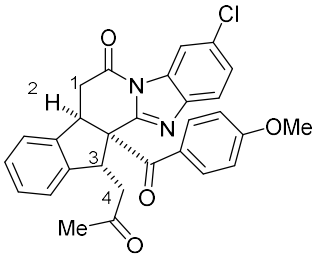
minor: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.24 (3H, s, COC*H*$_3$), 2.95 (1H, dd, *J* 17.7, 8.8, H–4a), 3.20 (1H, dd, *J* 17.7, 5.7, H–4b), 3.27–3.28 (2H, m, H–1a,b), 4.36 (1H, t, *J* 6.0, H–3), 5.30 (1H, dd, *J* 9.0, 5.6, H–2), 6.42 (1H, dd, *J* 3.7, 1.8, H–Fur), 7.20–7.22 (4H, m, H–Ar), 7.27–7.28 (1H, m, H-Fur), 7.35–7.39 (2H, m, H-azaAr), 7.66–7.68 (1H, m, H-azaAr), 8.25 (1H, dd, *J* 7.3, 2.1, H–Fur).

12a-Benzoyl-3-bromo-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±237)



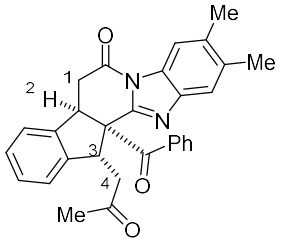
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-phenacyl-(6-bromo)benzimidazole (47.0 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound as inseparable mixture of two (29.1 mg, 57%) as an off-white solid. mp 88–89 °C; ν_{max} (film) 3073 (C-H), 2926 (C-H), 1721 (C=O), 1664 (C=O), 1449 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.99 (3H, s, COCH_3), 2.67–2.82 (2H, m, H–1a,b), 3.48 (1H, dt, *J* 18.3, 3.3, H–4a), 3.74 (1H, ddd, *J* 18.3, 5.8, 2.6, H–4b), 4.61 (1H, dt, *J* 5.8, 3.3, H–3), 5.40 (1H, dt, *J* 8.2, 5.4, H–2), 7.09–7.24 (4H, m, H–Ar), 7.36 (1H, td, *J* 8.6, 2.0, H-azaAr), 7.45–7.48 (2H, m, H-Ph), 7.53–7.56 (1H, m, H-Ph), 7.78 (1H, d, *J* 2.0, H-azaAr), 7.96 (1H, d, *J* 8.6, H-azaAr), 8.29 (1H, d, *J* 2.0, H-azaAr), 8.51 (2H, d, *J* 7.4, H-Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 30.9 (CO-*C*H$_3$), 33.1 (*C*H$_2$-4), 43.8 (*C*H$_2$-1), 2× 44.2 (*C*H-3), 49.0 (*C*H-2), 2× 65.6 (C_{quat}), 116.7 (*C*H-aAr), 118.3 (*C*-Br), 118.7 (*C*H-aAr), 119.1 (*C'*-Br), 122.5 (*C*H-Ar), 122.9 (*C*H-aAr), 2× 125.8 (*C*H-azaAr), 128.1 (*C*H-Ar), 128.6 (*C*H-Ar), 128.6 (2×*C*H-Ph), 130.6 (2×*C*H-Ph), 2× 133.9 (*C*H-Ph), 2× 134.9 (*C*-aAr), 138.7 (*C*-Ph), 141.1 (*C*1-Ar), 141.7 (*C*-azaAr), 143.4 (*C*6-Ar), 2× 153.3 (N=*C*(C)-N), 167.0 (CH-*C*=ON), 195.9 (*C*=OPh), 205.5 (*C*=OCH$_3$); *m/z* (NSI$^+$) 535 ([M+Na]$^+$, 100%), 1049 ([2M+Na]$^+$, 40%); HRMS (NSI$^+$) $C_{28}H_{21}O_3N_2{}^{79}Br_1Na$ [M+Na]$^+$, found 535.0614, requires 535.0628 (–2.6 ppm).

3-Chloro-12a-(4-methoxybenzoyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±238)



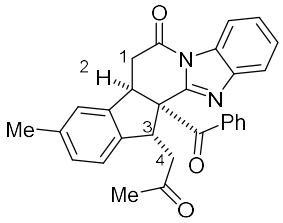
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-methoxy)phenacyl(6-chloro)benzimidazole (45.1 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 – 70:30 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound as inseparable mixture of two rotamers (30.1 mg, 62%) as an off-white foam. mp 102–103 °C; ν_{max} (film) 2926 (C-H), 1721 (C=O), 1655 (C=O), 1454 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.98 (3H, s, COCH_3), 2.68–2.75 (2H, m, H–1a,b), 3.48 (1H, dt, *J* 18.4, 3.0, H–4a), 3.77 (1H, ddd, *J* 18.3, 5.8, 2.5, H–4b), 2× 3.87 (Ar-OCH_3), 4.60 (1H, dt, *J* 5.8, 3.0, H–3), 5.38 (1H, q, *J* 6.4, H–2), 6.94 (2H, d, *J* 9.0, H-Ar$_{OMe}$), 7.10–7.24 (4H, m, H–Ar), 7.54 (1H, d, *J* 8.7, H-azaAr), 7.62 (1H, d, *J* 2.1, H-azaAr), 8.01 (1H, d, *J* 8.7, H-azaAr), 8.13 (1H, d, *J* 2.1, H-azaAr), 8.59 (2H, d, *J* 7.8, H-Ar$_{OMe}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.1 (CO-*C*H$_3$), 2× 33.2 (*C*H$_2$-4), 43.9 (*C*H$_2$-1), 2× 44.2 (*C*H-3), 2× 49.1 (*C*H-2), 55.7 (Ar-O*C*H$_3$), 2× 65.6 (*C*$_{quat}$), 113.8 (2×*C*H-Ar$_{OMe}$), 116.0 (*C*H-aAr), 116.5 (*C*H-aAr), 119.9 (*C*H-aAr), 120.6 (*C*H-aAr), 122.6 (*C*H-Ar), 2× 125.8 (*C*H-azaAr), 126.0 (*C*H-Ar), 127.7 (*C'*-Cl), 127.8 (*C'*-Cl), 128.2 (*C*H-Ar), 128.6 (*C*H-Ar), 130.1 (*C*-aAr), 130.9 (*C*-Ar$_{OMe}$), 131.5 (*C*-aAr), 132.0 (*C*-aAr), 133.5 (2×*C*H-Ar$_{OMe}$), 139.0 (*C*1-Ar), 140.8 (*C*-azaAr), 143.8 (*C*-azaAr), 143.9 (*C*6-Ar), 153.9 (N=*C*(C)-N), 154.6 (N=*C*(C)-N), 164.1 (*C*-OMe), 167.3 (CH-*C*=ON), 167.4 (CH-*C*=ON), 193.9 (*C*=OAr$_{OMe}$), 205.7 (*C*=OCH$_3$); *m/z* (NSI$^+$) 499 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{29}H_{24}O_3N_2{}^{35}Cl_1$ [M+H]$^+$, found 499.1408, requires 499.1419 (–2.2 ppm).

12a-Benzoyl-2,3-dimethyl-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±239)



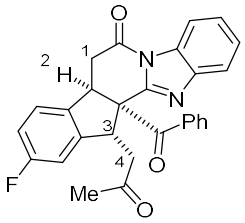
Following General Procedure 11, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-phenacyl(5,6-dimethyl)benzimidazole (39.5 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (38.4 mg, 83%) as a brown solid. mp 52–53 °C; ν_{max} (film) 2924 (C-H), 1719 (C=O), 1665 (C=O), 1464 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.99 (3H, s, COCH_3), 2×2.27 (3H, s, aAr-Me), 2.74–2.78 (2H, m, H–1a,b), 3.45 (1H, dd, *J* 18.3, 3.0, H–4a), 3.71 (1H, dd, *J* 18.3, 5.8, H–4b), 4.58 (1H, dd, *J* 5.8, 3.0, H–3), 5.38 (1H, dd, *J* 9.0, 5.1, H–2), 7.05–7.25 (4H, m, H–Ar), 7.40 (1H, s, H-azaAr), 7.45–7.48 (2H, m, H-Ph), 7.51–7.54 (1H, m, H-Ph), 7.90 (1H, s, H-azaAr), 8.51 (2H, d, *J* 7.5, H-Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.3 (aAr-CH$_3$), 20.4 (aAr-CH$_3$), 31.0 (CO-CH$_3$), 33.3 (CH$_2$-4), 43.9 (CH$_2$-1), 44.3 (CH-3), 48.9 (CH-2), 65.5 (C_{quat}), 115.9 (CH-aAr), 120.1 (CH-aAr), 122.6 (CH-Ar), 125.9 (CH-Ar), 128.1 (CH-Ar), 128.5 (CH-Ar), 128.5 (2×CH-Ph), 129.9 (*C*-aAr), 130.7 (2×CH-Ph), 133.7 (CH-Ph), 134.2 (aAr-CCH$_3$), 135.0 (*C*-Ph), 135.2 (aAr-CCH$_3$), 139.2 (*C*-azaAr), 140.7 (*C*1-Ar), 143.9 (*C*6-Ar), 151.9 (N=C(C)-N), 167.3 (CH-C=ON), 196.4 (C=OPh), 205.8 (C=OCH$_3$); *m/z* (NSI$^+$) 463 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{30}H_{27}O_3N_2$ [M+H]$^+$, found 463.2007, requires 463.2016 (–2.0 ppm).

12a-Benzoyl-9-methyl-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±240)



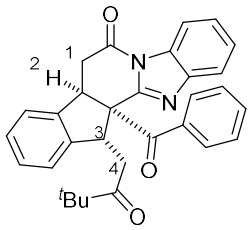
Following General Procedure 11, the corresponding TCP-ester (41.0 mg, 0.1 mmol), 2-phenacylbenzimidazole (35.5 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (37.3 mg, 83%) as a yellow solid. mp 79–81 °C; ν_{max} (film) 2922 (C-H), 1717 (C=O), 1663 (C=O), 1451 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.99 (3H, s, COC*H*$_3$), 2.25 (3H, s, C*H*$_3$–Ar), 2.69–2.76 (2H, m, H–1a,b), 3.47 (1H, dd, *J* 18.3, 2.9, H–4a), 3.75 (1H, dd, *J* 18.3, 5.8, H–4b), 4.58 (1H, dd, *J* 6.2, 2.8, H–3), 5.39 (1H, dd, *J* 8.4, 5.8, H–2), 6.92 (1H, d, *J* 7.7, H–Ar), 7.01 (1H, s, H–Ar), 7.12 (1H, d, *J* 7.7, H–Ar), 7.28–7.30 (2H, dd, *J* 5.9, 3.0, H-azaAr), 7.47 (2H, t, *J* 7.7, H-Ph), 7.54 (1H, t, *J* 7.2, H-Ph), 7.65 (1H, dd, *J* 6.1, 3.2, H-azaAr), 8.13 (1H, dd, *J* 6.2, 3.1, H-azaAr), 8.56 (2H, d, *J* 7.7, H-Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.5 (*C*H$_3$–Ar), 31.1 (CO-*C*H$_3$), 33.3 (*C*H$_2$-4), 44.1 (*C*H$_2$-1), 44.2 (*C*H-3), 48.8 (*C*H-2), 65.8 (C_{quat}), 115.7 (*C*H-aAr), 120.0 (*C*H-aAr), 123.3 (*C*H-Ar), 125.3 (*C*H-Ar), 125.6 (*C*H-azaAr), 125.7 (*C*H-azaAr), 128.6 (2×*C*H-Ph), 129.3 (*C*H-Ar), 130.8 (2×*C*H-Ph), 131.6 (*C*-aAr), 133.8 (*C*H-Ph), 135.2 (*C*-Ph), 138.0 (*C*-azaAr), 139.1 (*C*-CH$_3$), 140.9 (*C*1-Ar), 142.3 (*C*6-Ar), 152.9 (N=*C*(C)-N), 167.4 (CH-*C*=ON), 196.3 (*C*=OPh), 205.7 (*C*=OCH$_3$); *m/z* (NSI$^+$) 471 ([M+Na]$^+$, 100%), 919 ([2M+Na]$^+$, 30%); HRMS (NSI$^+$) $C_{29}H_{24}O_3N_2Na$ [M+Na]$^+$, found 471.1692, requires 471.1679 (+2.7 ppm).

12a-Benzoyl-10-fluoro-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±241)



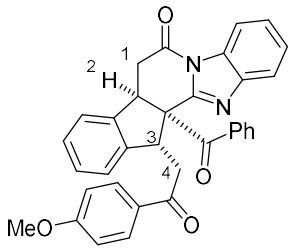
Following General Procedure 11, the corresponding TCP-ester (41.4 mg, 0.1 mmol), 2-phenacylbenzimidazole (35.5 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (37.1 mg, 82%) as a colorless oil; ν_{max} (film) 2926 (C-H), 1721 (C=O), 1667 (C=O), 1449 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.01 (3H, s, COCH_3), 2.72–2.77 (2H, m, H–1a,b), 3.43 (1H, dd, *J* 18.3, 3.2, H–4a), 3.75 (1H, dd, *J* 18.3, 5.8, H–4b), 4.55 (1H, dd, *J* 5.8, 3.2, H–3), 5.38 (1H, t, *J* 7.1, H–2), 6.85 (1H, td, *J* 8.7, 2.6, H–Ar), 6.99 (1H, dd, *J* 8.7, 2.6, H–Ar), 7.15 (1H, dd, *J* 8.5, 4.8, H–Ar), 7.29 (2H, dd, *J* 6.1, 3.2 Hz H-azaAr), 7.46 (2H, t, *J* 7.7, H-Ph), 7.54 (1H, t, *J* 7.4, H-Ph), 7.66 (1H, dd, *J* 6.4, 2.9, H-azaAr), 8.13 (1H, dd, *J* 6.4, 2.9, H-azaAr), 8.50 (2H, d, *J* 7.6, H-Ph); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −113.1; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 30.8 (CO-*C*H_3), 33.4 (*C*H_2-4), 43.6 (*C*H_2-1), 43.7 (*C*H-3), 48.6 (*C*H-2), 65.6 (C_{quat}), 113.5 (*C*H-Ar), 113.6 (d, $^2J_{CF}$ = 22.6, C_{Ar}-F), 114.9 (*C*H-Ar), 115.0 (d, $^2J_{CF}$ = 22.7, C_{Ar}-F), 115.6 (*C*H-azaAr), 119.9 (*C*H-azaAr), 123.7 (*C*H-Ar), 123.8 (d, $^3J_{CF}$ = 9.2, C_{Ar}-F), 125.3 (*C*H-azaAr), 125.8 (*C*H-azaAr), 128.6 (2×*C*H-Ph), 130.6 (2×*C*H-Ph), 131.4 (*C*-azaAr), 133.9 (*C*H-Ph), 134.5 (d, $^4J_{CF}$ = 2.3, C_{Ar}-F), 134.9 (*C*-Ph), 142.1 (*C*-azaAr), 146.0 (*C*1-Ar), 146.1 (*C*6-Ar), 152.4 (N=*C*(C)-N), 161.8 (*C*-F), 162.8 (d, $^1J_{CF}$ = 246.5, C_{Ar}-F), 167.0 (CH-*C*=ON), 195.8 (*C*=OPh), 205.2 (*C*=OCH$_3$); *m/z* (NSI$^+$) 255 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{15}H_{12}F_1N_2O_1$ [M+H]$^+$, found 255.0930, requires 255.0928 (+0.7 ppm).

12a-Benzoyl-12-(3,3-dimethyl-2-oxobutyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±242)



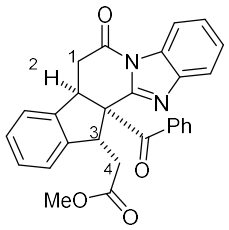
Following General Procedure 11, the corresponding TCP-ester (43.8 mg, 0.1 mmol), 2-phenacylbenzimidazole (39.5 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in THF (0.5 mL) and subsequent chromatography (90:10 – 80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (44.8 mg, 94%) as a colorless crystalline solid. mp 88–89 °C; ν_{max} (film) 2926 (C-H), 1728 (C=O), 1661 (C=O), 1530 (C_{Ar}-C_{Ar}), 1452 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.86 (9H, s, (CH_3)$_3$), 2.67 (1H, dd, *J* 17.3, 3.0, H–1a), 2.86 (1H, dd, *J* 17.1, 11.0, H–1b), 3.49 (1H, dd, *J* 18.3, 2.9, H–4a), 3.80 (1H, dd, *J* 18.3, 5.9, H–4b), 4.63 (1H, dd, *J* 6.1, 2.7, H–3), 5.45 (1H, dd, *J* 11.0, 3.1, H–2), 7.08–7.21 (4H, m, H-Ar), 7.26–7.27 (2H, m, H-azaAr), 7.45–7.48 (2H, m, H-Ph), 7.52–7.55 (1H, m, H-Ph), 7.64–7.66 (1H, m, H-azaAr), 8.11–8.13 (1H, m, H-azaAr), 8.56 (2H, d, *J* 7.6, H-Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 26.0 (CO-C(CH_3)$_3$), 33.4 (CH_2-4), 37.3 (CH_2-1), 44.4 (*C*H-3), 49.2 (*C*H-2), 65.8 (C_{quat}), 115.7 (*C*H-azaAr), 120.0 (*C*H-azaAr), 122.6 (*C*H-azaAr), 125.3 (*C*H-azaAr), 125.7 (*C*H-Ar), 126.1 (*C*H-Ar), 128.1 (*C*H-Ar), 128.4 (*C*H-Ar), 128.6 (2×*C*H-Ph), 130.8 (2×*C*H-Ph), 131.6 (*C*-azaAr), 133.8 (*C*H-Ph), 135.4 (*C*-Ph), 139.0 (*C*-azaAr), 142.3 (*C*1-Ar), 144.3 (*C*6-Ar), 152.9 (N=*C*(C)-N), 167.4 (CH-*C*=ON), 196.5 (*C*=OPh), 212.7 (*C*=O^{t}Bu); *m/z* (NSI$^+$) 477 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{31}H_{28}N_2O_3$ [M+H]$^+$, found 477.2175, requires 477.2178 (–0.3 ppm).

12a-Benzoyl-12-(2-(4-methoxyphenyl)-2-oxoethyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (±243)



Following General Procedure 11, the corresponding TCP-ester (48.8 mg, 0.1 mmol), 2-phenacylbenzimidazole (35.5 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 – 70:30 Petroleum ether : EtOAc, R_f 0.15) afforded the title compound (42.1 mg, 80%) as a yellow solid. mp 61–62 °C; ν_{max} (film) 2930 (C-H), 1728 (C=O), 1667 (C=O), 1452 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.17 (1H, dd, *J* 16.5, 3.1, H–1a), 3.32 (1H, dd, *J* 16.5, 11.2, H–1b), 3.51 (1H, dd, *J* 18.3, 3.1, H–4a), 3.79 (1H, dd, *J* 18.4, 5.9, H–4b), 3.80 (3H, s, OCH_3), 4.73 (1H, dd, *J* 6.1, 3.3, H–3), 5.60 (1H, dd, *J* 11.2, 3.0, H–2), 6.84 (2H, d, *J* 8.8, H–Ar_{OMe}), 7.05–7.15 (2H, m, H-azaAr), 7.20–7.29 (4H, m, H–Ar), 7.44–7.47 (2H, m, H-Ph), 7.50–7.53 (1H, m, H-Ph), 7.65 (1H, dd, *J* 5.6, 3.4, H-azaAr), 7.76 (2H, d, *J* 8.8, H–Ar_{OMe}), 8.14 (1H, dd, *J* 6.1, 3.0, H-azaAr), 8.57 (2H, d, *J* 7.6, H-Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 33.3 (*C*H_2-4), 38.5 (*C*H_2-1), 44.3 (*C*H-3), 49.5 (*C*H-2), 55.5 (O*C*H_3), 65.8 (C_{quat}), 113.7 (*C*H-Ar_{OMe}), 115.6 (*C*H-aAr), 119.9 (*C*H-aAr), 122.4 (*C*H-Ar), 125.2 (*C*H-Ar), 125.6 (*C*H-azaAr), 126.2 (*C*H-azaAr), 127.9 (*C*H-Ar), 128.3 (*C*H-Ar), 128.5 (2×*C*H-Ph), 129.9 (*C*-Ar_{OMe}), 130.4 (*C*H-Ar_{OMe}), 130.7 (2×*C*H-Ph), 131.5 (*C*-aAr), 133.7 (*C*H-Ph), 135.1 (*C*-Ph), 138.9 (*C*-azaAr), 142.2 (*C*1-Ar), 143.8 (*C*6-Ar), 152.8 (N=*C*(C)-N), 163.6 (*C*-OMe), 167.3 (CH-*C*=ON), 195.3 (*C*=OAr_{OMe}), 196.3 (*C*=OPh); *m/z* (NSI$^+$) 549 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{34}H_{26}O_4N_2Na$ [M+Na]$^+$, found 549.1770, requires 549.1785 (–2.7 ppm).

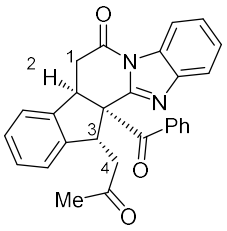
Methyl 2-(12a-benzoyl-6-oxo-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-12-yl)acetate (±244)



Following General Procedure 11, the corresponding TCP-ester (41.1 mg, 0.1 mmol), 2-phenacylbenzimidazole (35.5 mg, 0.15 mmol) and PS-BEMP (2.0 mmol/g loading, 75.0 mg) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (35.6 mg, 79%) as a yellow solid. mp 125–127 °C; ν_{max} (film) 2922 (C-H), 1732 (C=O), 1670 (C=O), 1445 (C_{Ar}-C_{Ar}); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.45–2.54 (1H, m, H–1a), 2.73 (1H, dd, *J* 15.3, 3.8, H–1b), 3.52–3.55 (1H, m, H–4a), 3.65 (3H, s, CO_2CH_3), 3.83 (1H, dd, *J* 18.4, 5.9, H–4b), 4.67–4.68 (1H, m, H–3), 5.39 (1H, dd, *J* 11.9, 3.8, H–2), 7.16–7.31 (6H, m, 4×H–Ar + 2× H-azaAr), 7.52–7.61 (3H, m, H-Ph), 7.67–7.69 (1H, m, H-azaAr), 8.15–8.17 (1H, m, H-azaAr), 8.67 (2H, d, *J* 7.9, H-Ph); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 33.2 (CH_2-4), 35.4 (CH_2-1), 44.0 (CH-3), 50.3 (CH-2), 51.9 (CO_2CH_3), 65.9 (C_{quat}), 115.8 (CH-aAr), 119.9 (CH-aAr), 122.8 (CH-Ar), 125.3 (CH-Ar), 125.6 (CH-azaAr), 125.8 (CH-azaAr), 128.5 (CH-Ar), 128.6 (CH-Ar), 128.6 (2×CH-Ph), 130.9 (2×CH-Ph), 131.6 (C-aAr), 133.9 (CH-Ph), 135.1 (C-Ph), 139.2 (C-azaAr), 142.2 (C1-Ar), 143.0 (C6-Ar), 152.7 (N=C(C)-N), 167.4 (CH-C=ON), 171.5 (CO_2CH_3), 195.7 (C=OPh); *m/z* (NSI$^+$) 451 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{28}H_{22}N_2O_4$ [M+H]$^+$, found 451.1660, requires 451.1658 (+0.4 ppm).

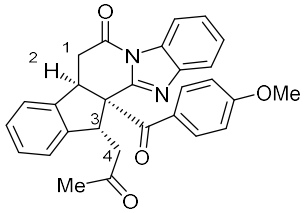
7.3.4.2 Data for enantioenriched indanes 229, 230, 240, 242, 243

(7a*R*,12*R*,12a*R*)-12a-Benzoyl-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-a]indeno[2,1-*c*]pyridin-6-one (229)



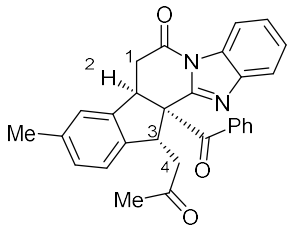
Following General Procedure 12, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-phenacylbenzimidazole (47.3 mg, 0.20 mmol) and $^{i}Pr_2NEt$ (34 μL, 0.20 mmol) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (26.1 mg, 60%) as a pink solid. The analytical data is in agreement with (±)-**54**. $[\alpha]_D^{20}$ −56.0 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak IA (97:3 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 14.8 min, t_R minor: 16.6 min, 88:12 er.

(7a*R*,12*R*,12a*R*)-12a-(4-Methoxybenzoyl)-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (230)



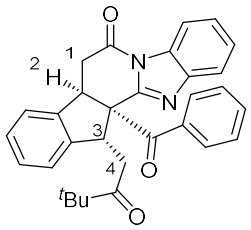
Following General Procedure 12, the corresponding TCP-ester (39.6 mg, 0.1 mmol), 2-(4-methoxy)phenacylbenzimidazole (53.2 mg, 0.20 mmol) and $^{i}Pr_2NEt$ (34 μL, 0.20 mmol) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 – 70:30 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (22.6 mg, 49%) as a pale pink solid. The analytical data is in agreement with (±)-**55**. $[\alpha]_D^{20}$ −16.0 (*c* 0.7, $CHCl_3$); Chiral HPLC analysis, Chiralpak IA (98:2 hexane : IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 29.8 min, t_R major: 34.0 min, 85:15 er (after single recryst. 99:1 er).

(7a*R*,12*R*,12a*R*)-12a-Benzoyl-9-methyl-12-(2-oxopropyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (240)



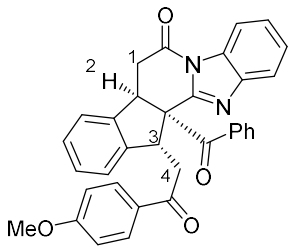
Following General Procedure 12, the corresponding TCP-ester (41.0 mg, 0.1 mmol), 2-phenacylbenzimidazole (47.3 mg, 0.20 mmol) and $^{i}Pr_2NEt$ (34 μL, 0.20 mmol) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (32.0 mg, 71%) as a yellow solid. The analytical data is in agreement with (±)-**65**. $[\alpha]_D^{20}$ −42.1 (*c* 0.9, $CHCl_3$); Chiral HPLC analysis, Chiralpak IA (97.5:2.5 hexane : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 19.5 min, t_R major: 20.8 min, 81:19 er.

(7a*R*,12*R*,12a*R*)-12a-Benzoyl-12-(3,3-dimethyl-2-oxobutyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (242)



Following General Procedure 12, the corresponding TCP-ester (43.8 mg, 0.1 mmol), 2-phenacylbenzimidazole (47.3 mg, 0.20 mmol) and $^{i}Pr_2NEt$ (34 μL, 0.20 mmol) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (90:10 Petroleum ether : EtOAc, R_f 0.2) afforded the title compound (29.6 mg, 62%) as a colorless solid. The analytical data is in agreement with (±)-**67**. $[\alpha]_D^{20}$ −74.3 (*c* 0.6, $CHCl_3$); Chiral HPLC analysis, Chiralpak IA (99:1 hexane : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 16.2 min, t_R minor: 19.8 min, 78:22 er.

(7a*R*,12*R*,12a*R*)-12a-Benzoyl-12-(2-(4-methoxyphenyl)-2-oxoethyl)-7,7a,12,12a-tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]indeno[2,1-*c*]pyridin-6-one (243)

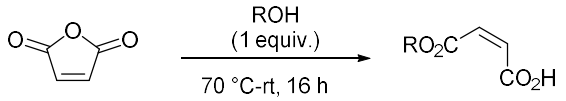


Following General Procedure 12, the corresponding TCP-ester (48.8 mg, 0.1 mmol), 2-phenacylbenzimidazole (47.3 mg, 0.20 mmol) and $^{i}Pr_2NEt$ (34 μL, 0.20 mmol) in CH_2Cl_2 (0.5 mL) and subsequent chromatography (80:20 – 70:30 Petroleum ether : EtOAc, R_f 0.15) afforded the title compound (30.0 mg, 57%) as a colorless solid. The analytical data is in agreement with (±)-**68**. $[\alpha]_D^{20}$ –42.1 (*c* 0.9, $CHCl_3$); Chiral HPLC analysis, Chiralpak IB (97:3 hexane : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 16.1 min, t_R major: 29.7 min, 85:15 er.

7.4 Experimental for Chapter 4

7.4.1 General procedures

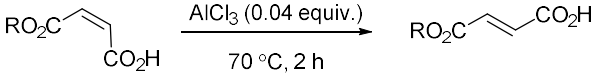
General Procedure 13: *Synthesis of cis-but-2-enedioic acid monoesters*



Maleic anhydride (1.02 equiv.) was melted in a sealed tube at 70 °C. The alcohol (1 equiv.) was added by syringe with stirring. The mixture was allowed to stir for 16 h at rt, then evaporated and the resulting solid dried under vacuum to give the corresponding acid without further purification.

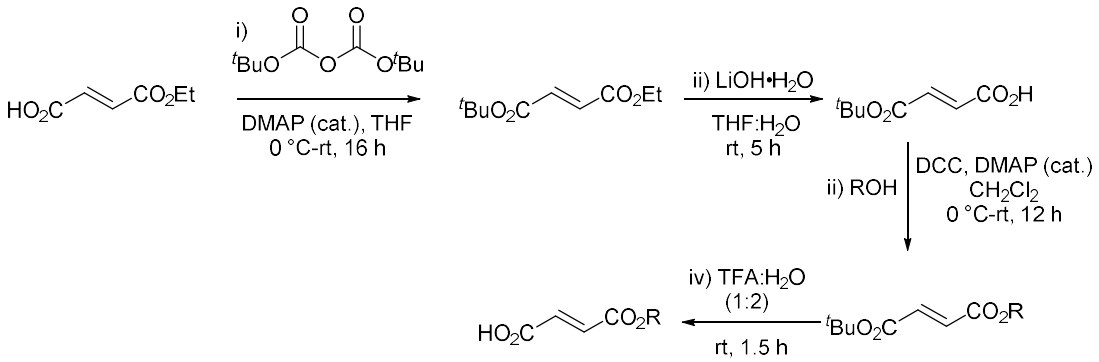
General Procedure 14: *Synthesis of trans-but-2-enedioic acid monoesters*

Method A: cis-trans isomerisation



Anhydrous $AlCl_3$ (0.04 equiv.) was added to the *cis*-but-2-enedioic acid monoester (1 equiv.) with stirring. The mixture was heated at 70 °C for 2 h. The cooled mixture was diluted with 1 M HCl and the aqueous phase extracted with ethyl acetate (3 × 40 mL). The organic extracts were collected, washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered and evaporated to give crude *trans*-but-2-enedioic acid monoester which was used without further purification.

Method B: Trans-esterification-hydrolysis



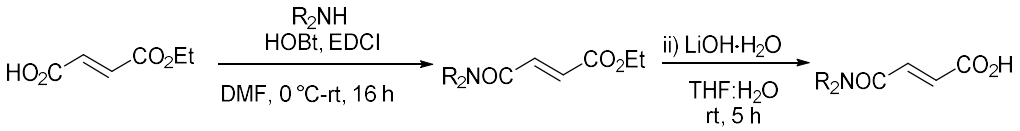
i) Di-*tert*-butyl dicarbonate (1.25 equiv.) and 4-(*N*,*N*-dimethylamino)pyridine (0.2 equiv.) were added to a stirred solution of monoethyl fumarate (1 equiv.) in THF (0.7 M) at 0 ºC. The reaction mixture was stirred for 14 h at rt, diluted with ethyl acetate and washed sequentially with 10% aqueous sulfuric acid, 10% aqueous NaOH and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford the corresponding ^{t}Bu-ester.

ii) $LiOH{\cdot}H_2O$ (1.1 equiv.) was added in small portions to a solution of ethyl ester (1 equiv.) in 1:1 THF:H_2O (1 M). The reaction mixture was stirred for 5 h at rt followed by acidic work up (2 M HCl, pH = 2) and extraction with CH_2Cl_2. The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the corresponding acid.

iii) The appropriate alcohol (1.02 equiv.) was added dropwise to a solution of the appropriate carboxylic acid (1 equiv.), DCC (1.1 equiv.) and DMAP (0.2 equiv.) in CH_2Cl_2 (1 M) at 0 °C. The reaction mixture was allowed to stir for 12 h at rt. The crude mixture was filtered to remove the by-product dicyclohexylurea and concentrated *in vacuo*. The residue was purified by flash silica column chromatography using a mixture of petroleum ether and EtOAc as eluent.

iv) The appropriate ester was dissolved in a mixture of TFA:CH_2Cl_2 (1:2, 0.75 M). The reaction was stirred at rt and monitored by TLC until completion. The crude mixture was concentrated *in vacuo* without further purification to give the corresponding carboxylic acid.

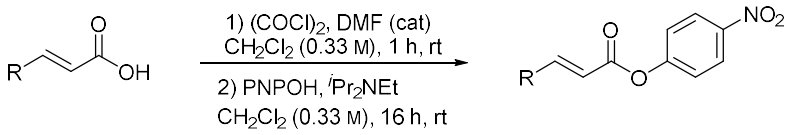
General Procedure 15: *Synthesis of trans-but-2-enedioic acid monoamides*



i) EDCI·HCl (1.1 equiv.) was added to a solution of monoethyl fumarate (1.1 equiv.), alcohol or amine (1 equiv.), and HOBt (1.1 equiv.) in DMF (1 M), and the mixture was allowed to stir for 16 h at rt. DMF was removed under vacuum and the residue was diluted with EtOAc. The organic layer was washed with 2% citric acid, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude mixture was purified by flash silica column chromatography using a mixture of petroleum ether and EtOAc as eluent.

ii) General Procedure 14, Method B, ii

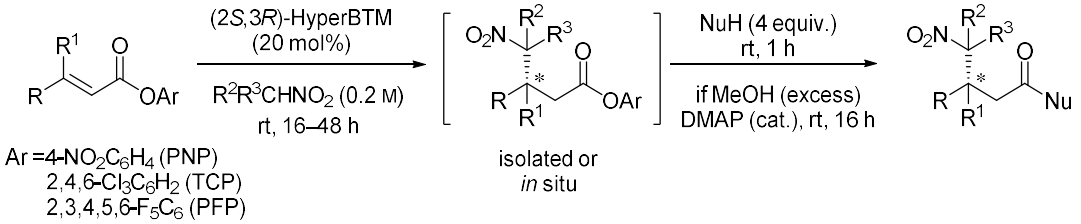
General Procedure 16: *Synthesis of aryl activated esters via acid chloride*



Oxalyl chloride (1 equiv.) and a few drops of *N*,*N*-dimethylformamide were added to a solution of the appropriate carboxylic acid (1 equiv.) in anhydrous CH_2Cl_2 (0.33 M) at rt under a nitrogen atmosphere, and stirred for 1 h. The resulting solution was added to a solution of

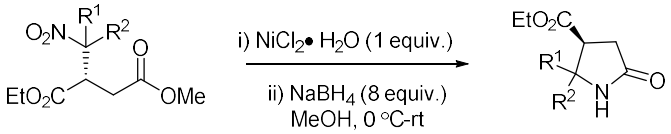
diisopropylethylamine (2 equiv.) and 4-nitrophenol (1 equiv.) in anhydrous CH_2Cl_2 (0.33 M) at rt, giving white fumes. The resulting solution was allowed to stir overnight at rt. The solvent was removed *in vacuo*, and the brown residue was suspended in Et_2O. The suspension was filtered, and the filtrate concentrated *in vacuo*. The residue was purified by flash silica column chromatography using a mixture of petroleum ether and EtOAc as eluent.

General Procedure 17: *Asymmetric Michael Addition with Nitro Alkyl Compounds*



The appropriate activated aryl ester (1 equiv.) and isothiourea HyperBTM (20 mol%) in a nitroalkane (0.2 M) were allowed to stir for 16-48 h at rt. For isolation of the aryl ester product, the reaction may be concentrated and purified by flash silica column chromatography. Alternatively, an appropriate nucleophile (4 equiv.) may be added and allowed to stir for a further 1 h at rt. In case of using MeOH (excess) as a nucleophile, DMAP was added (0.2 equiv.) and allowed to stir for 16 h at rt. The crude mixture was then concentrated *in vacuo*, and the residue purified by flash silica column chromatography using a mixture of petroleum ether and EtOAc as eluent.

General Procedure 18: *Synthesis of enantioenriched pyrrolidinones*

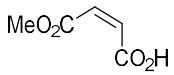


$NaBH_4$ (8 equiv.) was added to a suspension of the appropriate methyl ester (1 equiv.) and $NiCl_2 \cdot 6H_2O$ (1 equiv.) in MeOH (0.05 M) at 0 °C under a nitrogen atmosphere, and then allowed to stir for 16 h at room temperature. Saturated aqueous NH_4Cl and CH_2Cl_2 were added and the organic layer separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash silica column chromatography (2-10% MeOH/CH_2Cl_2) to afford the desired product.

7.4.2 Preparation of starting materials

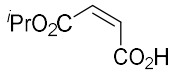
7.4.2.1 Data for *cis*-but-2-enedioic acid monoesters

(*Z*)-4-Methoxy-4-oxobut-2-enoic acid (S11)



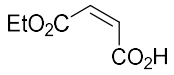
Following General Procedure 13, maleic anhydride (1.0 g, 10.2 mmol) and methanol (0.4 mL, 10 mmol) afforded the title compound (1.30 g, quant.) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.67 (3H, s, CH_3), 6.38 (1H, d, *J* 11.9, C*H*=CH), 6.39 (1H, d, *J* 11.9, CH=C*H*). Data in agreement with the literature.[11]

(*Z*)-4-Isopropoxy-4-oxobut-2-enoic acid (S12)



Following General Procedure 13, maleic anhydride (1.0 g, 10.2 mmol) and 2-propanol (0.77 mL, 10 mmol) afforded the title compound (1.45 g, 92%) as a colorless oil; ν_{max} (film) 2986 (br COOH), 1715 (C=O) 1643 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.35 (6H, d, *J* 6.2, CH(CH_3)$_2$), 5.18 (1H, sept., *J* 6.2, C*H*(CH_3)$_2$), 6.34 (1H, d, *J* 12.8, C*H*=CH), 6.46 (1H, d, *J* 12.8, C*H*=CH). Data in agreement with the literature.[11]

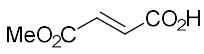
(*Z*)-4-Ethoxyoxy-4-oxobut-2-enoic acid (S13)



Following General Procedure 13, maleic anhydride (1.0 g, 10.2 mmol) and ethanol (0.58 mL, 10 mmol) afforded the title compound (1.44 g, quant.) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.37 (3H, t, *J* 7.1, CH_2CH_3), 4.36 (2H, q, *J* 7.1, C$H_2$$CH_3$), 6.38 (1H, d, *J* 12.8, C*H*=CH), 6.47 (1H, d, *J* 12.8, C*H*=CH). Data in agreement with the literature.[12]

7.4.2.2 Data for *trans*-but-2-enedioic acid monoesters

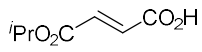
(*E*)-4-Methoxy-4-oxobut-2-enoic acid (S14)



Following General Procedure 14 (Method A), (*Z*)-4-methoxy-4-oxobut-2-enoic acid (1.3 g, 10.0 mmol) and $AlCl_3$ (53 mg, 0.4 mmol) afforded the title compound (1.03 g, 79%) as a colourless solid. mp 140–141 °C {Lit[12] 144–145 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.67 (3H, s, CH_3),

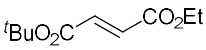
6.38 (1H, d, *J* 11.9, C*H*=CH), 6.39 (1H, d, *J* 11.9, CH=C*H*). Data in agreement with the literature.[12]

(*E*)-4-Isopropoxy-4-oxobut-2-enoic acid (S15)



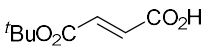
Following General Procedure 14 (Method A), (*Z*)-4-isopropoxy-4-oxobut-2-enoic acid (1.1 g, 7.0 mmol) and $AlCl_3$ (36 mg, 0.27 mmol) afforded the title compound (0.89 g, 81%) as a colourless solid. mp 49–51 °C {Lit[13] 48 °C}; ν_{max} (film) 2984 (br COOH), 1705 (C=O) 1645 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.30 (6H, d, *J* 6.2, CH(C*H*$_3$)$_2$), 5.12 (1H, sept, *J* 6.2, C*H*(CH$_3$)$_2$), 6.83 (1H, d, *J* 15.8, C*H*=CH), 6.92 (1H, d, *J* 15.8, C*H*=CH). Data in agreement with the literature.[11]

***tert*-Butyl ethyl fumarate (S16)**



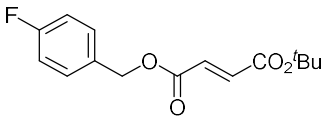
Following General Procedure 14 (Method B, i), monoethyl fumarate (2.88 g, 20 mmol), di-*tert*-butyl dicarbonate (5.44 g, 25 mmol), 4-(*N*,*N*-dimethylamino)pyridine (488 mg, 4 mmol) and THF (30 mL) afforded the title compound as a brown oil (3.98 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.31 (3H, t, *J* 7.1, CH_2CH_3), 1.50 (9H, s, C(CH$_3$)$_3$), 4.25 (2H, q, *J* 7.1, CH_2CH_3), 6.74 (1H, d, *J* 15.7, CH=C*H*–CO_2Et), 6.78 (1H, d, *J* 15.7, C*H*=CH-CO_2Et). Data in agreement with the literature.[14]

(*E*)-But-2-enedioic acid mono-*tert*-butyl ester (S17)



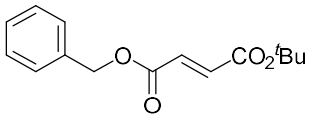
Following General Procedure 14 (Method B, ii), ethyl ester *tert*-butyl ethyl fumarate (3.97 g, 19.8 mmol) and LiOH·H_2O (0.92 g, 21.8 mmol) afforded the title compound (3.0 g, 88%) as a brown solid. mp 76–77 °C {Lit.[5] 79 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.51 (9H, s, C(CH$_3$)$_3$), 6.75 (1H, d, *J* 15.8, CH=C*H*–CO_2H), 6.86 (1H, d, *J* 15.8, C*H*=CH-CO_2H). Data in agreement with the literature.[15]

tert-Butyl (4-fluorobenzyl) fumarate (S18)



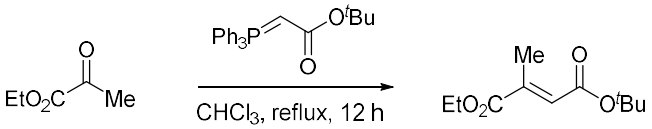
Following General Procedure 14 (Method B, iii), (*E*)-but-2-enedioic acid mono-*tert*-butyl ester (1.72 g, 10 mmol), DCC (2.27 g, 11 mmol), 4-(*N*,*N*-dimethlyamino)pyridine (244 mg, 2 mmol), 4-fluorobenzyl alcohol (1.30 g, 10.4 mmol) and CH_2Cl_2 (10 mL) gave, after flash silica column chromatography (90:10 Petroleum ether : EtOAc, R_f 0.23), the title compound (1.91 g, 68%) as a colourless oil; ν_{max} (film) 2982 (C-H), 1715 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.49 (9H, s, $C(CH_3)_3$), 5.19 (2H, s, CH_2Ar_F), 6.78 (1H, d, *J* 15.9, CH=C*H*–$CO_2{}^t$Bu), 6.81 (1H, d, *J* 15.9, C*H*=CH-$CO_2{}^t$Bu), 7.04–7.07 (2H, m, $CH_{Ar\text{-}F}$), 7.34–7.37 (2H, m, $CH_{Ar\text{-}F}$); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −113.2; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.1 ($C(CH_3)_3$), 66.4 (CH_2Ar_F), 82.2 ($C(CH_3)_3$), 115.8 (d, $^2J_{CF}$ = 20.3, CH_{Ar}-F), 130.5 (d, $^3J_{CF}$ = 8.4, CH_{Ar}-F), 131.3 (d, $^4J_{CF}$ = 3.0, CH_{Ar}-F), 132.3 (CH=*C*H–$CO_2{}^t$Bu), 136.4 (*C*H=CH–$CO_2{}^t$Bu), 163.0 (d, $^1J_{CF}$ = 246.6, CH_{Ar}-F), 164.1 (CO_2Ar_F), 165.1 ($CO_2{}^t$Bu); *m/z* (NSI^+) 298 ($[M+NH_4]^+$, 75%); HRMS (NSI^+) $C_{15}H_{21}O_4N_1F_1$ $[M+NH_4]^+$, found 298.1453, requires 298.1449 (+1.3 ppm).

tert-Butyl benzyl fumarate (S19)



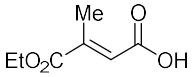
Following General Procedure 14 (Method B, iii), (*E*)-but-2-enedioic acid mono-*tert*-butyl ester (861 mg, 5 mmol), DCC (1.13 g, 5.5 mmol), 4-(*N*,*N*-dimethlyamino)pyridine (122 mg, 1 mmol), benzyl alcohol (0.53 mL, 5.1 mmol) and CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether : EtOAc, R_f 0.23) the title compound (774 mg, 59%) as colorless oil; ν_{max} (film) 2982, 2934 (C-H), 1715 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.49 (9H, s, $C(CH_3)_3$), 5.23 (2H, s, CH_2Ph), 6.78 (1H, d, *J* 15.8, CH=C*H*–$CO_2{}^t$Bu), 6.82 (1H, d, *J* 15.8, C*H*=CH-$CO_2{}^t$Bu), 7.31–7.42 (5H, m, CH_{Ph}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.1 ($C(CH_3)_3$), 67.1 (CH_2Ph), 82.1 ($C(CH_3)_3$), 128.5 (2×CH_{Ph}), 128.6 (CH_{Ph}), 128.8 (2×CH_{Ph}), 132.4 (CH=*C*H–$CO_2{}^t$Bu), 135.5 (*C*-Ph), 136.2 (*C*H=CH–$CO_2{}^t$Bu), 164.2 (CO_2Bn), 165.2 ($CO_2{}^t$Bu); *m/z* (NSI^+) 280 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{15}H_{22}O_4N$ $[M+NH_4]^+$, found 280.1547, requires 280.1543 (+1.3 ppm).

4-(*tert*-Butyl) 1-ethyl 2-methylfumarate (S20)



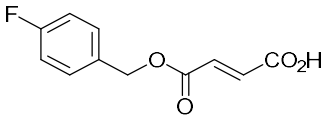
To a solution of ethyl 2-oxopropanoate (0.56 mL, 5 mmol, 1 equiv.) in $CHCl_3$ (10 mL) was added *tert*-butyl 2-(triphenyl-γ^5-phosphaneylidene)acetate (2.82 g, 7.5 mmol, 1.5 equiv.). The reaction mixture was heated under reflux overnight under Ar and then concentrated *in vacuo*. The residue was purified by flash silica column chromatography (95:5 – 90:10 Petroleum ether : EtOAc, R_f 0.20) to give the title compound (0.7 g, 65%) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.31 (3H, t, *J* 7.1, CH_2CH_3), 1.49 (9H, s, $C(CH_3)_3$), 2.24 (3H, d, , *J* 1.5, CH_3), 4.23 (2H, q, *J* 7.1, CH_2CH_3), 6.70 (1H, m, C=C*H*–CO_2*t*Bu). Data in agreement with the literature.[16]

(*E*)-4-Ethoxy-3-methyl-4-oxobut-2-enoic acid (S21)



Following General Procedure 14 (Method B, iv), 4-(*tert*-butyl) 1-ethyl 2-methylfumarate (0.7 g, 3.3 mmol) and TFA (4.3 mL, 0.75 M) in CH_2Cl_2 (9 mL) afforded the title compound (0.52 g, quant.) as a white solid. mp 73–75 °C {Lit[17] 68 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.1, CH_2CH_3), 2.32 (3H, d, , *J* 1.6, CH_3), 4.27 (2H, q, *J* 7.1, CH_2CH_3), 6.81 (1H, m, C=C*H*–CO_2OH). Data in agreement with the literature.[18]

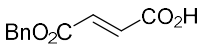
(*E*)-4-((4-Fluorobenzyl)oxy)-4-oxobut-2-enoic acid (365)



Following General Procedure 14 (Method B, iv), *tert*-butyl (4-fluorobenzyl) fumarate (1.91 g, 6.8 mmol) and TFA (9 mL, 0.75 M) in CH_2Cl_2 (18 mL) afforded the title compound (1.2 g, 95%) as a colourless solid. mp 134–135 °C; ν_{max} (film) 3071 (COOH, br), 1719 (C=O), 1695 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.21 (2H, s, CH_2Ar_F), 6.87 (1H, d, *J* 15.8, CH=C*H*–CO_2H), 6.96 (1H, d, *J* 15.8, C*H*=CH-CO_2H), 7.05–7.09 (2H, m, $CH_{Ar\text{-}F}$), 7.35–7.38 (2H, m, $CH_{Ar\text{-}F}$); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: –112.9; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 66.7 (CH_2Ar_F), 115.8 (d, $^2J_{CF}$ = 21.6, CH_{Ar}-F), 130.7 (d, $^3J_{CF}$ = 8.4, CH_{Ar}-F), 131.1 (d, $^4J_{CF}$ = 3.5, CH_{Ar}-F), 133.1 (CH=*C*H–CO_2H), 135.5 (*C*H=CH–CO_2H), 163.0 (d, $^1J_{CF}$ = 243.8, CH_{Ar}-F), 164.1 (CO_2Ar_F), 169.3 (CO_2H);

m/z (NSI$^-$) 223 [M–H]$^-$, 100%); HRMS (NSI$^+$) $C_{11}H_8O_4F$ [M–H]$^-$, found 223.0410, requires 223.0412 (–0.9 ppm).

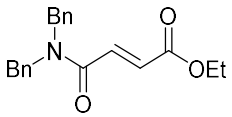
(*E*)-4-(Benzyloxy)-4-oxobut-2-enoic acid (S22)



Following General Procedure 14 (Method B, iv), *tert*-butyl (4-benzyl) fumarate (774 mg, 2.95 mmol) and TFA (3.9 mL, 0.75 M) in CH_2Cl_2 (8 mL) afforded the title compound (508 mg, quant.) as a colourless solid. mp 99–101 °C {Lit[19] 144–145 °C}; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 5.16 (2H, s, C*H*$_2$Ph-*cis*), 5.23 (2H, s, C*H*$_2$Ph-*trans*), 6.44 (1H, d, *J* 12.0, CH=C*H*–CO$_2$H), 6.40 (1H, d, *J* 12.0, C*H*=CH-CO$_2$H), 6.74 (2H, s, acrylic-*H*), 7.32–7.43 (5H, m, C*H*$_{Ph}$). Data in agreement with the literature.[20]

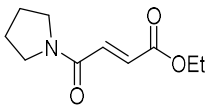
7.4.2.3 Data for *trans*-but-2-enedioic acid monoamides

Ethyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate (S23)



Following General Procedure 15 (i), dibenzylamine (1.92 mL, 10 mmol), HOBt (1.68 g, 11 mmol), monoethyl fumarate (1.59 g, 11 mmol), EDCI·HCl (2.10 g, 11 mmol) in THF (14 mL) afforded after SiO_2-chromatography (90:10 – 80:20 Petroleum ether : EtOAc, R_f 0.23) the title compound (2.66 g, 82%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.1, CH$_2$C*H*$_3$), 4.23 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 4.53 (2H, s, C*H*$_2$Ph), 4.65 (2H, s, C*H*$_2$Ph), 6.94 (1H, d, *J* 15.3, CH=C*H*–CO$_2$Et), 7.15–7.17 (2H, m, C*H*-Ph), 7.23–7.25 (2H, m, C*H*-Ph), 7.29–7.39 (6H, m, C*H*-Ph), 7.44 (1H, d, *J* 15.3, C*H*=CH-CO$_2$Et). Data in agreement with the literature.[21]

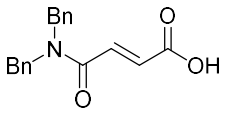
Ethyl (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoate (S24)



Following General Procedure 15 (i), pyrrolidine (0.82 mL, 10 mmol), HOBt (1.68 g, 11 mmol), monoethyl fumarate (1.59 g, 11 mmol), EDCI·HCl (2.10 g, 11 mmol) in THF (14 mL) afforded after SiO_2-chromatography (90:10 – 80:20 Petroleum ether : EtOAc, R_f 0.21) the title compound (971 mg, 49%) as a colourless oil; ν_{max} (film) 2980, 2880 (C-H), 1717, 1651 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.2, CH$_2$C*H*$_3$), 1.87–1.92 (2H, m, C*H*$_{2(pyrr)}$), 1.95–2.00 (2H, m, C*H*$_{2(pyrr)}$), 3.53–3.59 (4H, m, C*H*$_{2(pyrr)}$), 4.23 (2H, q, *J* 7.2, C*H*$_2$CH$_3$), 6.83 (1H, d, *J* 15.3,

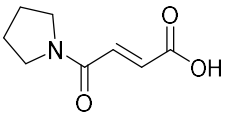
CH=C*H*–CO_2Et), 7.22 (1H, d, *J* 15.3, C*H*=CH-CO_2Et); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (CH_2CH_3), 24.3 (CH_{2pyrr}), 26.2 (CH_{2pyrr}), 46.3 (CH_{2pyrr}), 46.9 (CH_{2pyrr}), 61.2 (CH_2CH_3), 131.0 (CH=*C*H–CO_2Et), 134.6 (*C*H=CH–CO_2Et), 162.7 (*C*O_2Et), 166.0 (*C*ON); *m/z* (NSI^+) 220 ($[M+Na]^+$, 100%); HRMS (NSI^+) $C_{10}H_{16}O_3N_1$ $[M+H]^+$, found 198.1126, requires 198.1125 (+0.7 ppm).

(*E*)-4-(Dibenzylamino)-4-oxobut-2-enoic acid (S25)



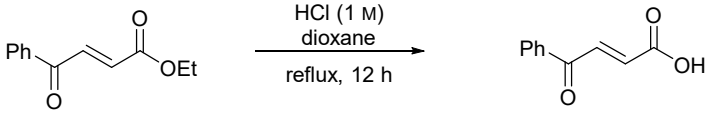
Following General Procedure 15 (ii), ethyl ester ethyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate (2.66 g, 8.2 mmol) and LiOH·H_2O (380 mg, 9.1 mmol) in THF (4 mL) and H_2O (4 mL) afforded the title compound (2.08 g, 86%) as a colourless solid. mp 172–174 °C {Lit[22] 174 °C}; ^1H NMR (500 MHz, DMSO-d_6) δ_H: 4.59 (2H, s, CH_2Ph), 4.67 (2H, s, CH_2Ph), 6.64 (1H, d, *J* 15.2, CH=C*H*–CO_2H), 7.17–7.19 (2H, m, C*H*-Ph), 7.26–7.38 (7H, m, 8×C*H*-Ph, C*H*=CH-CO_2H). Data in agreement with the literature.[23]

(*E*)-4-Oxo-4-(pyrrolidin-1-yl)but-2-enoic acid (S26)



Following General Procedure 3 (ii), ethyl (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoate (971 mg, 4.9 mmol) and LiOH·H_2O (227 mg, 5.4 mmol) in THF (2.5 mL) and H_2O (2.5 mL) afforded the title compound (348 mg, 42%) as a colourless solid. mp 152–154 °C; ν_{max} (film) 2974 (COOH, br), 1717 (C=O), 1661 (C=O); ^1H NMR (500 MHz, DMSO-d_6) δ_H: 1.77–1.82 (2H, m, C$H_{2(pyrr)}$), 1.86–1.92 (2H, m, C$H_{2(pyrr)}$), 3.37 (2H, t, *J* 6.8, C$H_{2(pyrr)}$), 3.57 (2H, t, *J* 6.8, C$H_{2(pyrr)}$), 6.52 (1H, d, *J* 15.3, CH=C*H*–CO_2H), 7.17 (1H, d, *J* 15.3, C*H*=CH-CO_2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 23.8 (CH_{2pyrr}), 25.6 (CH_{2pyrr}), 45.9 (CH_{2pyrr}), 46.2 (CH_{2pyrr}), 130.5 (CH=*C*H–CO_2H), 135.0 (*C*H=CH–CO_2H), 161.7 (*C*O_2H), 166.5 (*C*ON); *m/z* (NSI^-) 168 ($[M–Na]^-$, 100%); HRMS (NSI^+) $C_8H_{10}O_3N_1$ $[M–H]^–$, found 168.0667, requires 168.0666 (+0.5 ppm).

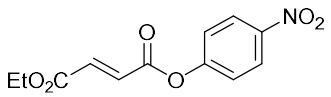
(*E*)-4-Oxo-4-(pyrrolidin-1-yl)but-2-enoic acid (S27)



To a solution of ethyl ethyl (*E*)-4-oxo-4-phenylbut-2-enoate (0.91 mL, 5 mmol) in dioxane (20 mL) 1 M HCl was added (10 mL). The reaction mixture was heated under reflux for 12 h. The crude mixture was extracted with EtOAc (3×). Combined organic layers were washed with brine and dried over $MgSO_4$. The mixture was filtered, concentrated, and dried *in vacuo* to afford the title compound (863 mg, 98%) as a yellow solid. mp 95–97 °C {Lit[24] 93–95 °C}; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 6.68 (1H, d, *J* 15.6, CH=C*H*–CO_2H), 7.49–7.58 (2H, C*H*-Ph), 7.69–7.74 (1H, C*H*-Ph), 7.88 (1H, d, *J* 15.6, C*H*=CH-CO_2H), 8.02–8.04 (2H, C*H*-Ph). Data in agreement with the literature.[25]

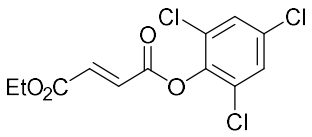
7.4.2.4 Data for aryl esters

Ethyl (4-nitrophenyl) fumarate (283)



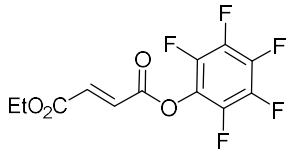
Following General Procedure 14 (Method B, iii), (*E*)-4-ethoxy-4-oxobut-2-enoic acid (2.88 g, 20.0 mmol), DCC (4.54 g, 22.0 mmol), 4-nitrophenol (PNPOH) (2.84 g, 20.4 mmol) and DMAP (488 mg, 4.0 mmol) in CH_2Cl_2 (20 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether : EtOAc, R_f 0.23) the title compound (3.91 g, 74%) as a yellow solid. mp 67–68 °C; ν_{max} (film) 2986 (C-H), 1749 (C=O) 1724 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.36 (3H, t, *J* 7.1, CH_2CH_3), 4.32 (2H, q, *J* 7.1, CH_2CH_3), 7.04 (1H, d, *J* 15.8, CH=C*H*–CO_2PNP), 7.09 (1H, d, *J* 15.8, C*H*=CH-CO_2PNP), 7.31–7.43 (2H, m, C*H*-Ar_{PNP}), 8.11–8.56 (2H, m, C*H*-Ar_{PNP}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (CH_2CH_3), 61.9 (CH_2CH_3), 122.4 (2×CH-Ar_{PNP}), 125.5 (2×CH-Ar_{PNP}), 131.8 (CH=CHCO$_2$PNP), 136.7 (CO_2Et-CH=CH), 145.7 (C-NO_2), 155.0 (CO_2C-Ar_{PNP}), 162.6 (CO_2PNP), 164.5 (CO_2Et); *m/z* (NSI$^+$) 266 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{12}H_{12}N_1O_6$ [M+H]$^+$, found 266.0655, requires 266.0659 (–1.6 ppm).

Ethyl (2,4,6-trichlorophenyl) fumarate (306)



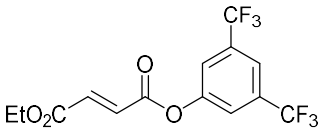
Following General Procedure 14 (Method B, iii), (*E*)-4-ethoxy-4-oxobut-2-enoic acid (360 mg, 2.5 mmol), DCC (567 mg, 2.75 mmol), 2,4,6-trichlorophenol (TCP-OH) (503 mg, 2.55 mmol) and DMAP (61 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether : EtOAc, R_f 0.20) the title compound (678 mg, 84%) as a yellow oil; ν_{max} (film) 2986 (C-H), 1749 (C=O) 1724 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.35 (3H, t, *J* 7.1, CH_2CH_3), 4.31 (2H, q, *J* 7.1, CH_2CH_3), 7.12 (1H, d, *J* 15.4, CH=C*H*–CO_2TCP), 7.08 (1H, d, *J* 15.4, C*H*=CH-CO_2TCP), 7.40 (2H, s, C*H*-Ar_{TCP}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (CH_2CH_3), 61.9 (CH_2CH_3), 128.8 (2×*C*H-Ar_{TCP}), 129.6 (*C*-Ar_{TCP}), 130.9 (CH=*C*HCO_2TCP), 132.6 (*C*-Ar_{TCP}), 137.0 (CO_2TCP-*C*H=CH), 142.6 (CO_2*C*-Ar_{TCP}), 161.3 (*C*O_2TCP), 164.5 (*C*O_2Et); *m/z* (NSI$^+$) 322 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{12}H_{10}{}^{35}Cl_3O_4$ [M+H]$^+$, found 322.09638, requires 322.9639 (–0.4 ppm).

Ethyl (perfluorophenyl) fumarate (307)



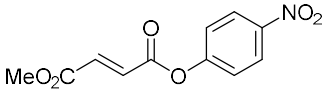
Following General Procedure 14 (Method B, iii), (*E*)-4-ethoxy-4-oxobut-2-enoic acid (360 mg, 2.5 mmol), DCC (567 mg, 2.75 mmol), pentafluorophenol (PFP-OH) (469 mg, 2.55 mmol) and DMAP (61 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) afforded after SiO_2-chromatography (97:3 – 90:10 Petroleum ether: EtOAc, R_f 0.21) the title compound (673 g, 87%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.35 (3H, t, *J* 7.1, CH_2CH_3), 4.32 (2H, q, *J* 7.1, CH_2CH_3), 7.06 (1H, d, *J* 15.8, CH=C*H*–CO_2PFP), 7.12 (1H, d, *J* 15.8, C*H*=CH-CO_2PFP). Data in agreement with the literature.[20]

3,5-Bis(trifluoromethyl)phenyl ethyl fumarate (308)



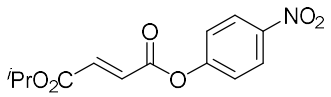
Following General Procedure 14 (Method B, iii), (*E*)-4-ethoxy-4-oxobut-2-enoic acid (288 mg, 2.0 mmol), DCC (454 mg, 2.2 mmol), 3,5-bis(trifluoromethyl)phenol (0.31 mL, 2.02 mmol) and DMAP (49 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) afforded after SiO_2-chromatography (95:5 – 90:10 Petroleum ether: EtOAc, R_f 0.3) the title compound (490 g, 69%) as a colourless oil; ν_{max} (film) 2988 (C-H), 1755 (C=O) 1724 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.36 (3H, t, *J* 7.1, CH_2CH_3), 4.32 (2H, q, *J* 7.1, CH_2CH_3), 7.04 (1H, d, *J* 15.8, CH=C*H*–CO_2Ar_{CF3}), 7.09 (1H, d, *J* 15.8, C*H*=CH-CO_2Ar_{CF3}), 7.67 (2H, s, C*H*-Ar_{CF3}), 7.80 (1H, s, C*H*-Ar_{CF3}); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −63.0; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (CH_2CH_3), 62.0 (CH_2CH_3), 120.3 (sept., $^3J_{CF}$ = 3.4, CH_{Ar}-CF_3), 122.4 (q, $^3J_{CF}$ = 2.9, 2×CH-Ar_{CF3}), 122.8 (q, $^1J_{CF}$ = 273.0, CF_3), 131.5 (CH=*C*HCO_2Ar_{CF3}), 133.3 (q, $^2J_{CF}$ = 34.1, C_{Ar}-CF_3), 136.9 (CO_2Ar_{CF3}-*C*H=CH), 150.8 (CO_2C-Ar_{CF3}), 162.7 (CO_2Ar_{CF3}), 164.4 (CO_2Et); *m/z* (NSI$^+$) 357 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{14}H_{11}F_6O_4$ [M+H]$^+$, found 357.0551, requires 357.0556 (–1.3 ppm).

Methyl (4-nitrophenyl) fumarate (S28)



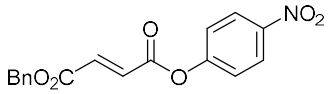
Following General Procedure 16, (*E*)-4-methoxy-4-oxobut-2-enoic (1.03 g, 7.90 mmol), oxalyl chloride (0.69 mL, 7.90 mmol), diisopropylethylamine (2.75 mL, 15.8 mmol) and 4-nitrophenol (PNPOH) (1.10 g, 7.90 mmol) in CH_2Cl_2 (25 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether: EtOAc, R_f 0.20) the title compound (1.43 g, 72%) as a yellow solid. mp 97–99 °C; ν_{max} (film) 2926 (C-H), 1732 (C=O) 1669 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.86 (3H, s, CO_2CH_3), 7.06 (1H, d, *J* 15.8, CH=C*H*–CO_2PNP), 7.07 (1H, d, *J* 15.8, C*H*=CH-CO_2PNP), 7.35–7.37 (2H, m, C*H*-Ar_{PNP}), 8.29–8.31 (2H, m, C*H*-Ar_{PNP}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 52.8 (CO_2CH_3), 122.4 (2×*C*H-Ar_{PNP}), 125.5 (2×*C*H-Ar_{PNP}), 132.1 (CH=*C*H–CO_2PNP), 136.2 (*C*H=CH–CO_2PNP), 145.7 (*C*-NO_2), 154.9 (CO_2C-Ar_{PNP}), 162.5 (CO_2PNP), 164.9 (CO_2Me); *m/z* (NSI$^+$) 252 ([M+H]$^+$, 20%); HRMS (NSI$^+$) $C_{11}H_{10}NO_6$ [M+H]$^+$, found 252.0509, requires 252.0503 (+2.4 ppm).

Isopropyl (4-nitrophenyl) fumarate (S29)



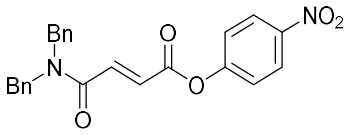
Following General Procedure 16, (*E*)-4-isopropoxy-4-oxobut-2-enoic acid (0.91 g, 5.70 mmol), oxalyl chloride (0.49 mL, 5.70 mmol), diisopropylethylamine (1.98 mL, 15.8 mmol) and 4-nitrophenol (PNPOH) (0.79 g, 5.7 mmol) afforded after SiO_2-chromatography (90:10 Petroleum ether: EtOAc, R_f 0.20) the title compound (1.25 g, 79%) as a yellow solid. mp 72–73 °C; ν_{max} (film) 2986 (C-H), 1749 (C=O) 1721 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.33 (6H, d, *J* 6.2, CH(CH_3)$_2$), 5.16 (1H, sept, *J* 6.2, C*H*(CH$_3$)$_2$), 7.02 (1H, d, *J* 15.8, CH=C*H*–CO$_2$PNP), 7.07 (1H, d, *J* 15.8, C*H*=CH-CO$_2$PNP), 7.35–7.37 (2H, m, C*H*-Ar$_{PNP}$), 8.30–8.32 (2H, m, C*H*-Ar$_{PNP}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.9 (CO$_2$CH(*C*H$_3$)$_2$), 69.7 (CO$_2$*C*H(CH$_3$)$_2$), 122.4 (2×*C*H-Ar$_{PNP}$), 125.5 (2×*C*H-Ar$_{PNP}$), 131.6 (CH=*C*HCO$_2$PNP), 137.3 (CO$_2$^{i}Pr-*C*H=CH), 145.7 (*C*-NO$_2$), 155.0 (CO$_2$*C*-Ar$_{PNP}$), 162.7 (*C*O$_2$PNP), 164.0 (*C*O$_2$^{i}Pr); *m/z* (NSI$^+$) 302 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{13}H_{13}O_6N_1Na$ [M+Na]$^+$, found 302.0633, requires 302.0635 (–0.7 ppm).

Benzyl (4-nitrophenyl) fumarate (S30)



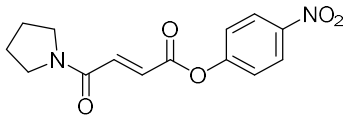
Following General Procedure 14 (Method B, iii), (*E*)-4-(benzyloxy)-4-oxobut-2-enoic acid (645 mg, 3.13 mmol), DCC (710 g, 3.44 mmol), 4-nitrophenol (PNP-OH) (440 mg, 3.16 mmol) and DMAP (76 mg, 0.63 mmol) in CH_2Cl_2 (3 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether: EtOAc, R_f 0.20) the title compound (607 g, 59%) as a white solid. mp 74–76 °C; ν_{max} (film) 3078 (C-H), 1738 (C=O) 1717 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.29 (2H, s, CH_2Ph), 7.07 (1H, d, *J* 15.8, CH=C*H*–CO$_2$PNP), 7.12 (1H, d, *J* 15.8, C*H*=CH-CO$_2$PNP), 7.34–7.36 (2H, m, C*H*-Ar$_{PNP}$), 7.35–7.41 (5H, m, CH_{Bn}), 8.29–8.31 (2H, m, C*H*-Ar$_{PNP}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 67.7 (*C*H$_2$Ph), 122.4 (2×*C*H-Ar$_{PNP}$), 125.5 (2×*C*H-Ar$_{PNP}$), 128.6 (2×*C*H$_{Bn}$), 128.8 (*C*H$_{Bn}$), 128.9 (2×*C*H$_{Bn}$), 132.3 (CH=*C*H–CO$_2$PNP), 135.1 (*C*-Ph), 136.3 (*C*H=CH–CO$_2$PNP), 145.8 (*C*-NO$_2$), 154.9 (CO$_2$*C*-Ar$_{PNP}$), 162.5 (*C*O$_2$PNP), 164.3 (*C*O$_2$Bn); *m/z* (NSI$^+$) 328 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{17}H_{14}O_6N$ [M+H]$^+$, found 328.0811, requires 328.0816 (–1.5 ppm).

4-Nitrophenyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate (S31)



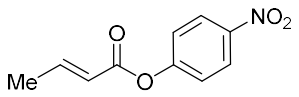
Following General Procedure 14 (Method B, iii), (*E*)-4-(dibenzylamino)-4-oxobut-2-enoic acid (2.08 g, 7.04 mmol), DCC (1.74 g, 8.44 mmol), 4-nitrophenol (PNPOH) (1.00 g, 7.18 mmol) and DMAP (172 mg, 1.41 mmol) in CH_2Cl_2 (7 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether: EtOAc, R_f 0.25) the title compound (2.19 g, 75%) as a yellow solid. mp 62–64 °C; ν_{max} (film) 2756 (C-H), 1748 (C=O) 1653 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.58 (2H, s, CH_2Ph), 4.69 (2H, s, CH_2Ph), 7.14 (1H, d, *J* 15.3, CH=C*H*–CO_2PNP), 7.16–7.19 (2H, m, CH_{Bn}), 7.26–7.27 (2H, m, CH_{Bn}), 7.31–7.33 (2H, m, C*H*-Ar_{PNP}), 7.34–7.40 (6H, m, CH_{Bn}), 7.64 (1H, d, *J* 15.3, C*H*=CH-CO_2PNP), 8.28–8.29 (2H, m, C*H*-Ar_{PNP}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 48.9 (*C*H_2Ph), 50.4 (*C*H_2Ph), 122.5 (2×*C*H-Ar_{PNP}), 125.4 (2×*C*H-Ar_{PNP}), 126.7 (2×*C*H_{Bn}), 128.0 (*C*H_{Bn}), 128.3 (*C*H_{Bn}), 128.6 (2×*C*H_{Bn}), 129.0 (2×*C*H_{Bn}), 129.3 (2×*C*H_{Bn}), 130.6 (CH=*C*H–CO_2PNP), 135.7 (*C*-Ph), 136.3 (*C*-Ph), 136.9 (*C*H=CH–CO_2PNP), 145.7 (*C*-NO_2), 155.1 (CO_2*C*-Ar_{PNP}), 163.2 (*C*O_2PNP), 164.9 (*C*ONBn_2); *m/z* (NSI$^+$) 413 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{24}H_{21}O_5N_2$ [M+H]$^+$, found 417.1445, requires 417.1445 (+0.0 ppm).

4-Nitrophenyl (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoate (S32)



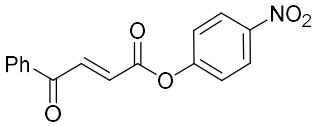
Following General Procedure 14 (Method B, iii), (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoic acid (348 mg, 2.06 mmol), DCC (468 g, 2.27 mmol), 4-nitrophenol (PNPOH) (292 mg, 2.10 mmol) and DMAP (50 mg, 0.41 mmol) in CH_2Cl_2 (2 mL) afforded after SiO_2-chromatography (85:15 Petroleum ether: EtOAc, R_f 0.20) the title compound (369 mg, 62%) as a colourless solid. mp 128–129 °C; ν_{max} (film) 2974 (C-H), 1744 (C=O) 1655 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.93–2.06 (4H, m, CH_{2pyrr}), 3.59–3.66 (4H, m, CH_{2pyrr}), 7.07 (1H, d, *J* 15.3, CH=C*H*–CO_2PNP), 7.34–7.36 (2H, m, C*H*-Ar_{PNP}), 7.46 (1H, d, *J* 15.3, C*H*=CH-CO_2PNP), 8.30–8.31 (2H, m, C*H*-Ar_{PNP}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.3 (*C*H_{2pyrr}), 26.1 (*C*H_{2pyrr}), 46.4 (*C*H_{2pyrr}), 47.0 (*C*H_{2pyrr}), 122.4 (2×*C*H-Ar_{PNP}), 125.3 (2×*C*H-Ar_{PNP}), 129.1 (CH=*C*H–CO_2PNP), 137.4 (*C*H=CH–CO_2PNP), 149.8 (*C*-NO_2), 155.0 (CO_2*C*-Ar_{PNP}), 161.8 (*C*O_2PNP), 163.4 (*C*ON); *m/z* (NSI$^+$) 291 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{14}H_{15}O_5N_2$ [M+H]$^+$, found 291.0977, requires 291.0975 (+0.5 ppm).

4-Nitrophenyl (*E*)-but-2-enoate (S33)



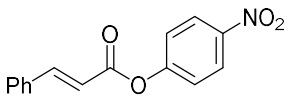
Following General Procedure 14 (Method B, iii), (*E*)-but-2-enoic acid (0.87 g, 10.0 mmol), DCC (2.27 g, 11.0 mmol), 4-nitrophenol (PNPOH) (1.42 g, 10.2 mmol) and DMAP (244 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether: EtOAc, R_f 0.21) the title compound (1.62 g, 78%) as an off-white solid. mp 59–61 °C; ν_{max} (film) 2959, 2871 (C-H), 1724 (C=O) 1645 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.01 (3H, dd, *J* 6.9, 1.7, C*H*$_3$), 6.03–6.08 (1H, m, CH=C*H*–CO_2PNP), 7.21–7.28 (1H, m, C*H*=CH-CO_2PNP), 7.29–7.31 (2H, m, C*H*-Ar$_{PNP}$), 8.26–8.29 (2H, m, C*H*-Ar$_{PNP}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 18.5 (*C*H$_3$), 121.4 (CH=*C*HCO_2PNP), 122.6 (2×*C*H-Ar$_{PNP}$), 125.3 (2×*C*H-Ar$_{PNP}$), 145.4 (*C*-NO_2), 148.9 (*C*H=CHCO_2PNP), 155.7 (CO_2*C*-Ar$_{PNP}$), 163.8 (*C*O_2PNP); HRMS (ESI$^+$) $C_{10}H_9N_1O_4Na$ [M+Na]$^+$, found 230.0423, requires 230.0424 (–0.4 ppm).

4-Nitrophenyl (*E*)-4-oxo-4-phenylbut-2-enoate (325)



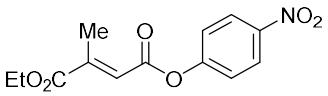
Following General Procedure 14 (Method B, iii), (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoic acid (440 mg, 2.5 mmol), DCC (567 mg, 2.75 mmol), 4-nitrophenol (PNPOH) (355 mg, 2.55 mmol) and DMAP (61 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) afforded after SiO_2-chromatography (97:3 – 90:10 Petroleum ether: EtOAc, R_f 0.30) the title compound (268 mg, 36%) as an orange solid. mp 128–130 °C; ν_{max} (film) 3080 (C-H), 1749 (C=O) 1668 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.10 (1H, d, *J* 15.5, CH=C*H*–CO_2PNP), 7.37–7.43 (2H, m, C*H*-Ar$_{PNP}$), 7.52–7.57 (2H, m, C*H*-Ph), 7.65–7.69 (1H, m, C*H*-Ph), 8.04–8.06 (2H, m, C*H*-Ph), 8.14 (1H, d, *J* 15.5, C*H*=CH-CO_2PNP), 8.32–8.34 (2H, m, C*H*-Ar$_{PNP}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 122.5 (2×*C*H-Ar$_{PNP}$), 125.5 (2×*C*H-Ar$_{PNP}$), 129.1 (2×*C*H-Ph), 129.2 (2×*C*H-Ph), 130.7 (CH=*C*HCO_2PNP), 134.4 (*C*H-Ph), 136.4 (*C*-Ph), 139.2 (*C*H=CHCO_2PNP), 145.8 (*C*-NO_2), 155.1 (CO_2*C*-Ar$_{PNP}$), 163.2 (*C*O_2PNP), 188.9 (*C*OPh); HRMS (ESI$^+$) $C_{16}H_{11}N_1O_5Na$ [M+Na]$^+$, found 320.0532, requires 320.0529 (+0.9 ppm).

4-Nitrophenyl cinnamate (326)



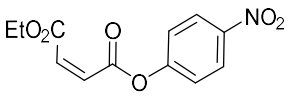
Following General Procedure 14 (Method B, iii), (*E*)-cinnamic acid (1.48 g, 10.0 mmol), DCC (2.27 g, 11.0 mmol), 4-nitrophenol (PNPOH) (1.42 g, 10.2 mmol) and DMAP (244 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether: EtOAc, R_f 0.25) the title compound (2.23 g, 83%) as an off-white solid. mp 143–145 °C; {Lit[26] 142–144 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.63 (1H, d, *J* 16.0, CH=C*H*–CO_2PNP), 7.37–7.39 (2H, m, C*H*-Ar_{PNP}), 7.44–7.47 (3H, m, C*H*-Ph), 7.60–7.62 (2H, m, C*H*-Ph), 7.92 (1H, d, *J* 16.0, C*H*=CH-CO_2PNP), 8.30–8.32 (2H, m, C*H*-Ar_{PNP}). Data in agreement with the literature.[26]

1-Ethyl 4-(4-nitrophenyl) 2-methylfumarate (329)



Following General Procedure 14 (Method B, iii), (*E*)-4-ethoxy-3-methyl-4-oxobut-2-enoic acid (514 mg, 3.25 mmol), DCC (738 mg, 3.58 mmol), 4-nitrophenol (PNPOH) (461 mg, 3.30 mmol) and DMAP (79 mg, 0.65 mmol) in CH_2Cl_2 (4 mL) afforded after SiO_2-chromatography (95:5 – 90:10 Petroleum ether: EtOAc, R_f 0.25) the title compound (754 mg, 83%) as a colourless solid. mp 57–59 °C; ν_{max} (film) 2986 (C-H), 1748 (C=O) 1719 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.36 (3H, t, *J* 7.1, CH_2CH_3), 2.38 (3H, d, *J* 1.6, C(2)CH_3), 4.31 (2H, q, *J* 7.1, CH_2CH$_3$), 7.00 (1H, q, *J* 1.6, C=C*H*–CO_2PNP), 7.29–7.56 (2H, m, C*H*-Ar_{PNP}), 8.15–8.37 (2H, m, C*H*-Ar_{PNP}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (CH_2CH_3), 14.9 (C*C*H$_3$), 62.2 (*C*H$_2$CH$_3$), 122.5 (2×*C*H-Ar_{PNP}), 124.5 (C=*C*H–CO_2PNP), 125.4 (2×*C*H-Ar_{PNP}), 145.5 (*C*-NO_2), 148.4 (*C*=CH–CO_2PNP), 155.1 (CO_2*C*-Ar_{PNP}), 163.3 (*C*O_2PNP), 166.6 (*C*O_2Et); *m/z* (NSI$^+$) 302 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) $C_{13}H_{13}N_1O_6$ [M+Na]$^+$, found 302.0634, requires 302.0635 (–0.4 ppm).

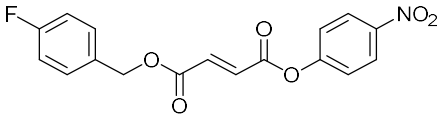
Ethyl (4-nitrophenyl) maleate (334)



Following General Procedure 16, (*Z*)-4-ethoxy-4-oxobut-2-enoic acid (1.44 g, 10 mmol), oxalyl chloride (0.87 mL, 10 mmol), diisopropylethylamine (3.48 mL, 20 mmol) and 4-nitrophenol (PNPOH) (1.39 g, 10 mmol) in CH_2Cl_2 (30 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether: EtOAc, R_f 0.15) the title compound (1.15 g, 43%) as a yellow solid. mp 58–60

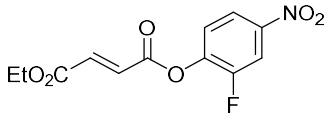
°C; ν_{max} (film) 2986 (C-H), 1755 (C=O) 1722 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.31 (3H, t, *J* 7.1, CH_2CH_3), 4.28 (2H, q, *J* 7.1, CH_2CH_3), 6.44 (1H, d, *J* 11.8, CH=C*H*–CO_2PNP), 6.48 (1H, d, *J* 11.8, C*H*=CH-CO_2PNP), 7.27–7.50 (2H, m, C*H*-Ar_{PNP}), 8.29–8.31 (2H, m, C*H*-Ar_{PNP}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.2 (CH_2CH_3), 61.9 (CH_2CH_3), 122.6 (2×CH-Ar_{PNP}), 125.4 (2×CH-Ar_{PNP}), 129.1 (CH=CHCO$_2$PNP), 131.5 (EtO_2C-CH=CH), 145.7 (C-NO_2), 155.0 (CO_2C-Ar_{PNP}), 163.2 (CO_2PNP), 164.9 (CO_2Et); *m/z* (NSI^+) 266 ([M+H]$^+$, 100%); HRMS (NSI^+) $C_{12}H_{12}N_1O_6$ [M+H]$^+$, found 266.0670, requires 266.0659 (+4.1 ppm).

4-Fluorobenzyl (4-nitrophenyl) fumarate (360)



Following General Procedure 16, (*E*)-4-((4-fluorobenzyl)oxy)-4-oxobut-2-enoic acid (1.45 g, 6.50 mmol), oxalyl chloride (0.57 mL, 6.50 mmol), diisopropyethylamine (2.26 mL, 13.0 mmol) and 4-nitrophenol (PNPOH) (0.90 g, 6.50 mmol) in CH_2Cl_2 (20 mL) afforded after SiO_2-chromatography (95:5 Petroleum ether: EtOAc, R_f 0.30) the title compound (1.04 g, 46%) as a yellow solid. mp 99–101 °C; ν_{max} (film) 3084 (C-H), 1748 (C=O) 1726 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.25 (2H, s, CH_2Ar_F), 7.07 (1H, d, *J* 15.4, CH=C*H*–CO_2PNP), 7.07–7.10 (2H, m, $CH_{Ar\text{-}F}$), 7.11 (1H, d, *J* 15.4, C*H*=CH-CO_2PNP), 7.34–7.35 (2H, m, C*H*-Ar_{PNP}), 7.38–7.40 (2H, m, $CH_{Ar\text{-}F}$), 8.29–8.31 (2H, m, C*H*-Ar_{PNP}); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −112.7; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 66.9 (CH_2Ar_F), 115.8 (d, $^{2}J_{CF}$ 21.9, CH_{Ar}-F), 122.4 (2×CH-Ar_{PNP}), 122.5 (2×CH-Ar_{PNP}), 130.7 (d, $^{3}J_{CF}$ 8.4, CH_{Ar}-F), 130.9 (d, $^{4}J_{CF}$ 3.0, C_{Ar}-F), 132.4 (CH=CH–CO_2PNP), 136.2 (CH=CH–CO_2PNP), 145.8 (C-NO_2), 154.9 (CO_2C-Ar_{PNP}), 162.4 (CO_2PNP), 162.9 (d, $^{1}J_{CF}$ 246.9, C_{Ar}-F), 164.2 (CO_2Ar_F); *m/z* (NSI^+) 346 ([M+H]$^+$, 100%); HRMS (NSI^+) $C_{17}H_{12}O_6NF$ [M+H]$^+$, found 346.0726, requires 346.0721 (+1.4 ppm).

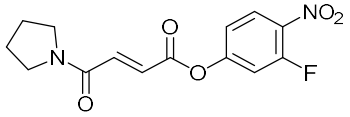
Ethyl (2-fluoro-4-nitrophenyl) fumarate (352)



Following General Procedure 14 (Method B, iii), (*E*)-4-ethoxy-4-oxobut-2-enoic acid (288 mg, 2.0 mmol), DCC (454 mg, 2.2 mmol), 2-fluoro-4-nitrophenol (317 g, 2.02 mmol) and DMAP (49 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether : EtOAc, R_f 0.21) the title compound (439 g, 77%) as a yellow solid. mp 62–64 °C; ν_{max} (film) 2985 (C-H), 1759 (C=O) 1726 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.36 (3H, t, *J* 7.1, CH_2CH_3), 4.32 (2H, q, *J* 7.1, CH_2CH_3), 7.06 (1H, d, *J* 15.8, CH=C*H*–CO_2Ar_F), 7.11 (1H, d, *J* 15.8, C*H*=CH-

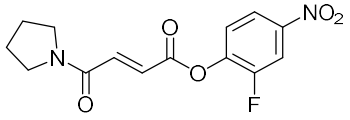
CO_2Ar_F), 7.41–7.44 (1H, m, C*H*-Ar_F), 8.10–8.13 (2H, m, C*H*-Ar_F); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −122.0; ^{19}F NMR (376 MHz, C_6D_6) δ_F: −124.0; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (CH_2CH_3), 62.0 (CH_2CH_3), 113.3 (d, $^2J_{CF}$ 23.5, CH_{Ar}-F), 120.4 (d, $^4J_{CF}$ 3.8, CH_{Ar}-F), 124.3 (*C*H-Ar_F), 130.8 (CH=*C*HCO_2Ar_F), 137.3 (CO_2Ar_F-*C*H=CH), 143.1 (d, $^3J_{CF}$ 13.1, C_{Ar}-F), 153.7 (d, $^1J_{CF}$ 253.7, C_{Ar}-F), 154.6 (CO_2C-Ar_F), 161.6 (CO_2Ar_F), 164.5 (CO_2Et); *m/z* (NSI^+) 284 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{12}H_{11}N_1O_6F$ $[M+H]^+$, found 284.0565, requires 284.0565 (–0.0 ppm).

3-Fluoro-4-nitrophenyl (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoate (353)



Following General Procedure 14 (Method B, iii), (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoic acid (310 mg, 1.83 mmol), DCC (415 g, 2.01 mmol), 3-fluoro-4-nitrophenol (293 mg, 1.87 mmol) and DMAP (45 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) afforded after SiO_2-chromatography (70:40 – 40:60 Petroleum ether: EtOAc, R_f 0.19) the title compound (410 mg, 73%) as a yellow solid. mp 129–131 °C; ν_{max} (film) 2880 (C-H), 1749 (C=O) 1655 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.93–2.06 (4H, m, CH_{2pyrr}), 3.59–3.66 (4H, m, CH_{2pyrr}), 7.04 (1H, d, *J* 15.3, CH=C*H*–CO_2Ar_F), 7.14–7.23 (2H, m, C*H*-Ar_F), 7.46 (1H, d, *J* 15.3, C*H*=CH-CO_2Ar_F), 8.15–8.18 (1H, m, C*H*-Ar_F); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −112.90; ^{19}F NMR (376 MHz, C_6D_6) δ_F: −114.99; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 24.4 (*C*H_{2pyrr}), 26.2 (*C*H_{2pyrr}), 46.6 (*C*H_{2pyrr}), 47.1 (*C*H_{2pyrr}), 112.3 (d, $^2J_{CF}$ = 24.0, CH_{Ar}-F), 117.9 (d, $^4J_{CF}$ = 3.9, C_{Ar}-F), 127.4 (*C*H-Ar_F), 128.8 (CH=*C*HCO_2Ar_F), 138.0 (CO_2Ar_F-*C*H=CH), 155.2 (d, $^3J_{CF}$ = 10.2, O-C_{Ar}-F), 156.3 (d, $^1J_{CF}$ = 264.9, C_{Ar}-F), 157.2 (d, $^2J_{CF}$ = 28.1, NO_2-C_{Ar}-F), 161.8 (CO_2Ar_F), 163.0 (*C*ON); *m/z* (NSI^+) 309 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{14}H_{14}O_5N_2F$ $[M+H]^+$, found 309.0885, requires 309.0881 (+1.3 ppm).

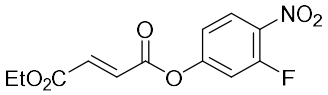
2-Fluoro-4-nitrophenyl (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoate (354)



Following General Procedure 14 (Method B, iii), (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoic acid (310 mg, 1.83 mmol), DCC (415 g, 2.01 mmol), 2-fluoro-4-nitrophenol (293 mg, 1.87 mmol) and DMAP (45 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) afforded after SiO_2-chromatography (70:40 – 40:60 Petroleum ether: EtOAc, R_f 0.18) the title compound (415 mg, 74%) as a yellow solid. mp 98–99 °C; ν_{max} (film) 2979 (C-H), 1757 (C=O) 1655 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.93–2.05 (4H, m, CH_{2pyrr}), 3.58–3.66 (4H, m, CH_{2pyrr}), 7.08 (1H, d, *J* 15.3, CH=C*H*–CO_2Ar_F), 7.39–7.43

(1H, m, C*H*-Ar_F), 7.48 (1H, d, *J* 15.3, C*H*=CH-CO_2Ar_F), 8.08–8.12 (2H, m, C*H*-Ar_F); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −121.97; ^{19}F NMR (376 MHz, C_6D_6) δ_F: −124.01; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.2 (*C*H_{2pyrr}), 26.1 (*C*H_{2pyrr}), 46.4 (*C*H_{2pyrr}), 47.0 (*C*H_{2pyrr}), 113.0 (d, $^2J_{CF}$ 23.6, CH_{Ar}-F), 120.2 (d, $^4J_{CF}$ 3.3, CH_{Ar}-F), 124.4 (*C*H-Ar_F), 128.0 (CH=*C*HCO_2Ar_F), 138.1 (CO_2Ar_F-*C*H=CH), 143.2 (d, $^2J_{CF}$ 12.9, O-C_{Ar}-F), 146.0 (d, $^3J_{CF}$ 7.5, NO_2-C_{Ar}-F), 153.5 (d, $^1J_{CF}$ 255.5, C_{Ar}-F), 161.6 (*C*O_2Ar_F), 162.3 (*C*ON); *m/z* (NSI$^+$) 309 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{14}H_{14}O_5N_2F$ [M+H]$^+$, found 309.0879, requires 309.0881 (–0.6 ppm).

Ethyl (3-fluoro-4-nitrophenyl) fumarate (355)

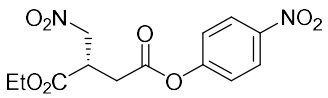


Following General Procedure 14 (Method B, iii), (*E*)-4-ethoxy-4-oxobut-2-enoic acid (288 mg, 2.0 mmol), DCC (454 mg, 2.2 mmol), 3-fluoro-4-nitrophenol (317 g, 2.02 mmol) and DMAP (49 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether: EtOAc, R_f 0.22) the title compound (372 g, 66%) as a yellow solid. mp 45–46 °C; ν_{max} (film) 2986 (C-H), 1755 (C=O) 1724 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.36 (3H, t, *J* 7.1, CH_2CH_3), 4.32 (2H, q, *J* 7.1, CH_2CH_3), 7.02 (1H, d, *J* 15.8, CH=C*H*–CO_2Ar_F), 7.08 (1H, d, *J* 15.8, C*H*=CH-CO_2Ar_F), 7.16 (1H, ddd, *J* 9.0, 2.4, 1.4, C*H*-Ar_F), 7.23 (1H, dd, *J* 11.1, 2.4, C*H*-Ar_F), 7.16 (1H, t, *J* 8.7, C*H*-Ar_F); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −112.7; ^{19}F NMR (376 MHz, C_6D_6) δ_F: −114.88; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (CH_2CH_3), 62.0 (*C*H_2CH$_3$), 112.2 (d, $^2J_{CF}$ 24.1, CH_{Ar}-F), 117.8 (d, $^3J_{CF}$ 4.0, CH_{Ar}-F), 127.5 (d, $^4J_{CF}$ 1.8, CH-Ar_F), 131.4 (CH=*C*HCO_2Ar_F), 132.0 (d, $^2J_{CF}$ 23.6, NO_2-C_{Ar}-F), 137.2 (CO_2Ar_F-*C*H=CH), 155.0 (d, $^3J_{CF}$ 10.4, O-C_{Ar}-F), 156.3 (d, $^1J_{CF}$ 267.2, C_{Ar}-F), 162.1 (*C*O_2Ar_F), 164.3 (*C*O_2Et); *m/z* (NSI$^+$) 284 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{12}H_{11}NO_6F$ [M+H]$^+$, found 284.0567, requires 284.0565 (+0.7 ppm).

7.4.3 Aryloxide-facilitated enantioselective Michael addition

7.4.3.1 Michael addition products

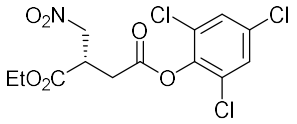
1-Ethyl 4-(4-nitrophenyl) (*S*)-2-(nitromethyl)succinate (300)



Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (80:20 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (35.8 mg, 55%) as a colorless oil; $[\alpha]_D^{20}$ –3.9 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum

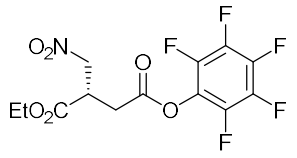
ether: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 28.5 min, t_R minor: 31.3 min, 96:4 er; ν_{max} (film) 2932, 2862 (C-H), 1748 (C=O), 1734 (C=O), 1558, 1381 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.32 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 3.04 (1H, dd, *J* 17.5, 6.0, CH_2COO), 3.20 (1H, dd, *J* 17.5, 6.7, CH_2COO), 3.68 (1H, *app* pent., *J* 6.0, CH), 4.26–4.32 (2H, m, $CO_2CH_2CH_3$), 4.85 (1H, dd, *J* 14.6, 5.6, CH_2NO_2), 4.89 (1H, dd, *J* 14.6, 6.0, CH_2NO_2), 7.32–7.34 (2H, m, C*H*-Ar$_{PNP}$), 8.30–8.32 (2H, m, C*H*-Ar$_{PNP}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 33.1 (CH_2COO), 39.1 (CH), 62.4 ($CO_2CH_2CH_3$), 74.4 (CH_2NO_2), 125.3 (2×CH-Ar$_{PNP}$), 125.3 (2×CH-Ar$_{PNP}$), 145.6 (*C*-NO_2), 154.9 (CO_2C-Ar$_{PNP}$), 168.7 (CO_2PNP), 169.7 (CO_2Et); *m/z* (NSI$^+$) 327 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{13}H_{15}O_8N_2$ [M+H]$^+$, found 327.0823, requires 327.0823 (+0.0 ppm).

1-Ethyl 4-(2,4,6-trichlorophenyl) (*S*)-2-(nitromethyl)succinate (309)



Following General Procedure 17, ethyl (2,4,6-trichlorophenyl) fumarate (64.8 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (90:10 Petroleum ether : EtOAc, R_f 0.13) afforded the title compound (31.5 mg, 41%) as a colorless oil; $[\alpha]_D^{20}$ –8.6 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (98:2 Petroleum ether: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R major: 19.3 min, t_R minor: 20.7 min, 94:6 er; ν_{max} (film) 2984, 2930 (C-H), 1776 (C=O), 1738 (C=O), 1553, 1379 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.13 (1H, dd, *J* 18.0, 7.0, CH_2COO), 3.29 (1H, dd, *J* 18.0, 5.5, CH_2COO), 3.56–3.70 (1H, m, CH), 4.26 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 4.82 (1H, dd, *J* 14.6, 5.5, CH_2NO_2), 4.89 (1H, dd, *J* 14.6, 5.9, CH_2NO_2), 7.39 (2H, s, C*H*-Ar$_{TCP}$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.2 ($CO_2CH_2CH_3$), 32.3 (CH_2COO), 39.0 (CH), 62.5 ($CO_2CH_2CH_3$), 74.2 (CH_2NO_2), 128.8 (2×CH-Ar$_{TCP}$), 129.5 (2×*C*-Ar$_{TCP}$), 132.7 (*C*-Ar$_{TCP}$), 142.6 (CO_2C-Ar$_{TCP}$), 167.5 (CO_2TCP), 167.6 (CO_2Et); *m/z* (NSI$^+$) 401 ([M+ NH_4]$^+$, 100%); HRMS (NSI$^+$) $C_{13}H_{16}O_6N_2{}^{35}Cl_3$ [M+NH_4]$^+$, found 401.0071, requires 401.0069 (+0.5 ppm).

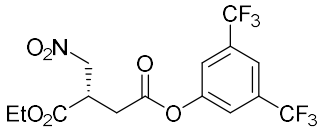
1-Ethyl 4-(perfluorophenyl) (*S*)-2-(nitromethyl)succinate (309)



Following General Procedure 17, ethyl (perfluorophenyl) fumarate (62.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography

(90:10 Petroleum ether : EtOAc, R_f 0.15) afforded the title compound (24.5 mg, 33%) as a colorless oil; $[\alpha]_D^{20}$ –13.5 (*c* 0.2, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (98:2 Petroleum ether: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R major: 16.1 min, t_R minor: 17.3 min, 96:4 er; ν_{max} (film) 2986, 2930 (C-H), 1788 (C=O), 1738 (C=O), 1520, 1379 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 3.10 (1H, dd, *J* 17.8, 6.1, CH_2COO), 3.28 (1H, dd, *J* 17.8, 6.5, CH_2COO), 3.64 (1H, *app* pent, *J* 6.0, CH), 4.26 (2H, q, *J* 7.2, $CO_2CH_2CH_3$), 4.81 (1H, dd, *J* 14.6, 5.8, CH_2NO_2); 4.86 (1H, dd, *J* 14.6, 5.6, CH_2NO_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −161.8 to –161.7 (2F, m, Ar_{PFP}), −157.0 to –156.9 (2F, m, Ar_{PFP}), −152.5 to –152.4 (1F, m, Ar_{PFP}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)[1] δ_C: 14.1 ($CO_2CH_2CH_3$), 32.3 (CH_2COO), 39.1 (CH), 62.7 ($CO_2CH_2CH_3$), 74.3 (CH_2NO_2), 167.3 (CO_2PFP), 169.4 (CO_2Et); *m/z* (NSI$^+$) 372 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{13}H_{11}O_6N_1F_5$ [M+H]$^+$, found 372.0499, requires 372.0501 (–0.5 ppm).

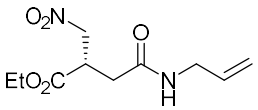
4-(3,5-Bis(trifluoromethyl)phenyl) 1-ethyl (*S*)-2-(nitromethyl)succinate (310)



Following General Procedure 17, 3,5-bis(trifluoromethyl)phenyl ethyl fumarate (71.2 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (95:5 – 90:10 Petroleum ether : EtOAc, R_f 0.13) afforded the title compound (41.7 mg, 45%) as a colorless oil; $[\alpha]_D^{20}$ –4.4 (*c* 0.7, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (98:2 Petroleum ether: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 9.0 min, t_R major: 10.7 min, 93:7 er; ν_{max} (film) 2988, 2936 (C-H), 1771 (C=O), 1738 (C=O), 1560, 1364 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 3.02 (1H, dd, *J* 17.6, 5.9, CH_2COO), 3.18 (1H, dd, *J* 17.6, 6.8, CH_2COO), 3.65 (1H, *app* pent., *J* 5.9, CH), 4.25–4.29 (2H, m, $CO_2CH_2CH_3$), 4.80–4.89 (2H, m, CH_2NO_2), 7.61 (2H, s, C*H*-Ar_{CF3}), 7.78 (1H, s, C*H*-Ar_{CF3}); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −63.0; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1 (CH_2CH_3), 33.1 (CH_2COO), 39.2 (CH), 62.6 ($CO_2CH_2CH_3$), 74.5 (CH_2NO_2), 120.2 (septet, $^3J_{CF}$ = 3.4, CH_{Ar}-CF_3), 122.4 (q, $^3J_{CF}$ = 3.0, 2×CH-Ar_{CF3}), 122.8 (q, $^1J_{CF}$ = 271.3, CF_3), 133.2 (q, $^2J_{CF}$ = 34.1, C_{Ar}-CF_3), 150.8 (CO_2C-Ar_{CF3}), 169.0 (CO_2Ar_{CF3}), 169.8 (CO_2Et); *m/z* (NSI$^+$) 418 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{15}H_{14}O_6N_1F_6$ [M+H]$^+$, found 418.0712, requires 418.0720 (–1.9 ppm).

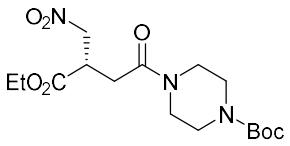
[1] Pentafluorophenyl carbons were not assignable due to the complex character of ^{19}F coupling.

Ethyl (*S*)-4-(allylamino)-2-(nitromethyl)-4-oxobutanoate (313)



Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), allylamine (30 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (28.3 mg, 58%) as a colorless oil; $[\alpha]_D^{20}$ +8.4 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (95:5 Petroleum ether: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 24.5 min, t_R major: 30.2 min, 96:4 er; ν_{max} (film) 2986, 2255 (C-H), 1734 (C=O), 1655 (C=O), 1557, 1379 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.26 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.58 (1H, dd, *J* 15.9, 7.0, CH_2CON), 2.76 (1H, dd, *J* 15.9, 5.8, CH_2CON), 3.57 (1H, *app* pent., *J* 5.7, CH), 3.88 (2H, *app* t, *J* 5.7, $NHCH_2$), 4.16–4.26 (2H, m, $CO_2CH_2CH_3$), 4.76–4.86 (2H, m, CH_2NO_2), 5.14–5.21 (2H, m, $CH=CH_2$), 5.71 (1H, s, NH), 5.78–5.85 (1H, m, $CH=CH_2$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 34.5 (CH_2CON), 39.5 (CH), 42.2 ($NHCH_2$), 62.1 ($CO_2CH_2CH_3$), 75.0 (CH_2NO_2), 117.0 ($CH=CH_2$), 133.8 ($CH=CH_2$), 169.3 (*C*ON), 170.8 (CO_2Et); *m/z* (NSI$^+$) 245 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{10}H_{17}O_5N_2$ [M+H]$^+$, found 245.1127, requires 245.1132 (–2.0 ppm).

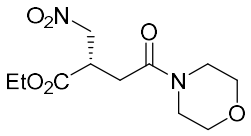
***tert*-Butyl (*S*)-4-(4-ethoxy-3-(nitromethyl)-4-oxobutanoyl)piperazine-1-carboxylate (314)**



Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), *N*-Boc-piperidine (152 mg) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (53.0 mg, 71%) as a colorless oil; $[\alpha]_D^{20}$ +5.6 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ODH (92:8 Petroleum ether: IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 41.0 min, t_R major: 45.4 min, 96:4 er; ν_{max} (film) 2982, 2930, 2868 (C-H), 1736 (C=O), 1690 (C=O), 1643 (C=O), 1557, 1368 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.26 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.46 (9H, $C(CH_3)_3$), 2.74 (1H, dd, *J* 16.9, 7.0, CH_2CON), 2.90 (1H, dd, *J* 16.9, 5.0, CH_2CON), 3.41–3.46 (6H, m, $CH_{2(pip)}$), 3.55–3.61 (3H, m, C*H*, $CH_{2(pip)}$), 4.17–4.24 (2H, m, $CO_2CH_2CH_3$), 4.79–4.87 (2H, m, CH_2NO_2); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.2 ($CO_2CH_2CH_3$), 28.5

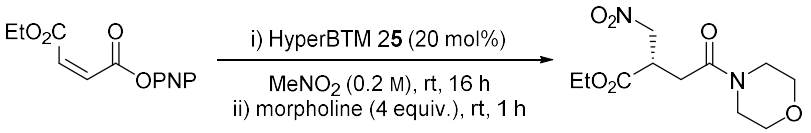
($C(CH_3)_3$), 31.8 (CH_2CON), 39.4 (CH), 41.8 ($CH_{2(pip)}$), 45.3 ($CH_{2(pip)}$), 62.0 ($CO_2CH_2CH_3$), 75.1 (CH_2NO_2), 80.6 ($C(CH_3)_3$), 154.6 (NCOO), 168.2 (CON), 170.9 (CO_2Et); *m/z* (NSI^+) 396 ($[M+Na]^+$, 100%; 769 ($[2M+Na]^+$, 90%); HRMS (NSI^+) $C_{16}H_{28}O_7N_3$ $[M+H]^+$, found 374.1925, r equires 374.1922 (+0.9 ppm).

Ethyl (*S*)-4-morpholino-2-(nitromethyl)-4-oxobutanoate (315)



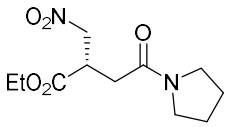
Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 g, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.12) afforded the title compound (40.2 mg, 73%) as a colorless oil; $[\alpha]_D^{20}$ +4.5 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether: IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 20.1 min, t_R major: 48.1 min, 95:5 er; ν_{max} (film) 2970, 2924, 2859 (C-H), 1734 (C=O), 1643 (C=O), 1555, 1379 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.26 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.72 (1H, dd, *J* 16.9, 7.1, CH_2CON), 2.88 (1H, dd, *J* 16.9, 4.9, CH_2CON), 3.45–3.47 (2H, m, $CH_{2(morph)}$), 3.57–3.62 (3H, m, CH, $CH_{2(morph)}$), 3.66–3.70 (4H, m, $CH_{2(morph)}$), 4.18–4.25 (2H, m, $CO_2CH_2CH_3$), 4.79–4.88 (2H, m, CH_2NO_2); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 31.6 (CH_2CON), 39.4 (CH), 42.3 ($CH_{2(morph)}$), 45.9 ($CH_{2(morph)}$), 62.0 ($CO_2CH_2CH_3$), 66.5 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 75.1 (CH_2NO_2), 168.2 (CON), 170.9 (CO_2Et); *m/z* (NSI^+) 297 ($[M+Na]^+$, 100%; 571 ([2M+Na], 100%); HRMS (NSI^+) $C_{11}H_{19}O_6N_2$ $[M+H]^+$, found 275.1240, requires 275.1238 (+0.9 ppm).

*Reaction using ethyl (4-nitrophenyl) maleate **334**:*



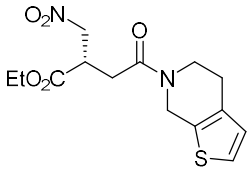
Following General Procedure 17, ethyl (4-nitrophenyl) maleate (53.0 g, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.12) afforded the title compound (35.7 mg, 65%) as a colorless oil; $[\alpha]_D^{20}$ +3.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 19.9 min, t_R major: 47.3 min, 93:7 er.

Ethyl (*S*)-2-(nitromethyl)-4-oxo-4-(pyrrolidin-1-yl)butanoate (316)



Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), pyrrolidine (66 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (27.4 mg, 53%) as colorless oil; $[\alpha]_D^{20}$ +8.2 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 18.8 min, t_R major: 20.8 min, 95:5 er; ν_{max} (film) 2976, 2943, 2876 (C-H), 1734 (C=O), 1636 (C=O), 1557, 1379 (NO_2 ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.26 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.87 (2H, p, $CH_{2(pyrr)}$, 2.67 (1H, dd, *J* 16.9, 7.4, CH_2CON), 2.83 (1H, dd, *J* 16.9, 4.8, CH_2CON), 3.37–3.47 (4H, m, $CH_{2(pyrr)}$), 3.58–3.62 (1H, m, CH), 4.17–4.24 (2H, m, $CO_2CH_2CH_3$), 4.84 (1H, dd, *J* 14.6, 5.4, CH_2NO_2), 4.86 (1H, dd, *J* 14.6, 7.5, CH_2NO_2); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.2 ($CO_2CH_2CH_3$), 24.5 $CH_{2(pyrr)}$), 26.2 $CH_{2(pyrr)}$), 33.1 (CH_2CON), 39.3 (CH), 46.0 ($CH_{2(pyrr)}$), 46.7 ($CH_{2(pyrr)}$), 61.9 ($CO_2CH_2CH_3$), 75.1 (CH_2NO_2), 167.9 (*C*ON), 171.2 (CO_2Et); *m/z* (NSI^+) 259 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{15}H_{25}O_6N_2$ $[M+H]^+$, found 259.1294, requires 259.1289 (+1.9 ppm).

Ethyl (*S*)-4-(4,7-dihydrothieno[2,3-c]pyridin-6(5H)-yl)-2-(nitromethyl)-4-oxobutanoate (317)



Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), 4,5,6,7-tetrahydrothieno[2,3-c]pyridine (112.0 mg) and subsequent chromatography (80:20 – 70:30 Petroleum ether : EtOAc, R_f 0.20) afforded the title compound as inseparable 1:1 mixture of rotamers (45.8 mg, 70%) as a colorless oil; $[\alpha]_D^{20}$ +5.6 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (92:8 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 41.3 min, t_R major: 47.3 min, 93:7 er; ν_{max} (film) 2970, 2924, 2859 (C-H), 1734 (C=O), 1645 (C=O), 1557, 1379 (NO_2);

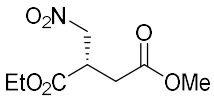
Rotamer 1: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.25 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.81 (1H, dd, dd, *J* 16.8, 7.1, CH_2CON), 2.85–2.88 (2H, m, $CH_{2(pyr)}$), 3.02 (1H, dd, *J* 16.8, 4.9, CH_2CON) 3.61–3.66 (1H, m, C*H*), 3.75 (2H, *app* t, *J* 5.7, $CH_{2(pyr)}$), 4.17–4.24 (2H, m, $CO_2CH_2CH_3$), 4.55 (1H, s,

C$H_{2(pyr)}$), 4.80–4.90 (2H, m, CH_2NO$_2$), 6.79 (1H, dd, *J* 5.2, 3.0, CH$_{Ar}$), 7.16 (1H, dd, *J* 11.6, 5.2, CH$_{Ar}$); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 14.1 (CO$_2$CH$_2$*C*H$_3$), 25.7 (CH$_{2(pyr)}$), 32.0 (*C*H$_2$CON), 39.5 (CH), 40.1 (CH$_{2(pyr)}$), 43.5 (CH$_{2(pyr)}$), 62.0 (CO$_2$*C*H$_2$CH$_3$), 75.1 (*C*H$_2$NO$_2$), 124.6 (CH$_{Ar}$), 125.2 (CH$_{Ar}$), 130.7 (C$_{Ar}$), 132.2 (C$_{Ar}$), 168.3 (*C*ON), 171.0 (*C*O$_2$Et);

Rotamer 2: ^{1}H NMR (500 MHz, CDCl$_3$) δ_H: 1.25 (3H, t, *J* 7.1, CO$_2$CH$_2$CH_3), 2.81 (1H, dd, dd, *J* 16.8, 7.1, CH_2CON), 2.92–2.94 (2H, m, C$H_{2(pyr)}$), 3.02 (1H, dd, *J* 16.8, 4.9, CH_2CON) 3.61–3.66 (1H, m, C*H*), 3.91 (2H, *app* t, *J* 5.7, C$H_{2(pyr)}$), 4.17–4.24 (2H, m, CO$_2$CH_2CH$_3$), 4.66 (1H, s, C$H_{2(pyr)}$), 4.80–4.90 (2H, m, CH_2NO$_2$), 6.79 (1H, dd, *J* 5.2, 3.0, CH$_{Ar}$), 7.16 (1H, dd, *J* 11.6, 5.2, CH$_{Ar}$); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 14.1 (CO$_2$CH$_2$*C*H$_3$), 24.8 (CH$_{2(pyr)}$), 32.4 (*C*H$_2$CON), 39.5 (CH), 43.0 (CH$_{2(pyr)}$), 45.6 (CH$_{2(pyr)}$), 62.0 (CO$_2$*C*H$_2$CH$_3$), 75.2 (*C*H$_2$NO$_2$), 123.8 (CH$_{Ar}$), 124.0 (CH$_{Ar}$), 132.2 (C$_{Ar}$), 134.4 (C$_{Ar}$), 168.6 (*C*ON), 171.1 (*C*O$_2$Et);

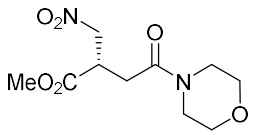
m/z (NSI$^+$) 327 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{14}H_{19}O_5N_2S_1$ [M+H]$^+$, found 327.1011, requires 327.1009 (+0.6 ppm).

1-Ethyl 4-methyl (*S*)-2-(nitromethyl)succinate (318)



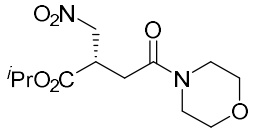
Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), methanol (3.0 mL), 4-(dimethylamino)pyridine (4.9 mg, 0.04 mmol) and subsequent chromatography (100% CH_2Cl_2, R_f 0.23) afforded the title compound (25.0 mg, 57%) as a colorless oil; $[\alpha]_D^{20}$ –2.4 (*c* 1.0, CHCl$_3$); Chiral HPLC analysis, Chiralpak ODH (98:2 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R major: 26.8 min, t_R minor: 29.1 min, 96:4 er; ν_{max} (film) 2957 (C-H), 1732 (C=O), 1557, 1379 (NO$_2$); ^{1}H NMR (500 MHz, CDCl$_3$) δ_H: 1.26 (3H, t, *J* 7.1, CO$_2$CH$_2$CH_3), 2.72 (1H, dd, *J* 17.3, 7.0, CH_2CO$_2$Me), 2.86 (1H, dd, *J* 17.3, 5.7, CH_2CO$_2$Me), 3.52–3.56 (1H, m, CH), 3.71 (3H, CO$_2$CH_3), 4.21 (2H, q, *J* 7.1, CO$_2$CH_2CH$_3$), 4.71 (1H, dd, *J* 14.5, 5.5, CH_2NO$_2$) 4.82 (1H, dd, *J* 14.5, 6.4, CH_2NO$_2$); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 14.1 (CO$_2$CH$_2$*C*H$_3$), 32.8 (*C*H$_2$CO$_2$Me), 39.2 (CH), 52.4 (CO$_2$*C*H$_3$), 62.2 (CO$_2$*C*H$_2$CH$_3$), 74.5 (*C*H$_2$NO$_2$), 170.4 (*C*O$_2$Me), 171.2 (*C*O$_2$Et); *m/z* (NSI$^+$) 220 ([M+H]$^+$, 75%); HRMS (NSI$^+$) $C_8H_{14}O_6N_1$ [M+H]$^+$, found 220.0817, requires 220.0816 (+0.6 ppm).

Methyl (*S*)-4-morpholino-2-(nitromethyl)-4-oxobutanoate (319)



Following General Procedure 17, methyl (4-nitrophenyl) fumarate (50.2 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (40.5 mg, 78%) as a colorless oil; $[\alpha]_D^{20}$ +4.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 25.2 min, t_R major: 47.5 min, 96:4 er; ν_{max} (film) 2959, 2922, 2859 (C-H), 1739 (C=O), 1639 (C=O), 1552, 1379 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.73 (1H, dd, *J* 17.0, 6.9, C*H*$_2$CON), 2.88 (1H, dd, *J* 17.0, 4.9, C*H*$_2$CON), 3.45–3.47 (2H, m, C*H*$_{2(morph)}$), 3.55–3.64 (3H, m, CH, C*H*$_{2(morph)}$), 3.66–3.69 (4H, m, C*H*$_{2(morph)}$), 3.75 (CO_2CH_3), 4.83 (2H, qd, *J* 14.5, 5.5, C*H*$_2$NO$_2$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 31.6 (*C*H$_2$CON), 39.3 (CH), 42.3 (CH$_{2(morph)}$), 45.8 (CH$_{2(morph)}$), 52.9 (CO_2CH_3), 66.5 (CH$_{2(morph)}$), 66.9 (CH$_{2(morph)}$), 75.0 (*C*H$_2$NO$_2$), 168.1 (*C*ON), 171.5 (*C*O$_2$Me); *m/z* (NSI$^+$) 261 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{10}H_{17}O_6N_2$ [M+H]$^+$, found 261.1082, requires 261.1087 (−1.9 ppm).

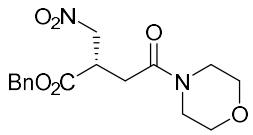
Isopropyl (*S*)-4-morpholino-2-(nitromethyl)-4-oxobutanoate (320)



Following General Procedure 17, isopropyl (4-nitrophenyl) fumarate (55.9 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (45.7 mg, 79%) as colorless oil; $[\alpha]_D^{20}$ +20.2 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 15.9 min, t_R major: 47.8 min, 96:4 er; ν_{max} (film) 2980, 2924, 2859 (C-H), 1728 (C=O), 1641 (C=O), 1553, 1377 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.23 (d, *J* 6.3, $CO_2CH(CH_3)_2$), 2.69 (1H, dd, *J* 16.9, 7.2, C*H*$_2$CON), 2.87 (1H, dd, *J* 16.9, 4.9, C*H*$_2$CON), 3.45–3.47 (2H, m, C*H*$_{2(morph)}$), 3.54–3.59 (3H, m, CH, C*H*$_{2(morph)}$), 3.65–3.69 (4H, m, C*H*$_{2(morph)}$), 4.81 (2H, dd, *J* 15.1, 5.5, C*H*$_2$NO$_2$), 5.05 (hept, *J* 6.3, ($CO_2CH(CH_3)_2$; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.7 ($CO_2CH(CH_3)_2$), 31.5 (*C*H$_2$CON), 39.5 (CH), 42.2 (CH$_{2(morph)}$), 45.9 (CH$_{2(morph)}$), 66.5 (CH$_{2(morph)}$), 66.9 (CH$_{2(morph)}$), 69.6

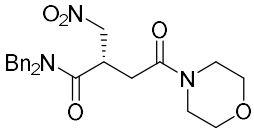
($CO_2CH(CH_3)_2$), 75.2 (CH_2NO_2), 168.2 (*C*ON), 170.4 ($CO_2{}^iPr$); *m/z* (NSI^+) 289 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{12}H_{21}O_6N_2$ $[M+H]^+$, found 289.1396, requires 289.1394 (+0.7 ppm).

Benzyl (*S*)-4-morpholino-2-(nitromethyl)-4-oxobutanoate (321)



Following General Procedure 17, the corresponding PNP-ester (65.5 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.13) afforded the title compound (41.0 mg, 61%) as a colorless oil; $[\alpha]_D^{20}$ +14.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 30.0 min, t_R major: 47.0 min, 94:6 er; ν_{max} (film) 2968, 2922, 2857 (C-H), 1738 (C=O), 1645 (C=O), 1555, 1381 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.74 (1H, dd, *J* 16.9, 6.9, CH_2CON), 2.88 (1H, dd, *J* 16.9, 4.9, CH_2CON), 3.41–3.43 (2H, m, C$H_{2(morph)}$), 3.58–3.59 (2H, m, C$H_{2(morph)}$), 3.64–3.68 (5H, m, CH, C$H_{2(morph)}$), 4.82–4.90 (2H, m, CH_2NO_2), 5.15–5.17 (2H, m, CO_2CH_2Ph), 7.32–7.38 (5H, m, CH_{Ph}); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 31.6 (CH_2CON), 39.5 (CH), 42.3 ($CH_{2(morph)}$), 45.9 ($CH_{2(morph)}$), 66.5 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 67.8 (CO_2CH_2Ph), 75.1 (CH_2NO_2), 128.5 (2×CH_{Ph}), 128.7 (CH_{Ph}), 128.8 (2×CH_{Ph}), 135.3 (C_{Ph}), 168.1 (*C*ON), 170.8 (CO_2Bn); *m/z* (NSI^+) 337 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{16}H_{21}O_6N_2$ $[M+H]^+$, found 337.1396, requires 337.1394 (+0.6 ppm).

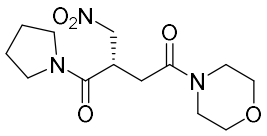
(*S*)-*N*,*N*-Dibenzyl-4-morpholino-2-(nitromethyl)-4-oxobutanamide (322)



Following General Procedure 17, 4-nitrophenyl (*E*)-4-(dibenzylamino)-4-oxobut-2-enoate (83.2 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (56.1 mg, 66%) as a colourless solid. mp 99–101 °C ; $[\alpha]_D^{20}$ +25.1 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 22.7 min, t_R minor: 32.6 min, 96:4 er; ν_{max} (film) 3030 (Ph), 2968, 2924, 2859 (C-H), 1640 (C=O), 1555, 1381 (NO_2), 1497, 1443, 908 (Ph); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.39 (1H, dd, *J* 16.6, 7.7, CH_2CON), 2.53 (1H, dd, *J* 16.6, 5.9, CH_2CON), 3.22–

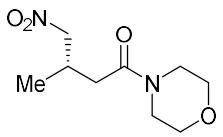
3.31 (2H, m, C$H_{2(morph)}$), 3.49–3.64 (6H, m, C$H_{2(morph)}$), 4.07–4.14 (1H, m, CH), 4.54–4.62 (2H, m, CH_2NO_2), 4.64–4.81 (2×CH_2Ph), 7.21–7.38 (10H, m, CH_{Ph}); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 33.1 (*C*H_2CON), 36.7 (CH), 42.2 ($CH_{2(morph)}$), 45.7 ($CH_{2(morph)}$), 50.1 (*C*H_2Ph), 51.0 (*C*H_2Ph), 66.4 ($CH_{2(morph)}$), 66.8 ($CH_{2(morph)}$), 75.7 (*C*H_2NO_2), 127.2 (2×CH_{Ph}), 127.7 (CH_{Ph}), 128.0 (CH_{Ph}), 128.2 (2×CH_{Ph}), 128.9 (2×CH_{Ph}), 129.2 (2×CH_{Ph}), 136.7 (C_{Ph}), 136.9 (C_{Ph}), 167.8 (*C*ON), 172.5 (*C*ONBn_2); *m/z* (NSI^+) 426 ($[M+H]^+$, 100%), 448 ($[M+Na]^+$, 55%); HRMS (NSI^+) $C_{23}H_{28}O_6N_3$ $[M+H]^+$, found 426.2022, requires 426.2023 (–0.3 ppm).

(*S*)-4-Morpholino-2-(nitromethyl)-1-(pyrrolidin-1-yl)butane-1,4-dione (323)



Following General Procedure 17, 4-nitrophenyl (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoate (58.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 µL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (35.9 mg, 60%) as a colorless oil; $[\alpha]_D^{20}$ +14.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (80:20 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 9.2 min, t_R major: 12.6 min, 96:4 er; ν_{max} (film) 2976, 2874, 2866 (C-H), 1636 (C=O), 1555, 1377 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.89 (2H, p, *J* 7.1, C$H_{2(pyrr)}$), 2.00 (2H, p, *J* 6.6, C$H_{2(pyrr)}$), 2.41 (1H, dd, *J* 16.3, 6.0, CH_2CON), 2.84 (1H, dd, *J* 16.3, 8.0, CH_2CON), 3.42–3.47 (4H, m, C$H_{2(pyrr)}$), 3.56–3.58 (2H, m, C$H_{2(morph)}$), 3.63–3.68 (5H, m, C$H_{2(morph)}$), 3.75–3.79 (1H, m, C$H_{2(morph)}$), 3.87–3.93 (1H, m, C*H*), 4.50 (1H, dd, *J* 13.6, 5.9, CH_2NO_2), 4.71 (1H, dd, *J* 13.6, 8.4, CH_2NO_2); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 24.5 $CH_{2(pyrr)}$), 26.1 $CH_{2(pyrr)}$), 33.2 (*C*H_2CON), 38.4 (*C*H), 42.2 ($CH_{2(morph)}$), 45.9 ($CH_{2(morph)}$), 46.4 ($CH_{2(pyrr)}$), 47.0 ($CH_{2(pyrr)}$), 66.6 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 76.1 (*C*H_2NO_2), 168.2 (*C*ON), 169.6 (*C*ON); *m/z* (NSI^+) 322 ($[M+Na]^+$, 100%; 621 $[2M+Na]^+$, 55%); HRMS (NSI^+) $C_{13}H_{22}O_5N_3$ $[M+H]^+$, found 300.1557, requires 300.1554 (+1.0 ppm).

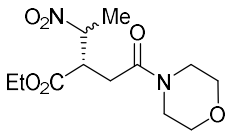
(*S*)-3-Methyl-1-morpholino-4-nitrobutan-1-one (324)



Following General Procedure 17, 4-nitrophenyl (*E*)-but-2-enoate (41.4 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 µL) and subsequent

chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (9.9 mg, 23%) as a colorless oil; $[\alpha]_D^{20}$ +24.0 (*c* 0.25, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 24.0 min, t_R major: 39.0 min, 91:9 er; ν_{max} (film) 2970, 2924, 2860 (C-H), 1639 (C=O), 1551, 1381 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.13 (3H, d, *J* 6.9, CH_3), 2.32 (1H, dd, *J* 16.1, 6.2, CH_2CON), 2.48 (1H, dd, *J* 16.1, 7.4, CH_2CON), 2.81–2.88 (1H, m, CH), 3.42–3.50 (2H, m, C$H_{2(morph)}$), 3.59–3.64 (2H, m, C$H_{2(morph)}$), 3.67–3.70 (4H, m, C$H_{2(morph)}$), 4.44 (1H, dd, *J* 11.9, 6.1, CH_2NO_2), 4.52 (1H, dd, *J* 11.9, 5.9, CH_2NO_2); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 17.8 (CH_3), 29.6 (CH), 33.3 (*C*H_2CON), 42.1 ($CH_{2(morph)}$), 46.0 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 67.0 ($CH_{2(morph)}$), 80.7 (*C*H_2NO_2), 169.1 (*C*ON); *m/z* (NSI$^+$) 239 ([M+Na]$^+$, 100%), 455 ([2M+Na]$^+$, 50%); HRMS (NSI$^+$) $C_9H_{17}O_4N_2$ [M+H]$^+$, found 217.1182, requires 217.1183 (–0.4 ppm).

Ethyl (*S*)-4-morpholino-2-(1-nitroethyl)-4-oxobutanoate (335)



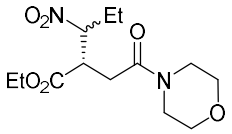
Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitroethane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound as an inseparable mixture of diastereomers (38.1 mg, 66%, 55:45 dr) as a colorless oil; $[\alpha]_D^{20}$ +5.4 (*c* 0.5, $CHCl_3$); ν_{max} (film) 2968, 2926, 2857 (C-H), 1736 (C=O), 1643 (C=O), 1553, 1393, 1362 (NO_2); *m/z* (NSI$^+$) 289 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{12}H_{21}O_6N_2$ [M+H]$^+$, found 289.1396, requires 289.1394 (+0.7 ppm).

major diastereomer: Chiral HPLC analysis, Chiralpak ODH (95:5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R major: 70.7 min, t_R minor: 78.7 min, 99:1 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.26–1.30 (3H, m, $CO_2CH_2CH_3$), 1.60 (3H, d, *J* 6.9, CH*C*H_3), 2.38 (1H, dd, *J* 16.3, 3.8, CH_2CON), 2.86 (1H, dd, *J* 16.8, 7.2, CH_2CON), 3.45–3.50 (2H, m, C$H_{2(morph)}$), 3.57–3.62 (3H, m, CH, C$H_{2(morph)}$), 3.64–3.71 (4H, m, C$H_{2(morph)}$), 4.17–4.24 (2H, m, $CO_2CH_2CH_3$), 4.98 (1H, *app* pent., *J* 6.9, C*H*NO_2); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.0 ($CO_2CH_2CH_3$), 16.7 (CH*C*H_3), 30.8 (*C*H_2CON), 42.2 ($CH_{2(morph)}$), 42.3 ($CH_{2(morph)}$), 44.7 (*C*HCO$_2$Et), 45.8 ($CH_{2(morph)}$), 61.8 ($CO_2CH_2CH_3$), 66.5 ($CH_{2(morph)}$), 66.8 ($CH_{2(morph)}$), 82.4 (*C*HNO_2), 168.3 (*C*ON), 170.7 (*C*O$_2$Et);

minor diastereomer: Chiralpak ODH (95:5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 91.2 min, t_R major: 99.6 min, >99:1 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.26–

1.30 (3H, m, $CO_2CH_2CH_3$), 1.60 (3H, d, *J* 6.9, $CHCH_3$), 2.62 (1H, dd, *J* 16.5, 5.0, CH_2CON), 2.90 (1H, dd, *J* 16.5, 9.1, CH_2CON), 3.45–3.50 (2H, m, $CH_{2(morph)}$), 3.57–3.62 (3H, m, CH, $CH_{2(morph)}$), 3.64–3.71 (4H, m, $CH_{2(morph)}$), 4.17–4.24 (2H, m, $CO_2CH_2CH_3$), 4.98 (1H, *app* pent., *J* 6.9, $CHNO_2$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 17.0 ($CHCH_3$), 30.6 (CH_2CON), 42.2 ($CH_{2(morph)}$), 42.3 ($CH_{2(morph)}$), 45.4 ($CHCO_2Et$), 45.8 ($CH_{2(morph)}$), 61.8 ($CO_2CH_2CH_3$), 66.5 ($CH_{2(morph)}$), 66.8 ($CH_{2(morph)}$), 82.9 ($CHNO_2$), 168.3 (*C*ON), 170.9 (CO_2Et).

Ethyl (*S*)-2-(2-morpholino-2-oxoethyl)-3-nitropentanoate (336)



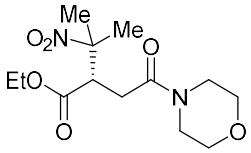
Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in 1-nitropropane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound as an separable mixture of diastereomers (56:44 dr, major: 24.6 mg, 41%; minor: 19.4, 32%) as a colorless oil;

major diastereomer: $[\alpha]_D^{20}$ +11.8 (*c* 0.4, $CHCl_3$); Chiral HPLC analysis, Chiralpak ODH (95:5 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R major: 46.0 min, t_R minor: 50.1 min, 99:1 er; ν_{max} (film) 2980, 2930, 2860 (C-H), 1734 (C=O), 1645 (C=O), 1553, 1373 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.00 (3H, t, *J* 7.3, $CHCH_2CH_3$), 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.81 (1H, dqd, *J* 14.8, 7.5, 4.6, $CHCH_2CH_3$), 2.10 (1H, ddq, *J* 14.8, 7.5, 9.8, $CHCH_2CH_3$), 2.39 (1H, dd, *J* 16.3, 3.3, CH_2CON), 2.87 (1H, dd, *J* 16.3, 10.2, CH_2CON), 3.44–3.51 (3H, m, CH, $CH_{2(morph)}$), 3.56–3.60 (2H, m, $CH_{2(morph)}$), 3.65–3.71 (4H, m, $CH_{2(morph)}$), 4.16–4.27 (2H, m, $CO_2CH_2CH_3$), 4.74 (1H, ddd, *J* 9.8, 7.0, 4.6, $CHNO_2$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 10.5 ($CHCH_2CH_3$), 14.2 ($CO_2CH_2CH_3$), 25.1 ($CHCH_2CH_3$), 31.1 (CH_2CON), 42.3 ($CH_{2(morph)}$), 44.7 ($CHCO_2Et$), 45.9 ($CH_{2(morph)}$), 61.9 ($CO_2CH_2CH_3$), 66.6 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 90.1 ($CHNO_2$), 168.4 (*C*ON), 171.3 (CO_2Et); *m/z* (NSI^+) 303 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{13}H_{23}O_6N_2$ $[M+H]^+$, found 303.1553, requires 303.1551 (+0.7 ppm).

minor diastereomer: $[\alpha]_D^{20}$ +15.8 (*c* 0.4, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R minor: 28.4 min, t_R major: 38.7 min, 99:1 er; ν_{max} (film) 2978, 2927, 2859 (C-H), 1734 (C=O), 1647 (C=O), 1553, 1375 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.00 (3H, t, *J* 7.3, $CHCH_2CH_3$), 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.88 (1H, dqd, *J* 14.9, 7.3, 4.4, $CHCH_2CH_3$), 2.11 (1H, dqd, *J* 14.9, 7.3, 10.0, $CHCH_2CH_3$), 2.63 (1H, dd, *J* 16.5, 5.0, CH_2CON), 2.84 (1H, dd, *J* 16.5, 8.0, CH_2CON), 3.47–3.49 (2H, m,

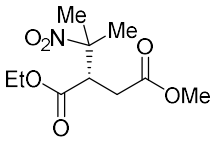
C$H_{2(morph)}$), 3.56–3.60 (3H, m, CH, C$H_{2(morph)}$), 3.66–3.70 (4H, m, C$H_{2(morph)}$), 4.16–4.24 (2H, m, $CO_2CH_2CH_3$), 4.78 (1H, *app* dt, *J* 10.0, 4.4, C*H*NO_2); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 10.7 ($CHCH_2CH_3$), 14.2 ($CO_2CH_2CH_3$), 25.0 ($CHCH_2CH_3$), 31.2 (CH_2CON), 42.3 ($CH_{2(morph)}$), 44.0 ($CHCO_2Et$), 45.9 ($CH_{2(morph)}$), 61.9 ($CO_2CH_2CH_3$), 66.6 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 89.8 ($CHNO_2$), 168.4 (*C*ON), 170.8 (CO_2Et); *m/z* (NSI^+) 303 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{13}H_{23}O_6N_2$ $[M+H]^+$, found 303.1553, requires 303.1551 (+0.7 ppm).

Ethyl (*S*)-3-methyl-2-(2-morpholino-2-oxoethyl)-3-nitrobutanoate (337)



Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in 2-nitropropane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 50:50 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (28.1 mg, 46%) as colorless oil; $[\alpha]_D^{20}$ +41.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 10.2 min, t_R major: 11.2 min, 98:2 er; ν_{max} (film) 2982, 2928, 2860 (C-H), 1730 (C=O), 1645 (C=O), 1543, 1383 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.28 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.62 (3H, s, C(CH_3)), 1.65 (3H, s, C(CH_3)), 2.23 (1H, dd, *J* 16.0, 2.9, CH_2CON), 2.89 (1H, dd, *J* 16.0, 11.4, CH_2CON), 3.41–3.44 (2H, m, C$H_{2(morph)}$), 3.54–3.57 (2H, m, C$H_{2(morph)}$), 3.63–3.68 (4H, m, C$H_{2(morph)}$), 3.72 (1H, dd, *J* 11.4, 2.9, C*H*), 4.13–4.26 (2H, m, $CO_2CH_2CH_3$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.2 ($CO_2CH_2CH_3$), 22.8 (C(CH_3)), 26.3 (C(CH_3)), 31.5 (CH_2CON), 42.2 ($CH_{2(morph)}$), 42.8 ($CH_{2(morph)}$), 49.6 ($CHCO_2Et$), 61.7 ($CO_2CH_2CH_3$), 66.5 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 88.6 ($C(CH_3)_2NO_2$), 168.5 (*C*ON), 171.3 (CO_2Et); *m/z* (NSI^+) 303 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{13}H_{23}O_6N_2$ $[M+H]^+$, found 303.1559, requires 303.1551 (+2.6 ppm).

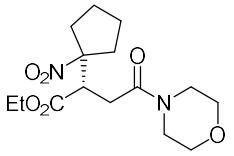
1-Ethyl 4-methyl (*S*)-2-(2-nitropropan-2-yl)succinate (338)



Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (663.1 mg, 2.5 mmol) and HyperBTM (154.2 mg, 0.5 mmol) in 2-nitropropane (12.5 mL), methanol (10 mL), 4-(dimethylamino)pyridine (61 mg, 0.5 mmol) and subsequent chromatography (100% CH_2Cl_2, R_f 0.20) afforded the title compound (234.9 mg, 38%) as a colorless oil; $[\alpha]_D^{20}$ –4.6 (*c* 0.5, $CHCl_3$);

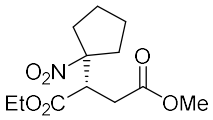
Chiral HPLC analysis, Chiralpak ADH (99:1 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 14.8 min, t_R major: 17.1 min, 98:2 er; ν_{max} (film) 2988, 2955 (C-H), 1736 (C=O), 1545, 1346 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.27 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.61 (3H, s, $C(CH_3)$), 1.63 (3H, s, $C(CH_3)$), 2.37 (1H, dd, *J* 16.8, 3.3, CH_2CO_2Me), 2.87 (1H, dd, *J* 16.8, 11.4, CH_2CO_2Me), 3.69 (3H, CO_2CH_3), 3.72 (1H, dd, *J* 11.4, 3.3, C*H*), 4.19 (2H, q, *J* 7.1, $CO_2CH_2CH_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 23.3 ($C(CH_3)$), 25.2 ($C(CH_3)$), 32.5 (CH_2CO_2Me), 49.2 ($CHCO_2Et$), 52.3 (CO_2CH_3), 61.8 ($CO_2CH_2CH_3$), 88.4 ($C(CH_3)_2NO_2$), 170.7 (CO_2Me), 171.5 (CO_2Et); *m/z* (NSI$^+$) 248 ([M+H]$^+$, 90%); HRMS (NSI$^+$) $C_{10}H_{18}O_6N_1$ [M+H]$^+$, found 248.1131, requires 248.1129 (+1.0 ppm).

Ethyl (*S*)-4-morpholino-2-(1-nitrocyclopentyl)-4-oxobutanoate (339)



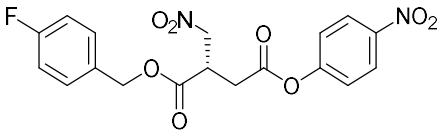
Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (53.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitrocyclopentane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 60:40 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (31.5 mg, 48%) as a colorless oil; $[\alpha]_D^{20}$ +58.0 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 16.2 min, t_R major: 20.7 min, 97:3 er; ν_{max} (film) 2961, 2924, 2857 (C-H), 1732 (C=O), 1647 (C=O), 1539, 1438 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.67–1.71 (4H, m, $CH_{2(cp)}$), 1.94–2.00 (1H, m, $CH_{2(cp)}$), 2.09–2.15 (1H, m, $CH_{2(cp)}$), 2.35 (1H, dd, *J* 16.2, 2.9, CH_2CON), 2.53–2.60 (1H, m, $CH_{2(cp)}$), 2.67–2.71 (1H, m, $CH_{2(cp)}$), 2.92 (1H, dd, *J* 16.2, 10.9, CH_2CON), 3.44–3.49 (2H, m, $CH_{2(morph)}$), 3.55–3.60 (2H, m, $CH_{2(morph)}$), 3.63–3.72 (5H, m, $CH_{2(morph)}$, CH), 4.14–4.28 (2H, m, $CO_2CH_2CH_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.3 ($CO_2CH_2CH_3$), 23.6 ($CH_{2(cp)}$), 24.0 ($CH_{2(cp)}$), 32.2 (CH_2CON), 35.1 ($CH_{2(cp)}$), 37.2 ($CH_{2(cp)}$), 42.3 ($CH_{2(morph)}$), 45.9 ($CH_{2(morph)}$), 48.7 ($CHCO_2Et$), 61.7 ($CO_2CH_2CH_3$), 66.6 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 100.8 ($C(CH_3)_2NO_2$), 168.9 (CON), 171.2 (CO_2Et); *m/z* (NSI$^+$) 329 ([M+H]$^+$, 100%); HRMS (NSI$^+$) $C_{15}H_{25}O_6N_2$ [M+H]$^+$, found 329.1710, requires 329.1707 (+0.9 ppm).

1-Ethyl 4-methyl (*S*)-2-(1-nitrocyclopentyl)succinate (340)



Following General Procedure 17, ethyl (4-nitrophenyl) fumarate (132.6 mg, 0.5 mmol) and HyperBTM (30.8 mg, 0.1 mmol) in nitrocyclopentane (2.5 mL), methanol (2.5 mL), 4-(dimethylamino)pyridine (12.2 mg, 0.1 mmol) and subsequent chromatography (100% CH_2Cl_2, R_f 0.25) afforded the title compound (57.4 mg, 42%) as a colorless oil; $[\alpha]_D^{20}$ –8.6 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ODH (98:2 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R major: 9.2 min, t_R minor: 48.7 min, 97:3 er; ν_{max} (film) 2957 (C-H), 1734 (C=O), 1541, 1437 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.26 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.64–1.79 (4H, m, $CH_{2(cp)}$), 1.90–1.96 (1H, m, $CH_{2(cp)}$), 2.03–2.09 (1H, m, $CH_{2(cp)}$), 2.45 (1H, dd, *J* 17.0, 3.3, CH_2CO_2Me), 2.52–2.57 (1H, m, $CH_{2(cp)}$), 2.60–2.65 (1H, m, $CH_{2(cp)}$), 2.88 (1H, dd, *J* 17.0, 11.1, CH_2CO_2Me), 3.58 (1H, dd, *J* 11.1, 3.3, CH), 3.67 (3H, CO_2CH_3), 4.13–4.23 (2H, m, $CO_2CH_2CH_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 23.9 ($CH_{2(cp)}$), 24.1 ($CH_{2(cp)}$), 33.2 (CH_2CO_2Me), 35.2 ($CH_{2(cp)}$), 36.7 ($CH_{2(cp)}$), 48.3 ($CHCO_2Et$), 52.2 (CO_2CH_3), 61.7 ($CO_2CH_2CH_3$), 100.2 ($C(CH_3)_2NO_2$), 170.6 (CO_2Me), 171.8 (CO_2Et); *m/z* (NSI$^+$) 274 ([M+H]$^+$, 50%); HRMS (NSI$^+$) $C_{12}H_{20}O_6N_1$ [M+H]$^+$, found 274.1287, requires 274.1285 (+0.7 ppm).

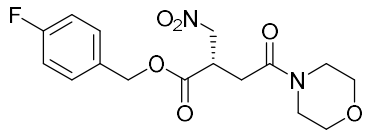
1-(4-Fluorobenzyl) 4-(4-nitrophenyl) (*S*)-2-(nitromethyl)succinate (S34)



Following General Procedure 17, 4-fluorobenzyl (4-nitrophenyl) fumarate (69.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (90:10 – 70:30 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (36.3 mg, 45%) as a colorless oil; $[\alpha]_D^{20}$ –5.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (80:20 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 21.8 min, t_R minor: 26.6 min, 95:5 er; ν_{max} (film) 3117, 2967 (C-H), 1763 (C=O), 1740 (C=O), 1558, 1348 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.01 (1H, dd, *J* 17.6, 5.9, $CH_2CO_2Ar_{PNP}$), 3.17 (1H, dd, *J* 17.6, 6.8, $CH_2CO_2Ar_{PNP}$), 3.69 (1H, *app* pent., *J* 5.9, CH), 4.80–4.89 (2H, m, CH_2NO_2), 5.15–5.21 (2H, m, $CO_2CH_2Ar_F$), 7.03–7.06 (2H, m, $CH_{Ar\text{-}F}$), 7.18–7.20 (2H, m, CH-Ar_{PNP}), 7.31–7.33 (2H, m, $CH_{Ar\text{-}F}$), 8.24–8.26 (2H, m, CH-Ar_{PNP}); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: –112.5; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 33.1 (CH_2CON), 39.2 (CH), 67.5 (CH_2Ar_F), 74.4 (CH_2NO_2), 115.8 (d, $^2J_{CF}$ 21.7,

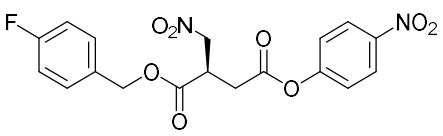
CH_{Ar}-F), 122.4 (2×*C*H-Ar_{PNP}), 125.4 (2×*C*H-Ar_{PNP}), 130.6 (d, $^4J_{CF}$ = 3.2, C_{Ar}-F), 130.8 (d, $^3J_{CF}$ 8.3, CH_{Ar}-F), 145.7 (*C*-NO_2), 154.8 (CO_2C-Ar_{PNP}), 162.0 (d, $^1J_{CF}$ 245.2, C_{Ar}-F), 168.7 (CO_2Ar_{PNP}), 169.7 (CO_2Ar_F); *m/z* (NSI^+) 424 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) $C_{18}H_{19}O_8N_3F_1$ $[M+NH_4]^+$, found 424.1149, requires 424.1151 (−0.4 ppm).

4-Fluorobenzyl (*S*)-4-morpholino-2-(nitromethyl)-4-oxobutanoate (S35)



Following General Procedure 17, 4-fluorobenzyl (4-nitrophenyl) fumarate (69.0 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL), morpholine (70 μL) and subsequent chromatography (80:20 – 30:70 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (41.4 mg, 58%) as a colorless oil; $[\alpha]_D^{20}$ +19.0 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (80:20 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R minor: 16.3 min, t_R major: 39.8 min, 93.5:6.5 er; ν_{max} (film) 2965, 2922, 2860 (C-H), 1738 (C=O), 1645 (C=O), 1554, 1381 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.74 (1H, dd, *J* 16.9, 6.8, CH_2CON), 2.87 (1H, dd, *J* 16.9, 4.9, CH_2CON), 3.42–3.44 (2H, m, C$H_{2(morph)}$), 3.57–3.59 (2H, m, C$H_{2(morph)}$), 3.63–3.67 (5H, m, CH, C$H_{2(morph)}$), 4.79–4.89 (2H, m, CH_2NO_2), 5.14 (2H, s, $CO_2CH_2Ar_F$), 7.03–7.07 (2H, m, $CH_{Ar\text{-}F}$), 7.29–7.32 (2H, m, $CH_{Ar\text{-}F}$); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −113.0; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 31.6 (*C*H_2CON), 39.4 (CH), 42.3 ($CH_{2(morph)}$), 45.8 ($CH_{2(morph)}$), 66.5 ($CH_{2(morph)}$), 66.9 ($CH_{2(morph)}$), 67.0 (*C*H_2Ar_F), 75.1 (*C*H_2NO_2), 115.7 (d, $^2J_{CF}$ = 21.6, CH_{Ar}-F), 130.5 (d, $^3J_{CF}$ = 8.3, CH_{Ar}-F), 131.1 (d, $^4J_{CF}$ = 3.2, C_{Ar}-F), 162.9 (d, $^1J_{CF}$ = 247.6, C_{Ar}-F), 168.0 (*C*ON), 170.8 (CO_2Ar_F); *m/z* (NSI^+) 355 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{16}H_{20}O_6N_2F$ $[M+H]^+$, found 355.1302, requires 355.1300 (+0.6 ppm).

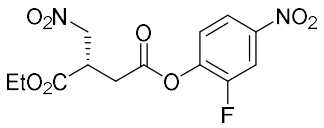
1-(4-Fluorobenzyl) 4-(4-nitrophenyl) (*R*)-2-(nitromethyl)succinate (362)



Following General Procedure 17, 4-fluorobenzyl (4-nitrophenyl) fumarate (69.0 mg, 0.2 mmol) and 8F-HyperBTM (13.0 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (90:10 – 70:30 Petroleum ether : EtOAc, R_f 0.10) afforded the title compound (41 mg, 50%) as a colorless oil; $[\alpha]_D^{20}$ +4.2 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH

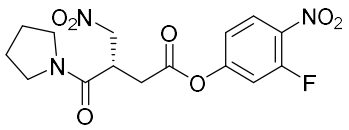
(80:20 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R minor: 22.1 min, t_R major: 27.0 min, 95:5 er. NMR data consistent with **S34**.

1-Ethyl 4-(2-fluoro-4-nitrophenyl) (*S*)-2-(nitromethyl)succinate (356)



Following General Procedure 17, ethyl (2-fluoro-4-nitrophenyl) fumarate (56.6 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (95:5 – 60:40 Petroleum ether : EtOAc, R_f 0.15) afforded the title compound (34.4 mg, 50%) as a colorless oil; $[\alpha]_D^{20}$ –3.6 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (90:10 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 39.9 min, t_R minor: 43.0 min, 97:3 er; ν_{max} (film) 3061, 2986 (C-H), 1775 (C=O), 1736 (C=O), 1558, 1352 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.07 (1H, dd, *J* 17.7, 6.2, CH_2CO_2), 3.24 (1H, dd, *J* 17.7, 6.5, CH_2CO_2), 3.65 (1H, *app* pent., *J* 6.0, CH), 4.26 (2H, dd, *J* 14.3, 7.1, $CO_2CH_2CH_3$), 4.80–4.89 (2H, m, CH_2NO_2), 7.09–7.18 (2H, m, C*H*-Ar_F), 8.12–8.16 (1H, m, C*H*-Ar_F); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −122.4; ^{19}F NMR (376 MHz, C_6D_6) δ_F: −124.06; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.1 ($CO_2CH_2CH_3$), 32.7 (CH_2COO), 39.1 (CH), 62.6 ($CO_2CH_2CH_3$), 74.3 (CH_2NO_2), 113.2 (d, $^2J_{CF}$ 23.6, CH_{Ar}-F), 120.4 (d, $^3J_{CF}$ 3.7, CH_{Ar}-F), 124.4 (d, $^4J_{CF}$ 1.4, *C*H-Ar_F), 143.1 (d, $^3J_{CF}$ 13.0, NO_2-C_{Ar}-F), 153.5 (d, $^1J_{CF}$ 255.2, C_{Ar}-F), 167.8 (CO_2Ar_F), 169.6 (CO_2Et); *m/z* (NSI$^+$) 362 ([M+NH_4]$^+$, 100%); HRMS (NSI$^+$) $C_{13}H_{17}O_8N_3F$ [M+NH_4]$^+$, found 362.0993, requires 362.0994 (–0.3 ppm).

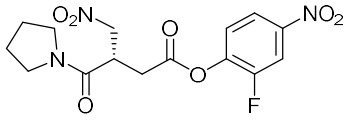
3-Fluoro-4-nitrophenyl (*S*)-3-(nitromethyl)-4-oxo-4-(pyrrolidin-1-yl)butanoate (357)



Following General Procedure 17, 3-fluoro-4-nitrophenyl (E)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoate (61.6 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (70:30 – 30:70 Petroleum ether : EtOAc, R_f 0.13) afforded the title compound (27.3 mg, 37%) as a colorless oil. *Note*: the ester product and 3-fluoro-4-nitrophenol were isolated as inseparable mixture; $[\alpha]_D^{20}$ +7.4 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (80:20 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 19.7 min, t_R minor: 30.6 min, 98:2 er; ν_{max} (film) 2976, 2882 (C-H), 1771 (C=O), 1638 (C=O), 1557, 1348

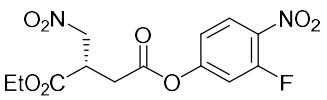
(NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.88–1.94 (2H, m, CH_{2pyrr}), 2.00–2.05 (2H, m, CH_{2pyrr}), 2.82 (1H, dd, *J* 17.5, 5.3, CH_2COO), 3.18 (1H, dd, *J* 17.5, 8.6, CH_2COO), 3.49 (2H, t, *J* 7.0, CH_{2pyrr}), 3.64–3.75 (2H, m, CH_{2pyrr}), 3.82–3.88 (1H, m, CH), 4.53 (1H, dd, *J* 13.9, 6.5, CH_2NO_2), 4.80 (1H, dd, *J* 13.9, 7.7, CH_2NO_2), 7.08 (1H, ddd, *J* 9.1, 2.4, 1.4, C*H*-Ar$_F$), 7.15 (1H, dd, *J* 11.1, 2.4, C*H*-Ar$_F$), 8.14 (1H, dd, *J* 9.1, 8.2, C*H*-Ar$_F$); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −112.7; ^{19}F NMR (376 MHz, C_6D_6) δ_F: −115.02; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.4 (*C*H_{2pyrr}), 26.1 (*C*H_{2pyrr}), 34.5 (*C*H_2COO), 38.0 (CH), 46.6 (*C*H_{2pyrr}), 47.1 (*C*H_{2pyrr}), 75.5 (*C*H_2NO_2), 112.3 (d, $^2J_{CF}$ 24.0, CH_{Ar}-F), 117.9 (d, $^3J_{CF}$ 3.9, CH_{Ar}-F), 127.4 (d, $^4J_{CF}$ 1.4, CH_{Ar}-F), 154.9 (d, $^2J_{CF}$ 10.7, NO_2C_{Ar}-F), 156.0 (d, $^1J_{CF}$ 289.7, C_{Ar}-F), 168.1 (*C*O_2Ar$_F$), 168.1 (*C*ON); HRMS (ESI$^+$) $C_{15}H_{17}O_7N_3F$ $[M+H]^+$, found 370.1051, requires 370.1045 (+1.1 ppm).

2-Fluoro-4-nitrophenyl (*S*)-3-(nitromethyl)-4-oxo-4-(pyrrolidin-1-yl)butanoate (358)



Following General Procedure 17, 2-fluoro-4-nitrophenyl (*E*)-4-oxo-4-(pyrrolidin-1-yl)but-2-enoate (61.6 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (80:20 – 30:70 Petroleum ether : EtOAc, R_f 0.15) afforded the title compound (22.4 mg, 30%) as a colorless oil. *Note*: the ester product and 2-fluoro-4-nitrophenol were isolated as inseparable mixture; $[\alpha]_D^{20}$ +8.7 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (80:20 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 19.3 min, t_R minor: 20.9 min, 96:4 er; ν_{max} (film) 2974, 2878 (C-H), 1773 (C=O), 1639 (C=O), 1553, 1342 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.89–2.05 (4H, m, CH_{2pyrr}), 2.86 (1H, dd, *J* 17.4, 5.7, CH_2COO), 3.21 (1H, dd, *J* 17.4, 8.4, CH_2COO), 3.48–3.52 (2H, m, CH_{2pyrr}), 3.66–3.73 (2H, m, CH_{2pyrr}), 3.85–3.91 (1H, m, CH), 4.54 (1H, dd, *J* 14.0, 5.9, CH_2NO_2), 4.84 (1H, dd, *J* 14.0, 8.4, CH_2NO_2), 7.05–7.08 (1H, m, C*H*-Ar$_F$), 7.35–7.38 (1H, m, C*H*-Ar$_F$), 7.97–7.99 (1H, m, C*H*-Ar$_F$); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −122.3; ^{19}F NMR (376 MHz, C_6D_6) δ_F: −124.18; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.3 (*C*H_{2pyrr}), 26.0 (*C*H_{2pyrr}), 33.8 (*C*H_2CO_2), 37.8 (CH), 46.5 (*C*H_{2pyrr}), 47.0 (*C*H_{2pyrr}), 75.3 (*C*H_2NO_2), 112.3 (d, $^2J_{CF}$ 22.9, CH_{Ar}-F), 117.2 (d, $^3J_{CF}$ 2.5, CH_{Ar}-F), 124.3 (d, $^3J_{CF}$ 1.2, CH_{Ar}-F), 151.0 (d, $^3J_{CF}$ 13.0, NO_2-C_{Ar}-F), 153.4 (d, $^1J_{CF}$ 253.2, C_{Ar}-F), 167.9 (*C*O_2Ar$_F$), 168.1 (*C*ON); HRMS (ESI$^+$) $C_{15}H_{17}O_7N_3F$ $[M+H]^+$, found 370.1047, requires 370.1045 (+0.5 ppm).

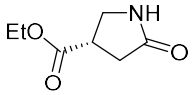
1-Ethyl 4-(3-fluoro-4-nitrophenyl) (*S*)-2-(nitromethyl)succinate (359)



Following General Procedure 17, ethyl (3-fluoro-4-nitrophenyl) fumarate (56.6 mg, 0.2 mmol) and HyperBTM (12.3 mg, 0.04 mmol) in nitromethane (1.0 mL) and subsequent chromatography (95:5 – 60:40 Petroleum ether : EtOAc, R_f 0.18) afforded the title compound (34.4 mg, 50%) as a colorless oil; $[\alpha]_D^{20}$ –8.6 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (92:8 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 40 °C) t_R major: 33.8 min, t_R minor: 37.4 min, 96:4 er; ν_{max} (film) 3063, 2984 (C-H), 1771 (C=O), 1734 (C=O), 1557, 1348 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 3.00 (1H, dd, *J* 17.6, 5.8, CH_2CO_2), 3.17 (1H, dd, *J* 17.6, 7.0, CH_2CO_2), 3.64 (1H, *app* pent., *J* 5.9, CH), 4.21–4.30 (2H, m, $CO_2CH_2CH_3$), 4.80–4.89 (2H, m, CH_2NO_2), 7.36–7.39 (1H, m, CH-Ar_F), 8.07–8.11 (2H, m, CH-Ar_F); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −112.9; ^{19}F NMR (376 MHz, C_6D_6) δ_F: −115.00; $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.0 ($CO_2CH_2CH_3$), 33.1 (CH_2COO), 39.1 (CH), 62.5 ($CO_2CH_2CH_3$), 74.3 (CH_2NO_2), 112.1 (d, $^2J_{CF}$ 24.0, CH_{Ar}-F), 117.8 (d, $^3J_{CF}$ 4.0, C_{Ar}-F), 127.3 (d, $^4J_{CF}$ 1.4, CH-Ar_F), 135.0 (d, $^3J_{CF}$ 7.0, CO_2C_{Ar}-F), 154.8 (d, $^2J_{CF}$ 7.0, NO_2C_{Ar}-F), 156.1 (d, $^1J_{CF}$ 267.2, C_{Ar}-F), 168.3 (CO_2Ar_F), 169.6 (CO_2Et); *m/z* (NSI^+) 345 ($[M+H]^+$, 100%); HRMS (NSI^+) $C_{13}H_{14}O_8N_2F$ $[M+H]^+$, found 345.0725, requires 345.0729 (–1.2 ppm).

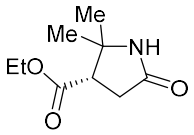
7.4.3.2 Product derivatisations

Ethyl (*S*)-5-oxopyrrolidine-3-carboxylate (344)



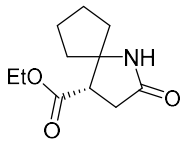
Following General Procedure 18, 1-ethyl 4-methyl (*S*)-2-(nitromethyl)succinate (135.0 mg, 0.62 mmol), $NiCl_2 \cdot 6H_2O$ (147.0 mg, 0.62 mmol), $NaBH_4$ (188 mg, 4.96 mmol) in MeOH (12.0 mL) and subsequent chromatography (98:2 – 90:10 CH_2Cl_2:MeOH, R_f 0.10) afforded the title compound (70.7 mg, 73%) as a colorless oil; $[\alpha]_D^{20}$ –4.7 (*c* 0.6, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (95:5 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R major: 20.5 min, t_R minor: 44.1 min, 94:6 er; ν_{max} (film) 3246 (NH), 3054 (C-H), 1732 (C=O), 1697 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.27 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.57 (1H, dd, *J* 17.2, 9.8, CH_2C=O), 2.88 (1H, dd, *J* 17.2, 7.7, CH_2C=O), 3.30–3.37 (1H, m, CH), 3.59–3.65 (2H, m, CH_2NH), 4.19 (2H, q, *J* 7.1, $CO_2CH_2CH_3$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.3 ($CO_2CH_2CH_3$), 33.1 (CH_2C=O), 39.1 (CH), 44.4 (CH_2NH), 61.6 ($CO_2CH_2CH_3$), 172.9 (CO_2Et), 176.5 (*C*ON); *m/z* (NSI$^+$) 158 ([M+H]$^+$, 100%; 180 ([M+Na]$^+$, 80%); HRMS (NSI$^+$) $C_7H_{12}O_3N_1$ [M+H]$^+$, found 158.0810, requires 158.0812 (–1.1 ppm).

Ethyl (*S*)-2,2-dimethyl-5-oxopyrrolidine-3-carboxylate (345)



Following General Procedure 18, 1-ethyl 4-methyl (*S*)-2-(2-nitropropan-2-yl)succinate (173.1 mg, 0.70 mmol), $NiCl_2 \cdot 6H_2O$ (166.4 mg, 0.70 mmol), $NaBH_4$ (212 mg, 5.60 mmol) in MeOH (14.0 mL) and subsequent chromatography (98:2 CH_2Cl_2 : MeOH, R_f 0.30) afforded the title compound (113.7 mg, 92%) as colorless crystals. mp 60–62 °C; $[\alpha]_D^{20}$ –2.3 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (97:3 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 40 °C) t_R major: 22.3 min, t_R minor: 31.7 min, 96:4 er; ν_{max} (film) 3215 (NH), 2978 (C-H), 1730 (C=O), 1692 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.15 (3H, s, $C(CH_3)_2$), 1.26 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.45 (3H, s, $C(CH_3)_2$), 2.42 (1H, dd, *J* 17.2, 8.8, CH_2C=O), 2.89 (1H, dd, *J* 17.2, 10.0, CH_2C=O), 3.02 (1H, dd, *J* 10.0, 8.8, CH), 4.12–4.23 (2H, m, $CO_2CH_2CH_3$), 6.27 (1H, s, NH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.3 ($CO_2CH_2CH_3$), 24.7 ($C(CH_3)_2$), 29.6 ($C(CH_3)_2$), 33.1 (CH_2C=O), 50.5 (CH), 58.4 ($C(CH_3)_2$), 61.2 ($CO_2CH_2CH_3$), 171.1 (CO_2Et), 175.2 (*C*ON); *m/z* (NSI$^+$) 186 ([M+H]$^+$, 100%; 208 ([M+Na]$^+$, 50%); HRMS (NSI$^+$) $C_9H_{16}O_3N_1$ [M+H]$^+$, found 186.1123, requires 186.1125 (–0.9 ppm).

Ethyl (*S*)-2-oxo-1-azaspiro[4.4]nonane-4-carboxylate (346)

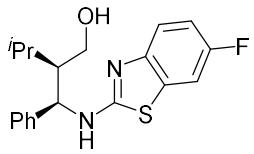


Following General Procedure 18, 1-ethyl 4-methyl (*S*)-2-(1-nitrocyclopentyl) (54.7 mg, 0.20 mmol), $NiCl_2 \cdot 6H_2O$ (47.5 mg, 0.20 mmol), $NaBH_4$ (60.5 mg, 1.60 mmol) in MeOH (5.0 mL) afforded the title compound (43.5 mg, 98%) without further purification as colorless crystals. mp 140–141 °C; $[\alpha]_D^{20}$ –18.0 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (98:2 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 30 °C) t_R minor: 39.3 min, t_R major: 42.8 min, 97:3 er; ν_{max} (film) 3210 (NH), 2965 (C-H), 1730 (C=O), 1690 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.27 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.60–1.63 (2H, m, $CH_{2(cp)}$), 1.67–1.73 (4H, m, $CH_{2(cp)}$), 1.79–1.84 (1H, m, $CH_{2(cp)}$), 1.96–2.00 (1H, m, $CH_{2(cp)}$), 2.48 (1H, dd, *J* 17.0, 8.7, CH_2C=O), 2.81 (1H, dd, *J* 17.0, 8.4, CH_2C=O), 3.20 (1H, *app* t, *J* 8.5, CH), 4.17 (2H, q, *J* 7.1, $CO_2CH_2CH_3$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.4 ($CO_2CH_2CH_3$),), 23.0 ($CH_{2(cp)}$), 23.7 ($CH_{2(cp)}$), 34.0 (CH_2CON), 35.3 ($CH_{2(cp)}$), 39.8 ($CH_{2(cp)}$), 48.4 (CH), 61.1 ($CO_2CH_2CH_3$), 69.0 (C_{quat}), 171.7 (CO_2Et), 175.5 (*C*ON); *m/z* (NSI^+) 212 ($[M+H]^+$, 100%), 445 ($[2M+Na]^+$, 90%); HRMS (NSI^+) $C_{11}H_{18}O_3N_1$ $[M+H]^+$, found 212.1281, requires 212.1281 (–0.1 ppm).

7.4.4 Mechanistic investigations

7.4.4.1 Synthesis of fluorinated catalyst and model compounds

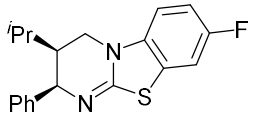
(*R*)-2-((*R*)-((6-Fluorobenzo[*d*]thiazol-2-yl)amino)(phenyl)methyl)-3-methylbutan-1-ol (S36)



(1*R*,2*R*)-2-(Hydroxymethyl)-3-methyl-1-phenylbutan-1-aminium chloride[27] (4.67 g, 20.33 mmol), 2-chloro-6-fluorobenzothiazole (4.04 g, 21.54 mmol) and $^iPr_2NEt$ (13.7 mL, 79.2 mmol) in chlorobenzene were heated at 145 °C for 70 h. The reaction mixture was cooled, washed with water (× 2), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by Biotage© column chromatography (eluent: 0 → 20%, EtOAc in CH_2Cl_2) to give (*R*)-2-((*R*)-((6-fluorobenzo[*d*]thiazol-2-yl)amino)(phenyl)methyl)-3-methylbutan-1-ol as an off white solid (2.78 g, 38%).

mp 60-61 °C; $[\alpha]_D^{20} = +43.5$ (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1}: 3275 (br, OH), 1606, 1548, 1458; Chiral HPLC analysis, Chiralpak AD-H (95:5 Hexane:IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 ºC) t_R(2*S*,3*S*): 25.1 min, t_R(2*R*,3*R*): 28.7 min, >99:1 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.79 (3H, d, *J* 6.8, C*H*$_3$), 1.12 (3H, d, *J* 6.7, C*H*$_3$), 1.62 (1H, app sept., *J* 6.8, CH(CH$_3$)$_2$), 2.14 (1H, ddt, *J* 10.7, 7.5, 4.0, C*H*CH$_2$OH), 3.64 (1H, app t, *J* 10.5, C*H*$_2$), 3.90 (1H, dd, *J* 10.3, 3.4, C*H*$_2$), 4.89 (1H, dd, *J* 8.0, 4.0, C*H*Ph), 4.96 (1H, s, O*H*), 6.95 (1H, app td, *J* 8.9, 2.7, ArC(5)*H*), 7.21 (1H, dd, *J* 8.1, 2.6, ArC(7)*H*), 7.23–7.35 (4H, m, PhC(3,4,5)*H* + ArC(4)*H*), 7.45–7.53 (2H, m, PhC(2,6)*H*), 7.89–8.01 (1H, N*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.8 (*C*H$_3$), 22.8 (*C*H$_3$), 26.9 (C*H*(CH$_3$)$_2$), 51.0 (*C*HCH$_2$OH), 60.6 (*C*H$_2$), 61.9 (*C*HPh), 107.7 (d, *J* 27.0, Ar*C*(5)H), 113.7 (d, *J* 23.8, Ar*C*(7)H), 118.7 (d, *J* 8.8, Ar*C*(4)H), 127.8 (Ph*C*(4)H), 128.2 (Ph*C*(2,6)H), 128.6 (Ph*C*(3,5)H), 130.7 (d, *J* 10.8, Ar*C*(7a)), 139.0 (Ph*C*(1)), 148.1 (Ar*C*(3a)), 158.1 (d, *J* 239.7, Ar*C*(6)), 167.7 (Ar*C*(2)); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −121.54; HRMS (ESI$^+$) $C_{19}H_{22}ON_2FS$ $[M+H]^+$ found 345.1425, requires 345.1431 (−0.7 ppm).

(2*R*,3*S*)-8-Fluoro-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine (361)

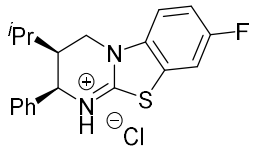


MsCl (0.94 mL, 12.1 mmol) was added to a solution of alcohol **S36** (2.78, 8.07 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 90 min. Then, MeOH (2.6 mL) and Et_3N were added and the reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled, concentrated *in vacuo* and purified by Biotage© column chromatography (eluent: 0 → 30%, EtOAc in CH_2Cl_2) to give a pale yellow solid, which was recrystallized from hot EtOAc/pentane to give (2*R*,3*S*)-8-fluoro-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine as a colourless solid (1.72 g, 65%).

mp (206-208 °C); $[\alpha]_D^{20} = -325.8$ (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1}: 2964, 2864, 1622, 1589, 1438; Chiral HPLC analysis, Chiralpak ID (90:10 Hexane:IPA, flow rate 1.5 $mLmin^{-1}$, 211 nm, 40 ºC) t_R(2*S*,3*R*): 15.5 min, t_R(2*R*,3*S*): 41.6 min, >99:1 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.86 (3H, d, *J* 6.7, C*H*$_3$), 1.15 (3H, d, *J* 6.5, C*H*$_3$), 1.25–1.35 (1H, m, C*H*(CH$_3$)$_2$), 1.97 (1H, app ddt, *J* 11.4, 9.4, 4.8, C*H*CH$_2$), 3.36 (1H, app t, *J* 11.4, C*H*$_2$), 3.86 (1H, ddd, *J* 11.7, 5.3, 1.8, C*H*$_2$), 4.94 (1H, dd, *J* 4.6, 1.7, C*H*Ph), 6.74 (1H, dd, *J* 8.7, 4.2, ArC(6)*H*), 6.96 (1H, app td, *J* 8.8, 2.6, ArC(7)*H*), 7.11 (1H, dd, *J* 7.9, 2.6, ArC(9)*H*), 7.19–7.25 (2H, m, PhC(2,6)*H*), 7.25–7.30 (1H, m, PhC(4)*H*), 7.31-7.36 (2H, m, PhC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.1 (*C*H$_3$), 22.1 (*C*H$_3$), 27.0 (*C*H(CH$_3$)$_2$), 40.9 (*C*HCH$_2$), 42.2 (*C*H$_2$), 61.3 (*C*HPh), 107.8 (d, *J* 8.3, Ar*C*(6)H),

109.8 (d, *J* 27.4, Ar*C*(9)H), 112.6 (d, *J* 23.7, Ar*C*(7)H), 124.5 (d, *J* 9.8, Ar*C*(9a)), 127.4 (Ph*C*(4)H), 128.1 (Ph*C*(2,6)H), 128.5 (Ph*C*(3,5)H), 137.2 (Ar*C*(5a)), 140.5 (Ph*C*(1)), 158.2 (Ar*C*(10a)), 158.5 (d, *J* 240.7, Ar*C*(8)); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F: −121.25; ^{19}F NMR (470 MHz, $MeNO_2$, C_6D_6-capillary, referenced to PhF, δ_F = −114.05) δ_F: −122.68; HRMS (ESI$^+$) $C_{19}H_{20}N_2FS$ $[M+H]^+$ found 327.1316, requires 327.1326 (−3.0 ppm).

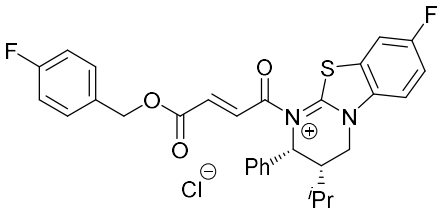
(2*R*,3*S*)-8-Fluoro-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-1-ium chloride (361·HCl)



HCl (2 M in Et_2O, 0.15 mL, 0.3 mmol) was added to a solution of (2*R*,3*S*)-8-fluoro-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine **36** (85 mg, 0.26 mmol) in anhydrous Et_2O (100 mL) at room temperature, and allowed to stir for 10 min. The colourless precipitate was collected by filtration and dried under high vacuum to give (2*R*,3*S*)-8-fluoro-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-1-ium chloride **36**·HCl as a colourless solid (66 mg, 0.18 mmol, 70%).

mp 85-110 °C (formed amorphous foam) 250-260 °C (melted); $[\alpha]_D^{20} = -179.8$ (*c* 0.5, $CHCl_3$); ν_{max} (solid)/cm^{-1}: 3397, 2962, 2874, 2716, 1616, 1593,17, 1476, 1454, 1329, 1279, 1256, 1196; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.92 (3H, d, *J* 6.7, $CH(CH_3)_A(CH_3)_B$), 1.19 (3H, d, *J* 6.4, $CH(CH_3)_A(CH_3)_B$), 1.33–1.47 (1H, m, C*H*$(CH_3)_2$), 2.08-2.22 (1H, m, C(3)*H*), 3.67 (1H, app t, *J* 11.4, C(4)H_AH_B), 4.25 (1H, app d, *J* 11.9, C(4)H_AH_B), 5.20 (1H, br s, C(2)*H*), 7.04–7.12 (2H, m, PhC(2,6)*H*), 7.21-7.39 (5H, m, ArC(6,7)*H* + PhC(3,4,5)*H*), 7.44 (1H, dd, *J* 7.2, 1.9, ArC(9)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.9 ($CH(CH_3)_A(CH_3)_B$), 21.8 ($CH(CH_3)_A(CH_3)_B$), 26.4 ($CH(CH_3)_2$), 41.1 (*C*(3)H), 43.4 (*C*(4)H_2), 56.2 (*C*(2)H), 110.8 (d, *J* 27.8, Ar*C*(9)H), 112.6 (d, *J* 8.7, Ar*C*(6)H), 115.5 (d, *J* 24.6, Ar*C*(7)H), 125.4 (d, *J* 10.3, Ar*C*(9a)), 127.4 (Ph*C*(2,6)H), 129.1 (Ph*C*(4)H), 129.3 (Ph*C*(3,5)H), 134.0 (Ar*C*(5a)), 135.9 (Ph*C*(1)), 160.4 (d, *J* 247.9, Ar*C*(8)), 164.0 (Ar*C*(10a)); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −114.02; ^{19}F{^{1}H} NMR (470 MHz, $MeNO_2$, C_6D_6-capillary, referenced to PhF, δ_F = −114.05) δ_F: −116.71 (3 mM sample).

(2*R*,3*S*)-8-Fluoro-1-((*E*)-4-((4-fluorobenzyl)oxy)-4-oxobut-2-enoyl)-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-1-ium chloride (366)



Oxalyl chloride (28 μL, 0.33 mmol) and DMF (1 drop) were added to a solution of (*E*)-4-((4-fluorobenzyl)oxy)-4-oxobut-2-enoic acid **365** (67 mg, 0.3 mmol) in anhydrous CH_2Cl_2 (1 mL) and allowed to stir for 1 h at rt under a nitrogen atmosphere. The solvent volume was then reduced by half under vacuum, and a further 0.5 mL anhydrous CH_2Cl_2 was added to make the total volume back to 1 mL. (2*R*,3*S*)-8-Fluoro-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidine **361** (64 mg, 0.2 mmol) was added in a single portion and the reaction stirred for a further 1 h. Anhydrous Et_2O (3.5 mL) was added and the precipitate filtered under a blanket of argon, washed with anhydrous Et_2O, and allowed to dry for 20 minutes to give a pale yellow solid (90 mg). The solid was transferred to a small vial and anhydrous THF (~0.5-1 mL) was added. The resulting gummy precipitate was filtered (under an argon blanket) through a Pasteur pipette plugged with cotton wool, and the colourless solid washed with further anhydrous THF (~5 mL in total). The Pasteur pipette containing the colourless solid was placed in a Schlenk tube and dried under high vacuum for 5 h. The solid was then transferred from the pipette using a spatula to give (2*R*,3*S*)-8-fluoro-1-((*E*)-4-((4-fluorobenzyl)oxy)-4-oxobut-2-enoyl)-3-isopropyl-2-phenyl-3,4-dihydro-2*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-1-ium chloride **S29** as a colourless solid (39 mg, 0.07 mmol, 34%).

mp 150 °C (decomposed); $[\alpha]_D^{20} = -151.2$ (c = 0.25, $CHCl_3$); ν_{max} (solid)/cm^{-1}: 2970, 1721, 1699, 1547, 1512, 1477, 1373, 1283, 1260, 1155; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.00 (3H, d, *J* 6.8, $CH(CH_3)_A(CH_3)_B$), 1.35 (3H, d, *J* 6.5, $CH(CH_3)_A(CH_3)_B$), 1.51-1.62 (1H, m, $CH(Me)_2$), 3.38-3.49 (1H, m, C(3)*H*), 3.94 (1H, app t, *J* 12.8, $C(4)H_AH_B$), 5.10 (1H, dd, *J* 13.0, 4.7, $C(4)H_AH_B$), 5.16 (1H, d, *J* 12.2, OCH_AH_BAr), 5.21 (1H, d, *J* 12.2, OCH_AH_BAr), 6.13 (1H, d, *J* 4.4, C(2)*H*), 6.98 (1H, d, *J* 15.2, C(2)H=C(3)*H*), 6.99-7.04 (2H, m, C(2)PhC(2,6)*H*), 7.04-7.12 (2H, m, $OCH_2ArC(3,5)H$), 7.32-7.44 (5H, m, C(2)PhC(3,4,5)*H* & $OCH_2ArC(2,6)H$), 7.53 (1H, app td, *J*, 8.7, 2.4, ArC(7)*H*), 7.56 (1H, d, *J* 15.2, C(2)*H*=C(3)H), 7.79 (1H, dd, *J*, 7.1, 2.4, ArC(9)*H*), 8.21 (1H, dd, *J*, 9.2, 3.8, ArC(6)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.8 ($CH(CH_3)_A(CH_3)_B$), 21.8 ($CH(CH_3)_A(CH_3)_B$), 26.9 ($CH(Me)_2$), 40.1 (*C*(3)H), 45.7 ($C(4)H_2$), 62.3 (*C*(2)H), 66.9 (OCH_2Ar), 110.5 (d, *J* 27.5, Ar*C*(9)H), 115.9 (d, *J* 21.6, $OCH_2ArC(3,5)H$), 117.0 (d, *J* 9.1, Ar*C*(6)H), 118.3 (d, *J* 25.2, Ar*C*(7)H), 127.0 (C(2)Ph*C*(2,6)H), 128.1 (d, *J* 10.4, Ar*C*(9a)), 130.0

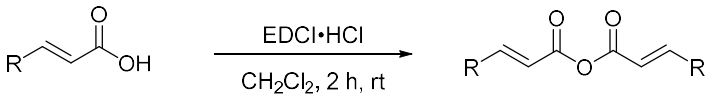
(C(2)Ph*C*(4)H), 130.1 (C(2)Ph*C*(3,5)H), 130.4 (*C*(2)H=C(3)H), 130.7 (d, *J* 8.4, OCH_2Ar*C*(2,6)H), 131.0 (d, *J* 3.1, OCH_2Ar*C*(1)), 133.2 (Ar*C*(5a)), 134.5 (C(2)Ph*C*(1)), 137.0 (C(2)H=*C*(3)H), 160.6 (Ar*C*(10a)), 161.5 (d, *J* 251.2, Ar*C*(8)), 163.0 (d, *J* 247.7, OCH_2Ar*C*(4)), 163.8 (*C*(4)=O), 165.6 (*C*(1)=O); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F: −112.83, −109.65; ^{19}F{^{1}H} NMR (470 MHz, $MeNO_2$, C_6D_6-capillary, referenced to PhF, δ_F = −114.05) δ_F: −114.25, −111.87 (5 mM sample); HRMS (ESI$^+$) $C_{30}H_{27}N_2O_3F_2S$ $[M-Cl]^+$, found 533.1690, requires 533.1705 (–2.8 ppm).

7.5 Experimental for Chapter 5

7.5.1 General Procedures

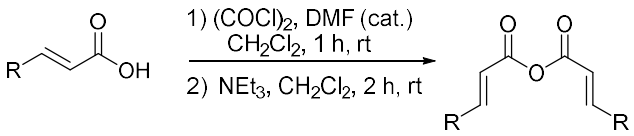
General Procedure 19: *Preparation of α,β-unsaturated homoanhydrides*

Method A: *via* EDCI coupling



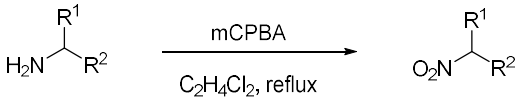
To a solution of carboxylic acid in CH_2Cl_2 was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide·HCl and the solution stirred for 2 h at room temperature. The solution was diluted with CH_2Cl_2 (50 mL) and then washed sequentially with water (2 × 50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the homoanhydride.[29]

Method B: *Via* acid chloride



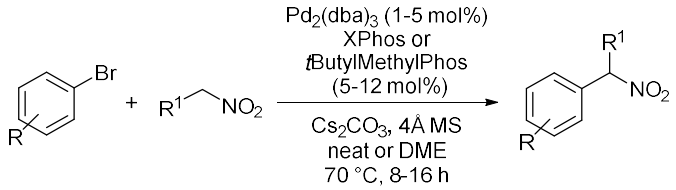
Oxalyl chloride (1 equiv.) and a few drops of *N*,*N*-dimethylformamide were added to a solution of the carboxylic acid (1 equiv.) in anhydrous CH_2Cl_2 (0.33 M) at rt under a nitrogen atmosphere, and stirred for 1 h. The resulting solution was added to a solution of triethylamine (1.1 equiv.) and another portion of carboxylic acid (1 equiv.) in anhydrous CH_2Cl_2 (0.33 M) at rt, giving white fumes. The resulting solution was allowed to stir at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue was suspended in petroleum ether. The suspension was filtered, and the filtrate concentrated to give the homoanhydride without further purification.

General procedure 20: Synthesis of nitro-compounds *via* amine oxidation[30]



m-Chloroperbenzoic acid (mCPBA) (4 equiv.) was dissolved in 30 mL of solvent in a three-neck flask equipped with a condenser and a pressure-equalizing dropping funnel. Amine (1 equiv.) in 3-5 mL of solvent was added dropwise to the refluxing peracid solution. Reflux was continued for the specified time after the addition; then, the reaction mixture was cooled, filtered, washed with 3 × 50 mL of 1 N NaOH, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude mixtures which were weighed and analysed by NMR. When the NMR analysis indicated only one component, this was either isolated by distillation or used without further purification.

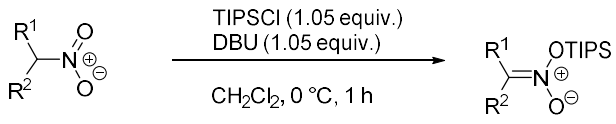
General procedure 21: Preparation of aryl nitromethanes[31]



Method A: According to the standard procedure reported by Jiao,[31] under argon atmosphere, a two-neck round-bottom flask was charged with Cs_2CO_3 (1.1 equiv.), powdered 4 Å molecular sieves (200 mg/mmol), $Pd_2(dba)_3$ (0.01–0.05 equiv.) and XPhos (0.05–0.12 equiv.). Nitromethane (0.33 M) was added followed by the aryl halide (1 equiv). The mixture was vigorously stirred at 60 °C. Upon consumption of the aryl halide, as monitored by TLC, the reaction mixture was allowed to cool to rt, diluted with CH_2Cl_2, and washed with saturated aq. NH_4Cl (× 2). The aqueous layer was extracted with CH_2Cl_2 (× 2). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by chromatography to afford pure aryl nitromethane.[31]

Method B: The standard procedure reported by Buchwald was modified as follows.[32] Under argon atmosphere, a two-neck round-bottom flask was charged with the appropriate amount of $Pd_2(dba)_3$ and 2-(di-*tert*-butylphosphinyl)-2′-methylbiphenyl (*t*-ButylMePhos) as indicated and 1.1 equiv. of Cs_2CO_3. The reaction vessel was capped with a rubber septum, evacuated, and backfilled with argon three times, and aryl bromide (1 equiv.), dry dimethoxyethane (0.2 M), and 1 equiv. of the appropriate nitroalkane were added sequentially via syringe under argon. The mixture was stirred vigorously for 1 min at room temperature, the reaction flask was heated at the given temperature for the time indicated. After the reaction was complete, as judged by TLC analysis, the reaction mixture was allowed to cool to ambient temperature. The unpurified mixture was quenched with a solution of sat. aqueous NH_4Cl, the aqueous phase was extracted with ether, and the combined organic phases were washed with brine. Then the solvent was removed, and the remaining oil was purified by flash silica column chromatography.

General procedure 22: Preparation of alkyl-substituted silyl nitronates [33]

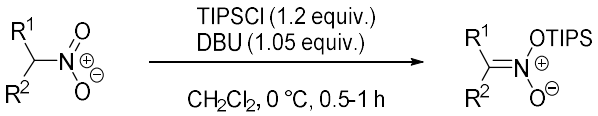


Note: All silyl nitronates have E- configurations.

The silyl chloride (1.05 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.05 equiv.) were added sequentially to a stirred solution of the nitroalkane (1 equiv.) in anhydrous CH_2Cl_2 at 0 °C. The solution was stirred for 1 h at 0 °C. The reaction mixture was then concentrated, and hexanes

were added. DBU·HCl was precipitated from the solution by trituration and then removed by decanting the hexanes solution of the silyl nitronate into a single-neck round-bottom flask. This solution was concentrated to yield the crude silyl nitronate. The crude material was purified by distillation or by flash silica column chromatography when possible or used directly in the Michael addition reaction as indicated below.

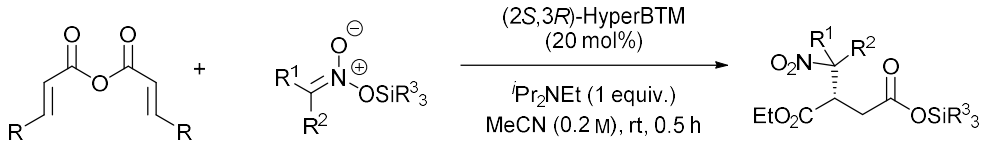
General procedure 23: Preparation of aryl-substituted silyl nitronates [31]



Note: All silyl nitronates have E- configurations.

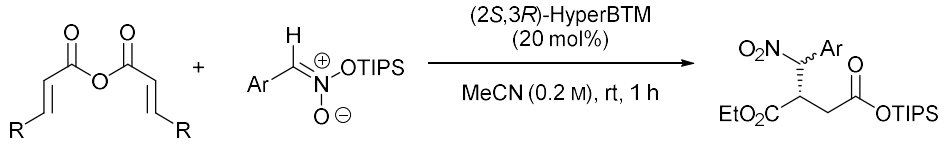
The silyl chloride (1.2 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.05 equiv.) were added sequentially to a stirred solution of the nitroalkane (1 equiv.) in anhydrous CH_2Cl_2 at 0 °C. The solution was stirred for 1 h at 0 °C. The reaction mixture was then concentrated, and hexanes were added. DBU·HCl was precipitated from the solution by trituration and then removed by decanting the hexanes solution of the silyl nitronate into a single-neck round-bottom flask. The crude mixture was then concentrated *in vacuo*, and the residue purified by flash silica column chromatography using a mixture of petroleum ether and EtOAc as eluent.

General procedure 24: *Asymmetric Michael Addition with Disubstituted Silyl Nitronates*



The appropriate homoanhydride (1 equiv.) and isothiourea HyperBTM (20 mol%) were dissolved in acetonitrile (0.4 M). Corresponding silyl nitronate (1.5 equiv.) in acetonitrile (0.6 M) and diisopropylethylamine (1 equiv.) were added to the reaction mixture and allowed to stir for 0.5 h at rt. The crude mixture was then concentrated *in vacuo*, and the residue purified by flash silica column chromatography using a mixture of petroleum ether and EtOAc as eluent.

General procedure 25: *Asymmetric Michael Addition with Monoaryl-Substituted Silyl Nitronates*

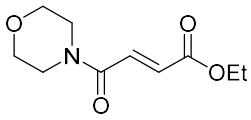


The appropriate homoanhydride (1 equiv.) and isothiourea HyperBTM (20 mol%) were dissolved in acetonitrile (0.4 M). Corresponding nitronate (2 equiv.) in acetonitrile (0.8 M) was added to the reaction mixture and allowed to stir for 1 h at rt. The crude mixture was then concentrated *in vacuo*, and the residue purified by flash silica column chromatography using a mixture of petroleum ether and EtOAc as eluent.

7.5.2 Preparation of starting materials

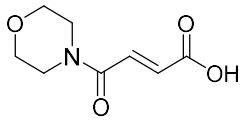
7.5.2.1 Data for *trans*-but-2-enedioic acid monoamides

Ethyl (*E*)-4-morpholino-4-oxobut-2-enoate (S37)



Following General Procedure 15 (i), morpholine (0.87 mL, 10 mmol), HOBt (1.68 g, 11 mmol), monoethyl fumarate (1.59 g, 11 mmol), EDCI·HCl (2.10 g, 11 mmol) in DMF (14 mL) afforded the title compound (1.49 mg, 70%) as a white solid. mp 70–71 °C {Lit[34] 68–70 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.1, CH_2CH_3), 3.58–3.60 (2H, m, $CH_{2(morph)}$), 3.69–3.71 (6H, m, $CH_{2(morph)}$), 4.25 (2H, q, *J* 7.1, CH_2CH_3), 6.79 (1H, d, *J* 15.3, CH=C*H*–CO_2Et), 7.35 (1H, d, *J* 15.3, C*H*=CH-CO_2Et). Data in agreement with literature.[34]

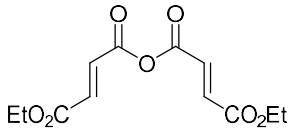
(*E*)-4-morpholino-4-oxobut-2-enoic acid (S38)



Following General Procedure 15 (ii), ethyl (*E*)-4-morpholino-4-oxobut-2-enoate (1.49 g, 7.0 mmol) and LiOH·H_2O (323 mg, 7.7 mmol) in THF (10 mL) and H_2O (10 mL) afforded the title compound (710 mg, 55%) as a colourless solid. mp 126–128 °C; ν_{max} (film) 2990 (COOH, br), 1717 (C=O), 1611 (C=O); ^{1}H NMR (500 MHz, $CHCl_3$) δ_H: 3.59–3.61 (2H, m, $CH_{2(morph)}$), 3.71–3.73 (6H, m, $CH_{2(morph)}$), 6.81 (1H, d, *J* 15.3, CH=C*H*–CO_2Et), 7.43 (1H, d, *J* 15.3, C*H*=CH-CO_2Et). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 42.7 (CH_{2morph}), 46.6 (CH_{2morph}), 66.8 (2×CH_{2morph}), 130.9 (CH=*C*H–CO_2H), 136.1 (*C*H=CH–CO_2H), 163.5 (*C*O_2H), 169.2 (*C*ON); HRMS (NSI$^-$) $C_8H_{10}O_4N$ [M-H]$^-$, found 184.0618, requires 184.0615 (+1.5 ppm).

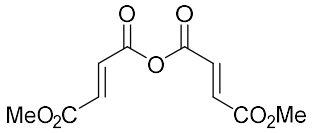
7.5.2.2 Data for α,β-unsaturated homoanhydrides

(*E*)-4-Methoxy-4-oxobut-2-enoic anhydride (407)



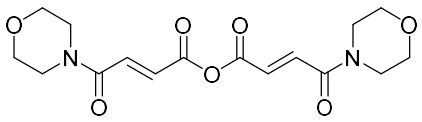
Following General Procedure 19 (Method A), (*E*)-4-ethoxy-4-oxobut-2-enoic acid (1.44 g, 10.0 mmol) and EDCI·HCl (1.12 g, 5.9 mmol) in CH_2Cl_2 (20 mL) afforded the title compound as a brown oil (797 mg, 59%); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34 (6H, t, *J* 7.1, C*H*$_3$), 4.29 (4H, q, *J* 7.1, C*H*$_2$CH$_3$), 6.88 (2H, d, *J* 15.8, CO_2EtCH=C*H*), 6.99 (2H, d, *J* 15.8, CO_2EtC*H*=CH). Data in agreement with the literature.[29]

(*E*)-4-Methoxy-4-oxobut-2-enoic anhydride (419)



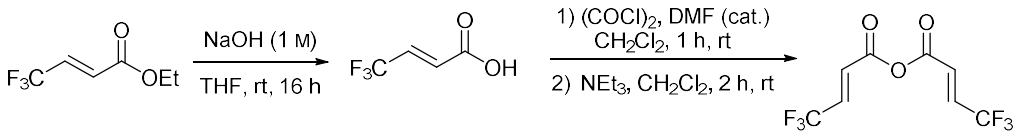
Following General Procedure 19 (Method A), (*E*)-4-Methoxy-4-oxobut-2-enoic acid (1.21 g, 9.3 mmol) and EDCI·HCl (1.05 g, 5.5 mmol) in CH_2Cl_2 (20 mL) afforded the title compound (567 mg, 52%) as a white solid. mp 79–81 °C; ν_{max} (film) 1800 (C=O), 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.85 (3H, s, CH_3), 6.89 (1H, d, *J* 15.8, $MeCO_2$CH=C*H*), 7.00 (1H, d, *J* 15.8, $MeCO_2$C*H*=CH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 52.9 (2×*C*H$_3$), 131.7 (2×*C*H=CH-CO_2Me), 137.0 (2×CH=*C*H-CO_2Me), 159.6 (2×CH=CH*C*O), 164.6 (2×*C*O_2Me). HRMS (ESI$^+$) $C_{10}H_{10}O_7Na$ [M+Na]$^+$, found 265.0316, requires 265.0319 (−1.0 ppm).

(*E*)-4-morpholino-4-oxobut-2-enoic anhydride (420)



Following General Procedure 19 (Method A), (*E*)-4-morpholino-4-oxobut-2-enoic acid (710 mg, 3.83 mmol) and EDCI·HCl (434 g, 2.25 mmol) in CH_2Cl_2 (10 mL) afforded the title compound (478 mg, 71%) as an off-white solid. mp 106–108 °C; ν_{max} (film) 1800 (C=O), 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.59–3.60 (4H, m, C*H*$_{2(morph)}$), 3.71–3.73 (12H, m, C*H*$_{2(morph)}$), 6.84 (1H, d, *J* 15.3, CH=C*H*–CON), 7.51 (1H, d, *J* 15.3, C*H*=CH-CON). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 42.7 (*C*H$_{2morph}$), 46.6 (*C*H$_{2morph}$), 66.8 (2×*C*H$_{2morph}$), 129.8 (CH=*C*H–CO_2H), 137.1 (*C*H=CH–CO_2H), 160.5 (*C*O_2H), 162.6 (*C*ON); HRMS (ESI$^+$) $C_{16}H_{21}O_7N_2$ [M+H]$^+$, found 353.1336, requires 353.1343 (−2.1 ppm).

7.5.2.3 Synthesis of (*E*)-4,4,4-trifluorobut-2-enoic anhydride (427)

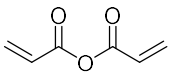


(*E*)-4,4,4-trifluorobut-2-enoic acid (S39):

Aqueous solution of 1 M NaOH (12 mL) was added to a solution of ethyl (*E*)-4,4,4-trifluorobut-2-enoate (1.49 mL, 10 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was then acidified to pH = 2 with 1 M HCl and concentrated *in vacuo*. The aqueous solution was diluted with brine and extracted with Et_2O (×3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford the title compound (1.06 g, 76%) as a white solid. mp 54–56 °C {Lit[35] 54–55 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.52 (1H, dq, *J* 15.8, 2.0, C*H*=CH), 6.89 (1H, dq, *J* 15.8, 6.4, CH=C*H*). Data in agreement with the literature.[36]

ii) Following General Procedure 19 (Method B), oxalyl chloride (0.43 mL, 5.0 mmol), (*E*)-4,4,4-trifluorobut-2-enoic acid (700 mg, 5.0 mmol) in CH_2Cl_2 (15 mL), triethylamine (0.77 mL, 5.5 mmol) and (*E*)-4,4,4-trifluorobut-2-enoic acid (700 mg, 5.0 mmol) in CH_2Cl_2 (15 mL) afforded the title compound (679 mg, 52%) as a yellow oil; ν_{max} (film) 1811 (C=O), 1732 (C=O), 1309 (C–F); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.57 (2H, dq, *J* 15.8, 1.9, C*H*=CH), 6.95 (2H, dq, *J* 15.8, 6.3, CH=C*H*); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F: −65.9 (2× C*F*$_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 121.5 (q, $^1J_{CF}$ 270.9, 2× *C*F$_3$), 127.0 (q, $^3J_{CF}$ 6.1, 2× *C*H=CH-CF$_3$), 135.5 (q, $^3J_{CF}$ 6.1, 2× CH=*C*H-CF$_3$), 158.3 (2× =CH*C*O). HRMS (ESI$^+$) $C_8H_8O_3F_6N$ $[M+NH_4]^+$, found 280.0404, requires 280.0408 (–1.4 ppm).

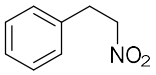
Acrylic anhydride (421)



Following General Procedure 19 (Method B), oxalyl chloride (0.86 mL, 10.0 mmol), acrylic acid (0.68 mL, 10.0 mmol) in CH_2Cl_2 (15 mL), triethylamine (0.77 mL, 5.5 mmol) and acrylic acid (0.68 mL, 10.0 mmol) in CH_2Cl_2 (30 mL) afforded the title compound (971 mg, 77%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.08 (2H, dq, *J* 10.5, 1.0, CH=C*H*), 6.19 (2H, dd, *J* 17.1, 10.5, C*H*=CH), 6.57 (2H, dd, *J* 17.1, 1.0, CH=C*H*). Data in agreement with the literature.[37]

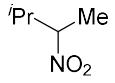
7.5.2.4 Data for nitroalkanes

2-Phenylnitroethane (S40)



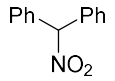
Following General Procedure 20, mCPBA (4.48 g, 20 mmol, 77% pure), 2-phenethylamine (0.63 mL, 5 mmol) and subsequent distillation afforded the title compound (655 mg, 87%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.33 (2H, t, *J* 7.4, C*H*$_2$Ph), 4.62 (2H, t, *J* 7.4, C*H*$_2$NO$_2$), 7.20–7.22 (2H, m, PhH), 7.28–7.29 (1H, m, PhH), 7.32–7.35 (2H, m, PhH). Data in agreement with literature.[30]

2-Methyl-3-nitrobutane (S41)



Following General Procedure 20, mCPBA (4.48 g, 20 mmol, 77% pure) and 1,2-dimethylpropylamine (0.58 mL, 5 mmol) afforded the title compound (655 mg, 87%) as a light yellow oil without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.97 (6H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.49 (3H, d, *J* 6.7, C*H*$_3$CHNO$_2$), 2.17–2.24 (1H, m, C*H*(CH$_3$)$_2$, 4.31–4.36 (1H, m, CH$_3$C*H*NO$_2$). Data in agreement with literature.[38]

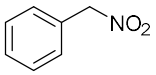
Diphenylnitromethane (S42)



Following General Procedure 20, mCPBA (4.48 g, 20 mmol, 77% pure) and benzhydrylamine (0.58 mL, 5 mmol) afforded the title compound (625 mg, 59%) as a brown oil and was used as a crude due to poor stability of the compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.86 (1H, s, CC*H*NO$_2$), 7.25-7.83 (10H, m, H-Ph). Data in agreement with literature.[39]

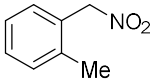
7.5.2.5 Data for aryl nitromethanes

Phenyl nitromethane (S43)



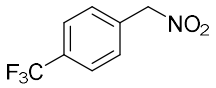
Following General Procedure 21 (Method A), bromobenzene (1.05 mL, 10.0 mmol), Cs_2CO_3 (3.58 g, 11.0 mmol), powdered 4 Å molecular sieves (2.0 g), $Pd_2(dba)_3$ (103.5 mg, 0.1 mmol) and XPhos (238.4 mg, 0.5 mmol) and nitromethane (30 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.40) the title compound (0.86 g, 63%) as a light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.45 (2H, s, CH_2), 7.44–7.47 (5H, m, ArH). Data in agreement with literature.[31]

o-Tolyl nitromethane (S44)



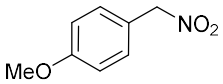
Following General Procedure 21 (Method A), 2-bromotoluene (0.6 mL, 5.0 mmol), Cs_2CO_3 (1.79 g, 5.5 mmol), powdered 4 Å molecular sieves (1.0 g), $Pd_2(dba)_3$ (52.0 mg, 0.05 mmol) and XPhos (119.2 mg, 0.25 mmol) and nitromethane (15 mL) afforded after SiO_2-chromatography (95:5 – 90:10 Petroleum ether : EtOAc, R_f 0.21) the title compound (0.60 g, 79%) as a light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (3H, s, CH_3), 5.50 (2H, s, CH_2), 7.25–7.27 (2H, m, ArH), 7.33–7.36 (2H, m, ArH). Data in agreement with literature.[31]

4-Trifluoromethylphenyl nitromethane (S45)



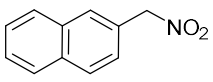
Following General Procedure 21 (Method A), 1-bromo-4-(trifluoromethyl)benzene (0.35 mL, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (26 mg, 0.025 mmol) and XPhos (60 mg, 0.125 mmol) and nitromethane (5 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.43) the title compound (0.37 g, 72%) as a light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.51 (2H, s, CH_2), 7.59–7.61 (2H, m, ArH), 7.71–7.73 (2H, m, ArH). Data in agreement with literature.[31]

4-Methoxyphenyl nitromethane (S46)



Following General Procedure 21 (Method A), 1-bromo-4-methoxybenzene (0.31 mL, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (26 mg, 0.025 mmol) and XPhos (60 mg, 0.125 mmol) and nitromethane (5 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.37) the title compound (0.25 g, 60%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.83 (3H, s, OCH_3), 5.37 (2H, s, CH_2), 6.93–6.95 (2H, m, ArH), 7.37–7.40 (2H, m, ArH). Data in agreement with literature.[31]

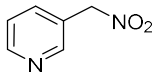
2-Naphthyl nitromethane (S47)



Following General Procedure 21 (Method A), 2-bromonaphthalene (517 mg, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (26 mg, 0.025 mmol) and XPhos (60 mg, 0.125 mmol) and nitromethane (5 mL) afforded after SiO_2-chromatography (95:5 – 90:10 Petroleum ether : EtOAc, R_f 0.45) the title compound (0.27 g, 58%) as a light yellow

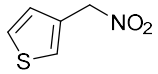
solid. mp 84–86 °C {Lit[40] 83–84 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.62 (2H, s, CH_2), 7.54–7.57 (3H, m, ArH), 7.87–7.94 (4H, m, ArH). Data in agreement with literature.[31]

3-(Nitromethyl)pyridine (S48)



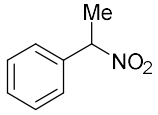
Following General Procedure 21 (Method A), 3-bromopyridine (0.24 mL, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (130 mg, 0.125 mmol) and XPhos (143 mg, 0.30 mmol) and nitromethane (5 mL) afforded after SiO_2-chromatography (90:10 – 80:20 Petroleum ether : EtOAc, R_f 0.15) the title compound (138 mg, 40%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.48 (2H, s, CH_2), 7.39–7.42 (1H, m, ArH), 7.82–7.84 (1H, m, ArH), 8.70–8.72 (2H, m, ArH). Data in agreement with literature.[40]

3-(Nitromethyl)thiophene (S49)



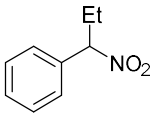
Following General Procedure 21 (Method A), 3-bromothiophene (0.23 mL, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (130 mg, 0.125 mmol) and XPhos (143 mg, 0.30 mmol) and nitromethane (5 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.25) the title compound (145 mg, 41%) as a yellow oil; ν_{max} (film) 3107 (C-H), 1553, 1368 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.48 (2H, s, CH_2), 7.19–7.20 (1H, m, ArH), 7.38–7.40 (1H, m, ArH), 7.48–7.49 (1H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 74.3 (CH_2), 127.2 (CH_{Ar}), 127.8 (CH_{Ar}), 128.1 (CH_{Ar}), 129.9 (C_{Ar}); HRMS submitted.

(1-Nitroethyl)benzene (S50)



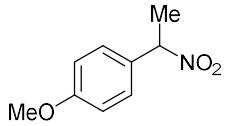
Following General Procedure 21 (Method A), bromobenzene (0.52 mL, 5.0 mmol), Cs_2CO_3 (1.79 g, 5.5 mmol), powdered 4 Å molecular sieves (1.0 g), $Pd_2(dba)_3$ (52.0 mg, 0.05 mmol) and XPhos (119.2 mg, 0.25 mmol) and nitromethane (15 mL) afforded after SiO_2-chromatography (95:5 – 90:10 Petroleum ether : EtOAc, R_f 0.35) the title compound (0.62 g, 82%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.90 (3H, d, *J* 6.9, CH_3), 5.62 (1H, q, *J* 6.9, C*H*NO_2), 7.40–7.48 (5H, m, ArH). Data in agreement with literature.[41]

(1-Nitropropyl)benzene (S51)



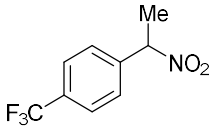
Following General Procedure 21 (Method A), bromobenzene (0.52 mL, 5.0 mmol), Cs_2CO_3 (1.79 g, 5.5 mmol), powdered 4 Å molecular sieves (1.0 g), $Pd_2(dba)_3$ (52.0 mg, 0.05 mmol) and XPhos (119.2 mg, 0.25 mmol) and 1-nitroproane (4.5 mL, 50.0 mmol) afforded after SiO_2-chromatography (95:5 – 90:10 Petroleum ether : EtOAc, R_f 0.37) the title compound (0.59 g, 69%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.99 (3H, t, *J* 7.4, CH_3), 2.07–2.16 (1H, m, CH_3CH_2), 2.47–2.56 (1H, m, CH_3CH_2), 5.37 (1H, dd, *J* 8.9, 6.4, C*H*NO_2), 7.40–7.48 (5H, m, ArH). Data in agreement with literature.[41]

1-methoxy-4-(1-nitroethyl)benzene (S52)



Following General Procedure 21 (Method A), 1-bromo-4-methoxybenzene (0.31 mL, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (26 mg, 0.025 mmol) and XPhos (60 mg, 0.125 mmol) and nitroethane (5 mL) afforded after SiO_2-chromatography (95:5 – 80:20 Petroleum ether : EtOAc, R_f 0.70) the title compound (0.41 g, 90%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.88 (3H, d, *J* 7.0, CH_3), 3.82 (3H, s, OCH_3), 5.57 (1H, q, *J* 7.0, C*H*NO_2), 6.90–6.93 (2H, m, ArH), 7.39–7.41 (2H, m, ArH). Data in agreement with literature.[41]

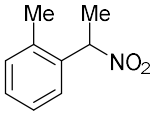
1-(1-Nitroethyl)-4-(trifluoromethyl)benzene (S53)



Following General Procedure 21 (Method A), 1-bromo-4-(trifluoromethyl)benzene (0.35 mL, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (26 mg, 0.025 mmol) and XPhos (60 mg, 0.125 mmol) and nitroethane (5 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.65) the title compound (0.52 g, 95%) as a yellow oil; ν_{max} (film) 1555, 1325 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.93 (3H, d, *J* 7.0, CH_3), 5.67 (1H, q, *J* 7.0, C*H*NO_2), 7.58–7.60 (2H, m, ArH), 7.68–7.70 (2H, m, ArH);); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F: –62.9 (C*F*$_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 19.5 (CH_3), 85.5 (*C*HNO_2), 123.8 (q, $^1J_{CF}$ 238.8, C_{Ar}-*C*F_3), 126.1 (q, $^3J_{CF}$ 3.5, *C*H$_{Ar}$-CF_3), 127.9 (CH$_{Ar}$), 132.0 (q,

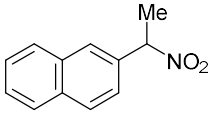
$^2J_{CF}$ 32.8, C_{Ar}-CF_3), 139.1 (C_{Ar}); HRMS (ESI$^-$) $C_9H_7O_3FNO_2$ $[M]^-$, found 218.0431, requires 218.0434 (–1.4 ppm).

1-Methyl-2-(1-nitroethyl)benzene (S54)



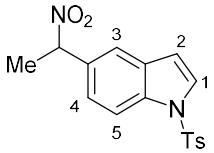
Following General Procedure 21 (Method A), 2-bromotoluene (0.3 mL, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (65 mg, 0.0625 mmol) and XPhos (72 mg, 0.15 mmol) and nitroethane (7 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.43) the title compound (169 mg, 50%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.90 (3H, d, *J* 6.9, CH_3), 5.91 (1H, q, *J* 6.9, C*H*NO_2), 7.21–7.23 (1H, m, ArH), 7 7.26–7.31 (2H, m, ArH), 7.44–7.46 (1H, m, ArH). Data in agreement with literature.[42]

2-(1-Nitroethyl)naphthalene (S55)



Following General Procedure 21 (Method A), 2-bromonaphthalene (518, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (65 mg, 0.0625 mmol) and XPhos (72 mg, 0.15 mmol) and nitroethane (7 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.45) the title compound (287 mg, 57%) as a yellow solid. mp 48–50 °C {Lit[41] 51 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.00 (3H, d, *J* 6.9, CH_3), 5.79 (1H, q, *J* 6.9, C*H*NO_2), 7.53–7.57 (3H, m, ArH), 7.85–7.92 (4H, m, ArH). Data in agreement with literature.[41]

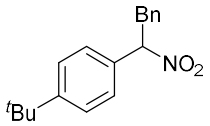
5-(1-nitroethyl)-1-tosyl-1*H*-indole (S56)



Following General Procedure 21 (Method A), 5-bromo-1-tosyl-1*H*-indole (876, 2.5 mmol), Cs_2CO_3 (0.90 g, 2.75 mmol), powdered 4 Å molecular sieves (0.5 g), $Pd_2(dba)_3$ (130 mg, 0.125 mmol) and XPhos (144 mg, 0.30 mmol) and nitroethane (7 mL) afforded after SiO_2-chromatography (90:10 Petroleum ether : EtOAc, R_f 0.33) the title compound (558 mg, 65%) as a thick yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.92 (3H, d, *J* 6.9, NO_2CHCH_3), 2.35 (3H, s, Ar-CH_3), 5.68 (1H, q, *J* 7.0, C*H*NO_2), 6.67 (1H, dd, *J* 3.7, 0.8, H-2), 7.23–7.26 (2H, m, Ar-H),

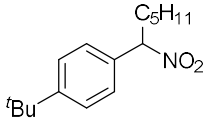
7.40 (1H, dd, *J* 8.7, 1.9, H-4), 7.61 (1H, d, *J* 3.7, H-1), 7.65 (1H, d, *J* 1.9, H-5), 7.75–7.77 (2H, m, Ar-H), 7.99 (1H, d, *J* 8.7, H-3). Data in agreement with the literature.[43]

1-(*tert*-Butyl)-4-(1-nitro-2-phenylethyl)benzene (S57)



Following General Procedure 21 (Method B), 1-bromo-4-(*tert*-butyl)benzene (0.43 mL, 2.5 mmol), Cs_2CO_3 (896 mg, 2.75 mmol), $Pd_2(dba)_3$ (130 mg, 0.125 mmol) and *t*-ButylMePhos (78 mg, 0.25 mmol) and 2-phenylnitroethane (778 mg, 2.5 mmol) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.70) the title compound (521 mg, 87%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.32 (9H, s, $(CH_3)_3$), 3.31 (1H, dd, *J* 14.5, 5.2, CH_2Ph), 3.80 (1H, dd, *J* 14.5, 9.9, CH_2Ph), 5.68 (1H, dd, *J* 9.9, 5.2 $CHNO_2$), 7.18–7.19 (2H, m, PhH), 7.28–7.29 (3H, m, PhH), 7.41–7.46 (4H, m, ArH). Data in agreement with literature.[41]

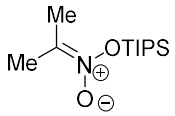
1-(*tert*-Butyl)-4-(1-nitrohexyl)benzene (S58)



Following General Procedure 21 (Method B), 1-bromo-4-(*tert*-butyl)benzene (0.43 mL, 2.5 mmol), Cs_2CO_3 (896 mg, 2.75 mmol), $Pd_2(dba)_3$ (130 mg, 0.125 mmol) and *t*-ButylMePhos (52 mg, 0.05 mmol) and 1-nitrohexane (0.35 mg, 2.5 mmol) afforded after SiO_2-chromatography (95:5 Petroleum ether : EtOAc, R_f 0.43) the title compound (366 mg, 56%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.88 (3H, t, *J* 7.3, $(CH_2)_3CH_3$), 1.28–1.34 (6H, m, $(CH_2)_3CH_3$), 1.31 (9H, s, $(CH_3)_3$), 2.03–2.08 (1H, m, CH_2CHNO_2), 2.44–2.51 (1H, m, CH_2CHNO_2), 5.43 (1H, dd, *J* 8.9, 6.2 $CHNO_2$), 7.38–7.42 (4H, m, ArH). Data in agreement with literature.[41]

7.5.2.6 Data for alkyl-substituted silyl nitronates

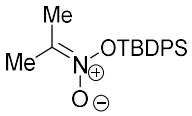
Triisopropylsilyl propan-2-ylideneazinate (411)



Following General Procedure 22, 2-nitropropane (0.45 mL, 5.00 mmol), DBU (0.79 mL, 5.25 mmol), triisopropylsilyl chloride (1.12 mL, 5.25 mmol) and CH_2Cl_2 (15 ml) afforded the title compound (1.06 g, 86%) as colorless oil without further purification; ν_{max} (film) 2943, 2866 (C-H), 1626 (C=N), 1464 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: ^{1}H NMR (500 MHz, CDCl3) δ: 1.08 (18H, d, *J* 7.4, $SiCH(CH_3)_2$), 1.27–1.36 (3H, m, SiCH), 2.02 (6H, s, 2×CH3); ^{13}C{^{1}H} NMR

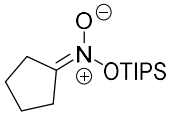
(126 MHz, $CDCl_3$) δ_C: 12.6 (Si*C*H(CH_3)$_2$), 17.9 (SiCH(*C*H_3)$_2$), 18.4 (N=C(*C*H_3)$_2$), 120.6 (N=*C*(CH_3)$_2$); HRMS (ESI$^+$) $C_{12}H_{28}O_2NSi$ $[M+H]^+$, found 246.1878, requires 246.1884 (–2.4 ppm).

tert-Butyldiphenylsilyl propan-2-ylideneazinate (417)



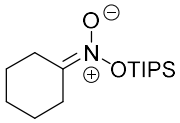
Following General Procedure 22, 2-nitropropane (0.18 mL, 2.00 mmol), DBU (0.31 mL, 2.10 mmol), *tert*-butyldiphenylsilyl chloride (0.55 mL, 2.10 mmol) and CH_2Cl_2 (6 ml) afforded the title compound as colorless oil. Due to its high instability this compound was used as a solution of the crude product in hexane; ν_{max} (film) 2932, 2859 (C-H), 1626 (C=N), 1427 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.11 (9H, s, $SiPh_2C(CH_3)_3$), 2.03 (6H, s, 2×CH_3), 7.35–7.41 (6H, m, CH_{Ar}), 7.71–7.73 (4H, m, CH_{Ar}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 18.8 (N=C(*C*H_3)$_2$), 19.2 (Si*C*(CH_3)$_3$), 26.7 (SiC(*C*H_3)$_3$), 110.5 (N=*C*(CH_3)$_2$), 127.9 (4×CH_{Ar}), 129.8 (2×CH_{Ar}), 134.9 (4×CH_{Ar}), 136.3 (2×C_{Ar}); HRMS: not found (decomp.)

Triisopropylsilyl cyclopentylideneazinate (431)



Following General Procedure 222, nitrocycloheptane (0.27 mL, 2.5 mmol), DBU (0.39 mL, 2.63 mmol), triisopropylsilyl chloride (0.56 mL, 2.63 mmol) and CH_2Cl_2 (8 ml) and subsequent chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.20) afforded the title compound (680 mg, quant.) as colorless oil; ν_{max} (film) 2945, 2866 (C-H), 1645 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.09 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.28–1.37 (3H, m, SiCH), 1.78–1.81 (4H, m, CH_{cp}), 2.51–2.54 (4H, m, CH_{cp}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.7 (Si*C*H(CH_3)$_2$), 18.2 (SiCH(*C*H_3)$_2$), 25.7 (2×CH_{cp}), 30.0 (2×CH_{cp}), 132.2 (N=*C*(CH_3)$_2$); HRMS (ESI$^+$) $C_{14}H_{30}O_2NSi$ $[M+H]^+$, found 272.2038, requires 272.2040 (–0.7 ppm).

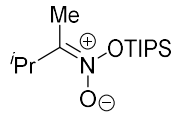
Triisopropylsilyl cyclohexylideneazinate (432)



Following General Procedure 22, nitrocyclohexane (0.30 mL, 2.5 mmol), DBU (0.39 mL, 2.63 mmol), triisopropylsilyl chloride (0.56 mL, 2.63 mmol) and CH_2Cl_2 (8 ml) afforded the title compound (635 mg, 89%) as colorless oil. ; ν_{max} (film) 2943, 2866 (C-H), 1614 (C=O); ^{1}H NMR

(500 MHz, $CDCl_3$) δ_H: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.09 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.27–1.36 (3H, m, SiCH), 1.49–1.53 (2H, m, CH_{chex}), 1.60–1.65 (4H, m, CH_{chex}), 2.53 (4H, *app* t, *J* 6.4, CH_{chex}); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.9 (Si*C*H(CH$_3$)$_2$), 18.2 (SiCH(*C*H$_3$)$_2$), 24.9 (CH_{chex}), 25.1 (2×CH_{chex}), 27.4 (2×CH_{chex}), 126.6 (N=*C*(CH$_3$)$_2$); HRMS (ESI$^+$) $C_{15}H_{32}O_2NSi$ $[M+H]^+$, found 286.2193, requires 286.2197 (−1.4 ppm).

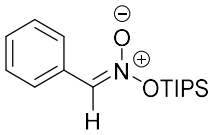
Triisopropylsilyl (*E*)-(3-methylbutan-2-ylidene)azinate (433)



Following General Procedure 22, 2-methyl-3-nitrobutane (533 mg, 4.55 mmol), DBU (0.39 mL, 2.63 mmol), triisopropylsilyl chloride (1.02 mL, 4.78 mmol) and CH_2Cl_2 (13 ml) and subsequent chromatography (99:1 – 95:5 Petroleum ether : EtOAc, R_f 0.63) afforded the title compound (1.02 g, 80%) as colorless oil; ν_{max} (film) 2945, 2868 (C-H), 1607 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 (6H, d, *J* 6.9, (CH_3)$_2$CHCH$_3$), 1.09 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.28–1.34 (3H, m, SiCH), 1.89 (3H, s, (CH$_3$)$_2$CHCH_3), 3.24 (1H, hept, *J* 6.9, (CH$_3$)$_2$C*H*CH$_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.3 (CH$_3$)$_2$*C*HCH$_3$), 12.9 (Si*C*H(CH$_3$)$_2$), 18.2 (SiCH(*C*H$_3$)$_2$), 18.9 (*C*H$_3$)$_2$CHCH$_3$), 29.4 (*C*H$_3$)$_2$CHCH$_3$), 128.5 (N=*C*(CH$_3$)$_2$); HRMS (ESI$^+$) $C_{14}H_{33}O_2NSi$ $[M+H]^+$, found 274.2189, requires 274.2197 (–2.9 ppm).

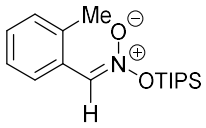
7.5.2.7 Data for aryl-substituted silyl nitronates

Triisopropylsilyl (*E*)-benzylideneazinate (437)



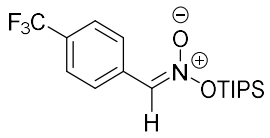
Following General Procedure 23, triisopropylsilyl chloride (0.51 mL, 2.4 mmol) and DBU (0.31 mL, 2.1 mmol) were added sequentially to a stirred solution of the aryl nitromethane (274 mg, 2.0 mmol) in anhydrous CH_2Cl_2 (7 mL) afforded after SiO_2-chromatography (100:0 – 95:5 Petroleum ether : EtOAc, R_f 0.45) the title compound (376 mg, 64%) as a light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.14 (18H, d, *J* 7.4, SiCH(CH_3)$_2$), 1.35–1.42 (3H, m, SiCH), 7.10 (1H, s, CHNO), 7.31–7.38 (1H, m, ArH), 7.40–7.42 (2H, m, ArH), 7.87–7.90 (2H, m, ArH). Data in agreement with literature.[31]

Triisopropylsilyl (*E*)-(2-methylbenzylidene)azinate (473)



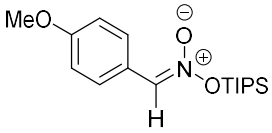
Following General Procedure 23, triisopropylsilyl chloride (1.02 mL, 4.8 mmol) and DBU (0.62 mL, 4.2 mmol) were added sequentially to a stirred solution of the aryl nitromethane (600 mg, 4.0 mmol) in anhydrous CH_2Cl_2 (12 mL) afforded after SiO_2-chromatography (95:5 – 90:10 Petroleum ether : EtOAc, R_f 0.35) the title compound (850 mg, 70%) as a light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.15 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.35−1.44 (3H, m, SiCH), 2.37 (3H, s, CH_3), 7.18–7.21 (1H, m, ArH), 7.23 (1H, s, CHNO), 7.23–7.39 (2H, m, ArH), 8.53–8.54 (1H, m, ArH). Data in agreement with literature.[41]

Triisopropylsilyl (*E*)-(4-(trifluoromethyl)benzylidene)azinate (S59)



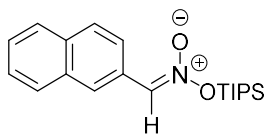
Following General Procedure 23, triisopropylsilyl chloride (0.46 mL, 2.2 mmol) and DBU (0.28 mL, 1.9 mmol) were added sequentially to a stirred solution of the aryl nitromethane (368 mg, 1.8 mmol) in anhydrous CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (98:2 – 95:5 Petroleum ether : EtOAc, R_f 0.60) the title compound (482 mg, 74%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.14 (18H, d, *J* 7.6, SiCH(CH_3)$_2$), 1.36−1.40 (3H, m, SiCH), 7.17 (1H, s, CHNO), 7.63 (2H, *app.* d, *J* 8.2, ArH), 7.99 (2H, *app.* d, *J* 8.2, ArH). Data in agreement with literature.[31]

Triisopropylsilyl (*E*)-(4-methoxybenzylidene)azinate (S60)



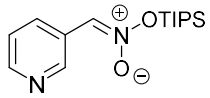
Following General Procedure 23, triisopropylsilyl chloride (0.38 mL, 1.8 mmol) and DBU (0.23 mL, 1.6 mmol) were added sequentially to a stirred solution of the aryl nitromethane (249 mg, 1.5 mmol) in anhydrous CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (98:2 – 95:5 Petroleum ether : EtOAc, R_f 0.23) the title compound (302 mg, 63%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.14 (18H, d, *J* 7.6, SiCH(CH_3)$_2$), 1.37−1.40 (3H, m, SiCH), 3.83 (3H, s, OCH_3), 6.91−6.93 (2H, m, ArH), 7.03 (1H, s, CHNO), 7.83−7.85 (2H, m, ArH). Data in agreement with literature.[31]

Triisopropylsilyl (*E*)-(naphthalen-2-ylmethylene)azinate (S61)



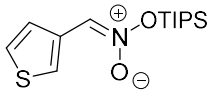
Following General Procedure 23, triisopropylsilyl chloride (0.37 mL, 1.75 mmol) and DBU (0.23 mL, 1.6 mmol) were added sequentially to a stirred solution of the aryl nitromethane (249 mg, 1.5 mmol) in anhydrous CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (99:1 – 95:5 Petroleum ether : EtOAc, R_f 0.68) the title compound (389 mg, 77%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.17 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.37–1.45 (3H, m, SiCH), 6.91–6.93 (2H, m, ArH), 7.24 (1H, s, CHNO), 7.48–7.50 (2H, m, ArH), 7.70–7.72 (1H, m, ArH), 7.79–7.83 (2H, m, ArH), 7.88–7.90 (1H, m, ArH), 8.64 (1H, s, ArH). Data in agreement with literature.[31]

Triisopropylsilyl (*E*)-(pyridin-3-ylmethylene)azinate (S62)



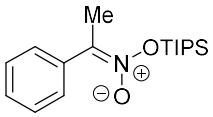
Following General Procedure 23, triisopropylsilyl chloride (0.26 mL, 1.2 mmol) and DBU (0.16 mL, 1.05 mmol) were added sequentially to a stirred solution of the aryl nitromethane (138 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (3 mL) afforded after SiO_2-chromatography (98:2 – 60:40 Petroleum ether : EtOAc, R_f 0.50) the title compound (111 mg, 40%) as a colorless oil; ν_{max} (film) 2945, 2868 (C-H), 1600, 1554 (C=N), 1464, 1435 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.13 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.35–1.41 (3H, m, SiCH), 7.14 (1H, s, CHNO), 7.33–7.35 (1H, m, ArH), 8.52–8.53 (2H, m, ArH), 8.75–8.76 (1H, m, ArH). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.7 (Si*C*H(CH$_3$)$_2$), 18.1 (SiCH(*C*H$_3$)$_2$), 113.1 (N=*C*HAr), 123.7 (CH_{Ar}), 126.5 (C_{Ar}), 133.5 (CH_{Ar}), 148.8 (CH_{Ar}), 149.4 (CH_{Ar}); HRMS (ESI$^+$) $C_{15}H_{27}O_2NSi$ $[M+H]^+$, found 295.1826, requires 295.1836 (–3.4 ppm).

Triisopropylsilyl (*E*)-(thiophen-3-ylmethylene)azinate (S63)



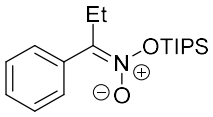
Following General Procedure 23, triisopropylsilyl chloride (0.20 mL, 0.96 mmol) and DBU (0.13 mL, 0.84 mmol) were added sequentially to a stirred solution of the aryl nitromethane (114 mg, 0.8 mmol) in anhydrous CH_2Cl_2 (3 mL) afforded after SiO_2-chromatography (99:1 – 95:5 Petroleum ether : EtOAc, R_f 0.67) the title compound (177 mg, 74%) as a colorless oil; ν_{max} (film) 2945, 2866 (C-H), 1605 (C=N), 1464, 1435 (C=C); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.13 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.33–1.42 (3H, m, SiCH), 7.18 (1H, s, CHNO), 7.24–7.25 (1H, m, ArH), 7.31–7.35 (1H, m, ArH), 8.18–8.19 (1H, m, ArH). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.6 (Si*C*H(CH$_3$)$_2$), 18.0 (SiCH(*C*H$_3$)$_2$), 111.5 (N=*C*HAr), 125.2 (CH_{Ar}), 125.6 (CH_{Ar}), 126.8 (CH_{Ar}), 130.5 (C_{Ar}); HRMS (ESI$^+$) $C_{14}H_{26}O_2NSSi$ $[M+H]^+$, found 300.1447, requires 300.1448 (–0.3 ppm).

Triisopropylsilyl (*E*)-(1-phenylethylidene)azinate (S64)



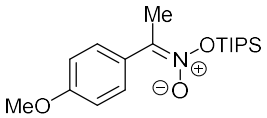
Following General Procedure 23, triisopropylsilyl chloride (0.95 mL, 4.4 mmol) and DBU (0.58 mL, 3.9 mmol) were added sequentially to a stirred solution of (1-nitroethyl)benzene (560 mg, 3.7 mmol) in anhydrous CH_2Cl_2 (11 mL) afforded after SiO_2-chromatography (99:1 – 95:5 Petroleum ether : EtOAc, R_f 0.55) the title compound (1.06 g, 93%) as a yellow oil; ν_{max} (film) 2945, 2888 (C-H), 1682 (C=N), 1484 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.11 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.32–1.39 (3H, m, SiCH), 2.40 (3H, s, CH_3), 7.29–7.31 (1H, m, ArH), 7.37–7.40 (2H, m, ArH), 7.76–7.78 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.9 (Si*C*H(CH$_3$)$_2$), 18.0 (N=C(*C*H$_3$)Ar), 18.2 (SiCH(*C*H$_3$)$_2$), 121.9 (N=*C*(CH$_3$)Ar), 128.2 (2×CH$_{Ar}$), 128.3 (2×CH$_{Ar}$), 128.4 (CH$_{Ar}$), 133.7 (C$_{Ar}$); HRMS (ESI$^+$) $C_{17}H_{30}O_2NSi$ $[M+H]^+$, found 308.2036, requires 308.2040 (−1.3 ppm).

Triisopropylsilyl (*E*)-(1-phenylpropylidene)azinate (S65)



Following General Procedure 23, triisopropylsilyl chloride (0.29 mL, 1.4 mmol) and DBU (0.18 mL, 1.2 mmol) were added sequentially to a stirred solution of (1-nitropropyl)benzene (189 mg, 1.1 mmol) in anhydrous CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (99:1 – 95:5 Petroleum ether : EtOAc, R_f 0.60) the title compound (317 mg, 86%) as a colorless oil; ν_{max} (film) 2943, 2866 (C-H), 1558 (C=N), 1484 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.11 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.23 (3H, t, *J* 7.5, CH$_2$CH_3), 1.31–1.38 (3H, m, SiCH), 2.80 (2H, q, *J* 7.5, CH_2CH$_3$), 7.29–7.32 (1H, m, ArH), 7.37–7.40 (2H, m, ArH), 7.72–7.74 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 10.9 (CH$_2$*C*H$_3$), 12.9 (Si*C*H(CH$_3$)$_2$), 18.2 (SiCH(*C*H$_3$)$_2$), 25.3 (*C*H$_2$CH$_3$), 126.6 (N=*C*(CH$_3$)Ar), 128.2 (2×CH$_{Ar}$), 128.3 (2×CH$_{Ar}$), 128.4 (CH$_{Ar}$), 133.0 (C$_{Ar}$); HRMS (ESI$^+$) $C_{17}H_{30}O_2NSi$ $[M+H]^+$, found 322.2193, requires 322.2197 (−1.2 ppm).

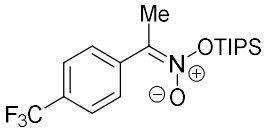
Triisopropylsilyl (*E*)-(1-(4-methoxyphenyl)ethylidene)azinate (474)



Following General Procedure 23, triisopropylsilyl chloride (0.58 mL, 2.7 mmol) and DBU (0.35 mL, 2.4 mmol) were added sequentially to a stirred solution of 1-methoxy-4-(1-nitroethyl)benzene (407 mg, 2.3 mmol) in anhydrous CH_2Cl_2 (7 mL) afforded after SiO_2-chromatography (99:1 – 95:5 Petroleum ether : EtOAc, R_f 0.45) the title compound (677 mg,

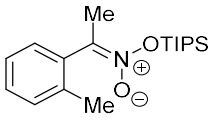
89%) as a yellow oil; ν_{max} (film) 2943, 2866 (C-H), 1607 (C=N), 1464 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.11 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.31–1.40 (3H, m, SiCH), 2.38 (3H, s, N=CCH$_3$), 3.82 (3H, s, OCH$_3$), 6.89–6.92 (2H, m, ArH), 7.77–7.79 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.9 (Si*C*H(CH$_3$)$_2$), 17.8 (N=C(*C*H$_3$)Ar), 18.2 (SiCH(*C*H$_3$)$_2$), 55.4 (OCH$_3$), 113.5 (2×CH$_{Ar}$), 121.6 (N=*C*(CH$_3$)Ar), 125.9 (C$_{Ar}$), 129.8 (2×CH$_{Ar}$), 159.4 (*C*-OCH$_3$); HRMS (ESI$^+$) $C_{18}H_{32}O_3NSi$ [M+H]$^+$, found 338.2139, requires 338.2146 (–2.1 ppm).

Triisopropylsilyl (*E*)-(1-(4-(trifluoromethyl)phenyl)ethylidene)azinate (S66)



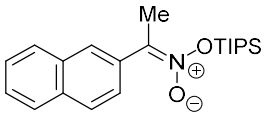
Following General Procedure 23, triisopropylsilyl chloride (0.60 mL, 2.81 mmol) and DBU (0.37 mL, 2.46 mmol) were added sequentially to a stirred solution of 1-trifluoromethyl-4-(1-nitroethyl)benzene (519 mg, 2.35 mmol) in anhydrous CH_2Cl_2 (7 mL) afforded after SiO_2-chromatography (100:0 – 95:5 Petroleum ether : EtOAc, R_f 0.75) the title compound (688 mg, 78%) as a yellow oil; ν_{max} (film) 2945, 2868 (C-H), 1690 (C=N), 1578, 1464 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.11 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.33–1.38 (3H, m, SiCH), 2.42 (3H, s, N=CCH$_3$), 7.63–7.64 (2H, m, ArH), 7.91–7.92 (2H, m, ArH); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F: –62.9 (C*F*$_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.8 (Si*C*H(CH$_3$)$_2$, 18.2 N=C(*C*H$_3$)Ar), 18.2 (SiCH(*C*H$_3$)$_2$), 121.9 (q, $^{1}J_{CF}$ 274.6, C$_{Ar}$-*C*F$_3$), 125.1 (q, $^{3}J_{CF}$ 3.6, *C*H$_{Ar}$-CF$_3$), 127.3 (N=*C*(CH$_3$)Ar), 128.6 (CH$_{Ar}$), 130.0 (q, $^{2}J_{CF}$ 30.4, *C*$_{Ar}$-CF$_3$), 137.1 (*C*$_{Ar}$); HRMS (ESI$^+$) $C_{18}H_{29}F_3O_2NSi$ [M+H]$^+$, found 376.1903, requires 376.1914 (–2.9 ppm).

Triisopropylsilyl (*E*)-(1-(*o*-tolyl)ethylidene)azinate (S67)



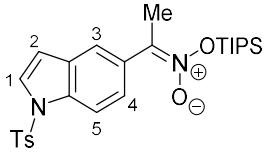
Following General Procedure 23, triisopropylsilyl chloride (0.23 mL, 1.07 mmol) and DBU (0.14 mL, 0.94 mmol) were added sequentially to a stirred solution of the aryl nitromethane (147 mg, 0.94 mmol) in anhydrous CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (98:2 – 95:5 Petroleum ether : EtOAc, R_f 0.66) the title compound (182 mg, 64%) as a light yellow oil; ν_{max} (film) 2945, 2866 (C-H), 1601 (C=N), 1464 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.15 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.35–1.44 (3H, m, SiCH), 2.37 (3H, s, CH$_3$), 7.18–7.21 (1H, m, ArH), 7.23 (1H, s, CHNO), 7.23–7.39 (2H, m, ArH), 8.53–8.54 (1H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.7 (Si*C*H(CH$_3$)$_2$, 18.1 (SiCH(*C*H$_3$)$_2$), 19.2 (N=C(*C*H$_3$)Ar), 19.7 (Ar-CH$_3$), 125.8 (CH$_{Ar}$), 127.7 (CH$_{Ar}$), 128.7 (CH$_{Ar}$), 130.3 (CH$_{Ar}$), 134.7 (N=*C*(CH$_3$)Ar), 136.5 (C$_{Ar}$-CH$_3$); HRMS (ESI$^+$) $C_{18}H_{32}O_2NSi$ [M+H]$^+$, found 322.2194, requires 322.2202 (–2.5 ppm).

Triisopropylsilyl (*E*)-(1-(naphthalen-2-yl)ethylidene)azinate (S68)



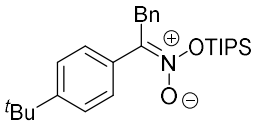
Following General Procedure 23, triisopropylsilyl chloride (0.30 mL, 1.4 mmol) and DBU (0.18 mL, 1.22 mmol) were added sequentially to a stirred solution of the aryl nitromethane (234 mg, 1.16 mmol) in anhydrous CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (98:2 – 95:5 Petroleum ether : EtOAc, R_f 0.75) the title compound (250 mg, 57%) as a light yellow solid; ν_{max} (film) 2947, 2868 (C-H), 1580 (C=N), 1464 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.12 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.33–1.39 (3H, m, SiCH), 2.50 (3H, s, CH_3), 7.48–7.50 (2H, m, ArH), 7.80–7.90 (4H, m, ArH), 8.25 (1H, s, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.7 (Si*C*H(CH$_3$)$_2$, 18.3 (SiCH(*C*H$_3$)$_2$), 18.3 (N=C(*C*H$_3$)Ar), 125.7 (CH$_{Ar}$), 126.5 (CH$_{Ar}$), 126.9 (CH$_{Ar}$), 127.5 (CH$_{Ar}$), 127.6 (CH$_{Ar}$), 128.1 (CH$_{Ar}$), 128.6 (CH$_{Ar}$), 131.1 (N=*C*(CH$_3$)Ar), 131.2 (C$_{Ar}$), 132.9 (C$_{Ar}$), 133.0 (C$_{Ar}$); HRMS (ESI$^+$) $C_{21}H_{32}O_2NSi$ $[M+H]^+$, found 358.2189, requires 358.2202 (–3.6 ppm).

Triisopropylsilyl (*E*)-(1-(1-tosyl-1*H*-indol-5-yl)ethylidene)azinate (S69)



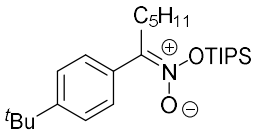
Following General Procedure 23, triisopropylsilyl chloride (0.36 mL, 1.68 mmol) and DBU (0.22 mL, 1.47 mmol) were added sequentially to a stirred solution of the aryl nitromethane (483 mg, 1.40 mmol) in anhydrous CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.47) the title compound (545 mg, 78%) as a light yellow oil; ν_{max} (film) 2945, 2866 (C-H), 1582 (C=N), 1464 (C-H), 1375 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.09 (18H, d, *J* 7.4, SiCH(C*H*$_3$)$_2$), 1.31–1.37 (3H, m, SiCH), 2.34 (3H, s, Ar-CH$_3$), 2.50 (3H, s, CH$_3$), 6.66 (1H, dd, *J* 3.7, 0.8, H-2), 7.20–7.22 (2H, m, Ar-H), 7.56 (1H, d, *J* 3.7, H-1), 7.69 (1H, dd, *J* 8.7, 1.8, H-4), 7.96 (1H, d, *J* 8.7, H-3), 7.73–7.75 (2H, m, Ar-H), 8.04 (1H, d, *J* 1.8, H-5); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.9 (Si*C*H(CH$_3$)$_2$), 17.9 (N=C(*C*H$_3$)Ar), 18.2 (SiCH(*C*H$_3$)$_2$), 21.7 (Ar-CH$_3$), 109.5 (C-1), 113.2 (C-5), 121.7 (C-4), 124.9 (C-2), 126.7 (2×CH$_{Ar}$), 127.2 (C-3), 128.9 (C$_{ind}$), 130.1 (2×CH$_{Ar}$), 130.6 (C$_{ind}$), 134.3 (N=*C*(CH$_3$)Ar), 135.2 (C$_{Ar}$), 145.2 (C$_{Ar}$-CH$_3$); HRMS (ESI$^+$) $C_{26}H_{37}O_4N_2SSi$ $[M+H]^+$, found 501.2230, requires 501.2243 (–2.6 ppm).

Triisopropylsilyl (*E*)-(1-(4-(*tert*-butyl)phenyl)-2-phenylethylidene)azinate (S70)



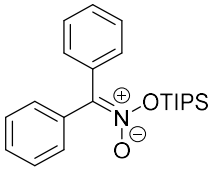
Following General Procedure 23, triisopropylsilyl chloride (0.52 mL, 2.45 mmol) and DBU (0.32 mL, 2.14 mmol) were added sequentially to a stirred solution of the aryl nitromethane (487 mg, 2.04 mmol) in anhydrous CH_2Cl_2 (6 mL) afforded after SiO_2-chromatography (98:2 Petroleum ether : EtOAc, R_f 0.73) the title compound (611 mg, 69%) as a light yellow solid; ν_{max} (film) 2959, 2868 (C-H), 1558 (C=N), 1458 (C-H), 1385 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.04 (18H, d, *J* 7.4, SiCH(CH_3)$_2$), 1.30 (9H, s, (CH_3)$_3$), 1.33–1.35 (3H, m, SiCH), 4.17 (2H, s, CH_2Ph), 7.26–7.27 (5H, m, PhH), 7.36–7.38 (2H, m, ArH), 7.75–7.78 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.9 (Si*C*H(CH$_3$)$_2$, 18.2 (SiCH(*C*H$_3$)$_2$), 18.2 (N=C(*C*H$_3$)Ar), 31.3 (C(*C*H$_3$)$_3$), 34.8 (*C*(CH$_3$)$_3$), 37.2 (*C*H$_2$Ph), 123.6 (C_{Ar}), 125.3 (2×CH_{Ar}), 126.5 (CH_{Ph}), 128.1 (2×CH_{Ar}), 128.3 (2×CH_{Ph}), 128.7 (2×CH_{Ph}), 130.2 (N=*C*(CH$_3$)Ar), 137.2 (C_{Ph}), 151.6 (C(CH$_3$)$_3$*C*$_{Ar}$); HRMS (ESI$^+$) $C_{27}H_{42}O_2NSi$ [M+H]$^+$, found 440.2970, requires 440.2979 (–2.0 ppm).

Triisopropylsilyl (*E*)-(1-(4-(*tert*-butyl)phenyl)hexylidene)azinate (S71)



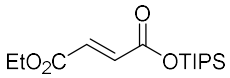
Following General Procedure 23, triisopropylsilyl chloride (0.23 mL, 1.08 mmol) and DBU (0.14 mL, 0.945 mmol) were added sequentially to a stirred solution of the aryl nitromethane (237 mg, 0.90 mmol) in anhydrous CH_2Cl_2 (3 mL) afforded after SiO_2-chromatography (100:0 – 95:5 Petroleum ether : EtOAc, R_f 0.75) the title compound (287 mg, 76%) as a colorless oil; ν_{max} (film) 2947, 2866 (C-H), 1570 (C=N), 1464 (C-H), 1383 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.88 (3H, t, *J* 6.9, (CH$_2$)$_3$C*H*$_3$), 1.04 (18H, d, *J* 7.4, SiCH(C*H*$_3$)$_2$), 1.31 (9H, s, (C*H*$_3$)$_3$), 1.32–1.35 (4H, m, (C*H*$_2$)$_3$CH$_3$), 1.33–1.36 (3H, m, SiCH), 1.61–1.67 (2H, m, C*H*$_2$CH$_2$CHNO$_2$), 2.73–2.76 (2H, m, CH$_2$C*H*$_2$CHNO$_2$), 7.39–7.40 (2H, m, ArH), 7.70–7.72 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 13.0 (Si*C*H(CH$_3$)$_2$, 14.2 (CH$_2$)$_3$*C*H$_3$), 18.3 (SiCH(*C*H$_3$)$_2$), 22.6 ((CH$_2$)$_2$*C*H$_2$CH$_3$), 22.6 ((CH$_2$)$_2$*C*H$_2$CH$_3$), 26.4 ((*C*H$_2$)$_2$CH$_2$CH$_3$), 31.3 (C(*C*H$_3$)$_3$), 31.6 ((*C*H$_2$)$_2$CH$_2$CH$_3$), 32.0 (*C*H$_2$C=N), 34.8 (*C*(CH$_3$)$_3$), 125.2 (2×CH_{Ar}), 125.8 (C_{Ar}), 128.0 (2×CH_{Ar}), 130.2 (N=*C*(C$_5$H$_{11}$)Ar), 151.4 (C(CH$_3$)$_3$*C*$_{Ar}$); HRMS (ESI$^+$) $C_{25}H_{46}O_2NSi$ [M+H]$^+$, found 420.3286, requires 440.3292 (–1.4 ppm).

Triisopropylsilyl (diphenylmethylene)azinate (S72)



Following General Procedure 23, triisopropylsilyl chloride (0.75 mL, 3.5 mmol) and DBU (0.46 mL, 3.1 mmol) were added sequentially to a stirred solution of aryl nitromethane (625 mg, 2.9 mmol) in anhydrous CH_2Cl_2 (9 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.70) the title compound (370 mg, 53%) as a colorless oil; ν_{max} (film) 2943, 2866 (C-H), 1675 (C=N), 1454 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.98 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.04−1.23 (3H, m, SiCH), 7.15–7.41 (10H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.4 (Si*C*H(CH$_3$)$_2$), 18.1 (SiCH(*C*H$_3$)$_2$), 77.0 (N=*C*(Ph)Ph), 126.1 (4×CH$_{Ph}$), 127.0 (2×CH$_{Ar}$), 128.3 (4×CH$_{Ph}$), 145.9 (2×C$_{Ph}$); HRMS (ESI$^+$) $C_{22}H_{32}O_2NSi$ $[M+H]^+$, found 370.2192, requires 370.2197 (−1.3 ppm).

7.5.2.8 Data for ethyl (triisopropylsilyl) fumarate (408)

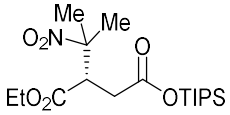


Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl propan-2-ylideneazinate (36.8 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.55) afforded the title compound (7.2 mg, 24%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.09 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.33 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.34−1.38 (3H, m, SiCH), 4.26 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 6.79 (1H, d, *J* 15.8, CH=C*H*CO_2TIPS), 6.85 (1H, d, *J* 15.8, C*H*=CHCO_2TIPS). Data in agreement with the literature.[45]

7.5.3 Enantioselective Michael addition of silyl nitronates

7.5.3.1 Data for Michael addition silyl esters

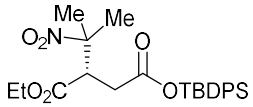
1-Ethyl 4-(triisopropylsilyl) (*S*)-2-(2-nitropropan-2-yl)succinate (412)



Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl propan-2-ylideneazinate (36.8 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.55) afforded the title compound (35.8 mg,

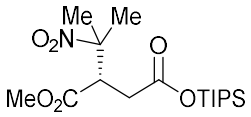
92%) as a colorless oil; $[\alpha]_D^{20}$ +6.4 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R minor: 12.2 min, t_R major: 12.9 min, 99:1 er; ν_{max} (film) 2947, 2870 (C-H), 1722 (C=O), 1545, 1344 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.08 (18H, d, *J* 7.1, SiCH(CH_3)$_2$), 1.23–1.31 (3H, m, SiCH), 1.26 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.61 (3H, s, C(CH_3)), 1.64 (3H, s, C(CH_3)), 2.38 (1H, dd, *J* 17.2, 3.1, CH_2CO_2TIPS), 2.90 (1H, dd, *J* 17.2, 11.4, CH_2CO_2TIPS), 3.67 (1H, dd, *J* 11.4, 3.1, C*H*), 4.17 (2H, q, *J* 7.1, $CO_2CH_2CH_3$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 14.1 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 23.3 (C(*C*H$_3$)), 25.4 (C(*C*H$_3$)), 34.1 (*C*H$_2$CO$_2$TIPS), 49.6 (*C*HCO$_2$Et), 61.8 ($CO_2CH_2CH_3$), 88.5 (*C*(CH$_3$)$_2$NO$_2$), 170.8 (*C*O$_2$TIPS), 170.9 (*C*O$_2$Et); HRMS (NSI^+) $C_{18}H_{35}O_6N_1Si$ $[M+Na]^+$, found 412.2117, requires 412.2126 (–2.2 ppm).

4-(*tert*-Butyldiphenylsilyl) 1-ethyl (*S*)-2-(2-nitropropan-2-yl)succinate (418)



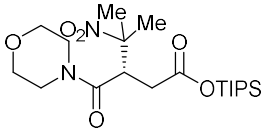
Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), *tert*-butyldiphenylsilyl propan-2-ylideneazinate (49.1 mg, 0.15 mmol), diisopropylethylamine (17 µL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 – 95:5 Petroleum ether : EtOAc, R_f 0.40) afforded the title compound (29.5 mg, 63%) as a colorless oil; $[\alpha]_D^{20}$ +7.7 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R major: 26.7 min, t_R minor: 28.1 min, 97:3 er; ν_{max} (film) 2934, 2860 (C-H), 1732 (C=O), 1545, 1344 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.09 (9H, s, SiC(CH_3)$_3$), 1.17 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.62 (3H, s, C(CH_3)), 1.64 (3H, s, C(CH_3)), 2.51 (1H, dd, *J* 17.2, 3.2, CH_2CO_2TIPS), 3.04 (1H, dd, *J* 17.2, 11.4, CH_2CO_2TIPS), 3.69 (1H, dd, *J* 11.4, 3.2, C*H*), 4.07–4.14 (2H, m, $CO_2CH_2CH_3$), 7.36–7.41 (6H, m, CH_{Ar}), 7.62–7.67 (4H, m, CH_{Ar}); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.0 ($CO_2CH_2CH_3$), 19.3 (Si*C*(*C*H$_3$)$_3$), 23.5 (C(*C*H$_3$)), 25.3 (C(*C*H$_3$)), 27.0 (SiC(*C*H$_3$)$_3$), 34.3 (*C*H$_2$CO$_2$TIPS), 49.5 (*C*HCO$_2$Et), 61.8 ($CO_2CH_2CH_3$), 88.4 (*C*(CH$_3$)$_2$NO$_2$), 127.9 (4×CH_{Ar}), 130.3 (2×CH_{Ar}), 131.5 (2×C_{Ar}), 135.4 (2×CH_{Ar}), 170.2 (*C*O$_2$TIPS), 170.7 (*C*O$_2$Et); HRMS (NSI^+) $C_{25}H_{37}O_6N_2Si$ $[M+NH_4]^+$, found 489.2427, requires 489.2415 (+2.5 ppm).

1-Methyl 4-(triisopropylsilyl) (*S*)-2-(2-nitropropan-2-yl)succinate (422)



Following General Procedure 24, (*E*)-4-methoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl propan-2-ylideneazinate (36.8 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.50) afforded the title compound (35.5 mg, 95%) as a colorless oil; $[\alpha]_D^{20}$ +17.5 (*c* 1.4, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 12.2 min, t_R major: 13.8 min, 98:2 er; ν_{max} (film) 2949, 2870 (C-H), 1740 (C=O), 1545, 1346 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.05 (18H, dd, *J* 7.5, 1.7 SiCH(CH_3)$_2$), 1.25−1.31 (3H, m, SiCH), 1.61 (3H, s, C(CH_3)), 1.63 (3H, s, C(CH_3)), 2.39 (1H, dd, *J* 17.2, 3.1, CH_2CO$_2$TIPS), 2.91 (1H, dd, *J* 17.2, 11.5, CH_2CO$_2$TIPS), 3.69 (1H, dd, *J* 11.5, 3.1, C*H*), 3.71 (3H, s, CO$_2$CH_3); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 17.8 (SiCH(*C*H$_3$)$_2$), 23.2 (C(*C*H$_3$)), 25.5 (C(*C*H$_3$)), 34.1 (*C*H$_2$CO$_2$TIPS), 49.6 (*C*HCO$_2$Me), 52.6 (CO$_2$*C*H$_3$), 88.5 (*C*(CH$_3$)$_2$NO$_2$), 170.9 (*C*O$_2$TIPS), 171.3 (*C*O$_2$Et); HRMS (NSI$^+$) $C_{17}H_{34}O_6N_1Si$ $[M+H]^+$, found 376.2151, requires 376.5150 (+0.3 ppm).

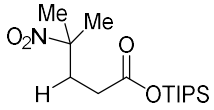
Triisopropylsilyl (*S*)-4-methyl-3-(morpholine-4-carbonyl)-4-nitropentanoate (423)



Following General Procedure 24, (*E*)-4-morpholino-4-oxobut-2-enoic anhydride (35.2 mg, 0.1 mmol), triisopropylsilyl propan-2-ylideneazinate (36.8 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (90:10 Petroleum ether : EtOAc, R_f 0.35) afforded the title compound (36.5 mg, 85%) as a colorless oil which crystallised upon standing; $[\alpha]_D^{20}$ +21.4 (*c* 1.1, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (95:5 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R major: 4.5 min, t_R minor: 5.2 min, 97:3 er; ν_{max} (film) 2947, 2868 (C-H), 1713 (C=O), 1636 (C=ON), 1541, 1375 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.03 (18H, d, *J* 7.5 SiCH(CH_3)$_2$), 1.20−1.29 (3H, m, SiCH), 1.61 (3H, s, C(CH_3)), 1.67 (3H, s, C(CH_3)), 2.39 (1H, dd, *J* 17.3, 2.6, CH_2CO$_2$TIPS), 3.06 (1H, dd, *J* 17.3, 11.3, CH_2CO$_2$TIPS), 3.45−3.48 (1H, m, CH$_{morph}$), 3.57−3.88 (7H, m, CH$_{morph}$), 4.02 (1H, dd, *J* 11.3, 2.6, C*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 11.9 (Si*C*H(CH$_3$)$_2$, 17.8 (SiCH(*C*H$_3$)$_2$), 23.3 (C(*C*H$_3$)), 24.9 (C(*C*H$_3$)), 35.3 (*C*H$_2$CO$_2$TIPS), 42.8 (*C*H$_{morph}$), 43.2 (*C*HCON), 47.6 (*C*H$_{morph}$), 66.7 (*C*H$_{morph}$), 66.9 (*C*H$_{morph}$), 89.9 (*C*(CH$_3$)$_2$NO$_2$),

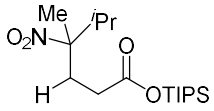
169.4 (*C*O_2TIPS), 171.3 (*C*ON); HRMS (NSI$^+$) $C_{20}H_{39}O_6N_2Si$ $[M+H]^+$, found 431.2570, requires 431.2572 (–0.4 ppm).

Triisopropylsilyl 4-methyl-4-nitropentanoate (424)



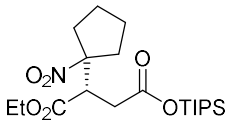
Following General Procedure 24, acrylic anhydride (12.6 mg, 0.1 mmol), triisopropylsilyl propan-2-ylideneazinate (36.8 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.53) afforded the title compound (24.4 mg, 77%) as a colorless oil; ν_{max} (film) 2947, 2870 (C-H), 1715 (C=O), 1539, 1348 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.06 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.26–1.32 (3H, m, SiCH), 1.60 (6H, s, C(C*H*$_3$)), 2.23–2.26 (2H, m, C*H*$_2$CO$_2$TIPS; C*H*$_2$CNO$_2$), 2.34–2.38 (2H, m, C*H*$_2$CO$_2$TIPS; C*H*$_2$NO$_2$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 17.9 (SiCH(*C*H$_3$)$_2$), 26.0 (C(*C*H$_3$)), 30.8 (*C*H$_2$CO$_2$TIPS), 35.8 (*C*H$_2$CNO$_2$), 87.5 (*C*(CH$_3$)$_2$NO$_2$), 172.3 (*C*O$_2$TIPS); HRMS (NSI$^+$) $C_{15}H_{32}O_4N_1Si$ $[M+H]^+$, found 318.2098, requires 318.2095 (+0.9 ppm).

Triisopropylsilyl 4,5-dimethyl-4-nitrohexanoate (425)



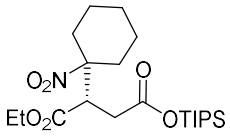
Following General Procedure 24, acrylic anhydride (12.6 mg, 0.1 mmol), triisopropylsilyl (*E*)-(3-methylbutan-2-ylidene)azinate (41.0 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.47) afforded the title compound (16.8 mg, 49%) as a colorless oil; $[\alpha]_D^{20}$ +5.5 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ODH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 7.9 min, t_R major: 8.8 min, 50:50 er; ν_{max} (film) 2947, 2870 (C-H), 1713 (C=O), 1537, 1385 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.89 (3H, d, *J* 6.9, (C*H*$_3$)$_2$CHC), 0.97 (3H, d, *J* 6.9, (C*H*$_3$)$_2$CHC), 1.06 (18H, d, *J* 7.4, SiCH(C*H*$_3$)$_2$), 1.25–1.31 (3H, m, SiCH), 1.43 (3H, s, C(C*H*$_3$)), 2.06–2.10 (1H, m, C*H*$_2$CNO$_2$), 2.24–2.28 (1H, m, C*H*$_2$CNO$_2$), 2.34–2.40 (3H, m, (CH$_3$)$_2$C*H*C; C*H*$_2$CO$_2$TIPS); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 16.8 (C(*C*H$_3$)), 17.5 (C*H*$_3$)$_2$CHC), 17.6 (C*H*$_3$)$_2$CHC), 17.9 (SiCH(*C*H$_3$)$_2$), 30.5 (*C*H$_2$CNO$_2$), 32.8 (*C*H$_2$CO$_2$TIPS), 37.2 (CH$_3$)$_2$*C*HC), 94.9 (*C*(^{i}PrMe)NO$_2$), 172.6 (*C*O$_2$TIPS); HRMS (NSI$^+$) $C_{17}H_{36}O_4N_1Si$ $[M+H]^+$, found 346.2411, requires 346.2414 (–0.9 ppm).

1-Ethyl 4-(triisopropylsilyl) (*S*)-2-(1-nitrocyclopentyl)succinate (434)



Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl cyclopentylideneazinate (40.7 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.48) afforded the title compound (30.8 mg, 74%) as a colorless oil; $[\alpha]_D^{20}$ +8.9 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 17.8 min, t_R major: 21.9 min, 99:1 er; ν_{max} (film) 2947, 2868 (C-H), 1738 (C=O), 1543, 1371 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.06 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.24–1.31 (3H, m, SiCH), 1.26 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.70–1.79 (4H, m, CH_{cp}), 1.93–1.99 (1H, m, CH_{cp}), 2.04–2.10 (1H, m, CH_{cp}), 2.49 (1H, dd, *J* 17.5, 3.1, CH_2CO$_2$TIPS), 2.54–2.60 (1H, m, CH_{cp}), 2.62–2.68 (1H, m, CH_{cp}), 2.93 (1H, dd, *J* 17.5, 11.1, CH_2CO$_2$TIPS), 3.56 (1H, dd, *J* 11.1, 3.1, C*H*), 4.18 (2H, q, *J* 7.2, $CO_2CH_2CH_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 14.2 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 23.8 (CH_{2Cp}), 24.1 (CH_{2Cp}), 34.8 (CH_{2Cp}), 35.3 (CH_{2Cp}), 36.7 (*C*H$_2$CO$_2$TIPS), 48.6 (*C*HCO$_2$Et), 61.7 ($CO_2CH_2CH_3$), 92.4 (*C*NO$_2$), 170.7 (*C*O$_2$TIPS), 171.3 (*C*O$_2$Et); HRMS (NSI$^+$) $C_{20}H_{38}O_6N_1Si$ $[M+H]^+$, found 416.2463, requires 416.2463 (–0.0 ppm).

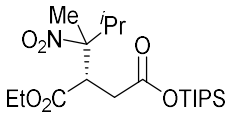
1-Ethyl 4-(triisopropylsilyl) (*S*)-2-(1-nitrocyclohexyl)succinate (435)



Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl cyclohexylideneazinate (42.8 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.58) afforded the title compound (25.7 mg, 60%) as a colorless oil; $[\alpha]_D^{20}$ +19.3 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak ODH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 10.1 min, t_R major: 11.2 min, 98:2 er; ν_{max} (film) 2945, 2870 (C-H), 1730 (C=O), 1543, 1375 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.04 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.19–1.29 (3H, m, SiCH), 1.26 (3H, t, *J* 7.4, $CO_2CH_2CH_3$), 1.33–1.42 (2H, m, CH_{chex}), 1.60–1.74 (6H, m, CH_{chex}), 2.49 (1H, dd, *J* 17.3, 3.2, CH_2CO$_2$TIPS), 2.50–2.56 (2H, m, CH_{chex}), 2.91 (1H, dd, *J* 17.3, 11.9, CH_2CO$_2$TIPS), 3.28

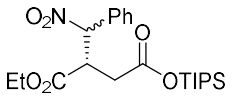
(1H, dd, *J* 11.9, 3.2, C*H*), 4.13–4.20 (2H, m, $CO_2CH_2CH_3$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 11.9 ($SiCH(CH_3)_2$, 14.0 ($CO_2CH_2CH_3$), 17.7 ($SiCH(CH_3)_2$), 22.1 (CH_{2Chex}), 22.2 (CH_{2Chex}), 24.4 (CH_{2Chex}), 31.4 (CH_{2Chex}), 33.1 (CH_{2Chex}), 33.4 (CH_2CO_2TIPS), 50.4 ($CHCO_2Et$), 61.6 ($CO_2CH_2CH_3$), 91.8 (CNO_2), 170.4 (CO_2TIPS), 171.1 (CO_2Et); HRMS (NSI^+) $C_{21}H_{40}O_6N_1Si$ $[M+H]^+$, found 430.2618, requires 430.2619 (–0.2 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(3-methyl-2-nitrobutan-2-yl)succinate (436)



Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(3-methylbutan-2-ylidene)azinate (41.0 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.55) afforded the title compound (22.6 mg, 54%) as a colorless oil; $[\alpha]_D^{20}$ +43.7 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak ODH (>99:1 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R minor: 9.3 min, t_R major: 10.3 min, >99:1 er; ν_{max} (film) 2947, 2870 (C-H), 1732 (C=O), 1541, 1373 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.95 (3H, d, *J* 6.9, $(CH_3)_2CHC$), 1.00 (3H, d, *J* 6.9, $(CH_3)_2CHC$), 1.05 (18H, dd, *J* 7.5, 1.6, $SiCH(CH_3)_2$), 1.24–1.31 (3H, m, SiCH), 1.27 (3H, t, *J* 7.4, $CO_2CH_2CH_3$), 1.55 (3H, s, $C(CH_3)$), 2.38 (1H, sept, $(CH_3)_2CHC$) 2.51 (1H, dd, *J* 17.3, 2.6, CH_2CO_2TIPS), 2.99 (1H, dd, *J* 17.3, 11.6, CH_2CO_2TIPS), 3.63 (1H, dd, *J* 11.6, 2.6, C*H*), 4.12–4.21 (2H, m, $CO_2CH_2CH_3$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 14.1 ($CO_2CH_2CH_3$), 16.9 ($C(CH_3)$), 17.5 ($(CH_3)_2CHC$), 17.5 ($(CH_3)_2CHC$), 17.8 ($SiCH(CH_3)_2$), 34.3 (CH_2CO_2TIPS), 34.7 $(CH_3)_2CHC$, 47.7 ($CHCO_2Et$), 61.8 ($CO_2CH_2CH_3$), 94.2 ($C(CH_3)_2NO_2$), 171.1 (CO_2TIPS), 171.4 (CO_2Et); HRMS (NSI^+) $C_{20}H_{40}O_6N_1Si$ $[M+H]^+$, found 418.2620, requires 418.2619 (+0.1 ppm).

1-Ethyl 4-(triisopropylsilyl) (*S*)-2-(nitro(phenyl)methyl)succinate (438)



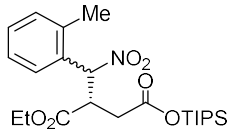
Following General Procedure 25, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-benzylideneazinate (58.6 mg, 0.2 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.45) afforded the title compound as an inseparable mixture of diastereomers (22.2 mg, 51%, 82:18 dr) as a colorless oil; $[\alpha]_D^{20}$ –47.8 (*c* 0.5, $CHCl_3$); ν_{max} (film) 2945, 2868 (C-H), 1738, 1717

(C=O), 1558, 1458, 1371 (NO_2); HRMS (NSI^+) $C_{22}H_{39}O_6N_2Si$ $[M+NH_4]^+$, found 455.2570, requires 455.2572 (−0.4 ppm).

major diastereomer: Chiral HPLC analysis, Chiralpak ADH (98.5:1.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 25 °C) t_R minor: 14.7 min, t_R major: 15.4 min, 98:2 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.00 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.21−1.30 (3H, m, SiCH), 1.26 (3H, t, *J* 7.5, $CO_2CH_2CH_3$), 2.23 (1H, dd, *J* 17.9, 5.6, C*H*$_2$CO$_2$TIPS), 2.81 (1H, dd, *J* 17.9, 4.3, C*H*$_2$CO$_2$TIPS), 3.89–3.93 (1H, m, C*H*CO$_2$Et), 4.18–4.24 (2H, m, $CO_2CH_2CH_3$), 6.07 (1H, d, *J* 11.0, C*H*NO$_2$), 7.39–7.45 (5H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 11.9 (Si*C*H(CH$_3$)$_2$, 14.1 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 34.3 (*C*H$_2$CO$_2$TIPS), 41.2 (*C*HCO$_2$Et), 62.1 ($CO_2CH_2CH_3$), 89.6 (*C*HNO$_2$), 128.1 (2×CH$_{Ar}$), 129.6 (2×CH$_{Ar}$), 130.5 (CH$_{Ar}$), 132.7 (C$_{Ar}$), 170.6 (*C*O$_2$TIPS), 171.1 (*C*O$_2$Et);

minor diastereomer: Chiralpak ADH (98.5:1.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 25 °C) t_R major: 14.2 min, t_R minor: 16.3 min, >99:1 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.06 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.21−1.30 (3H, m, SiCH), 1.24 (3H, t, *J* 7.5, $CO_2CH_2CH_3$), 2.66 (1H, dd, *J* 17.3, 3.4, C*H*$_2$CO$_2$TIPS), 3.01 (1H, dd, *J* 17.3, 9.9, C*H*$_2$CO$_2$TIPS), 3.89–3.93 (1H, m, C*H*CO$_2$Et), 4.18–4.24 (2H, m, $CO_2CH_2CH_3$), 5.69 (1H, d, *J* 10.3, C*H*NO$_2$), 7.39–7.45 (5H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 13.7 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 35.6 (*C*H$_2$CO$_2$TIPS), 46.2 (*C*HCO$_2$Et), 61.6 ($CO_2CH_2CH_3$), 91.4 (*C*HNO$_2$), 128.3 (2×CH$_{Ar}$), 129.1 (2×CH$_{Ar}$), 130.4 (CH$_{Ar}$), 132.3 (C$_{Ar}$), 166.8 (*C*O$_2$TIPS), 167.5 (*C*O$_2$Et).

1-Ethyl 4-(triisopropylsilyl) (*S*)-2-(nitro(o-tolyl)methyl)succinate (439)



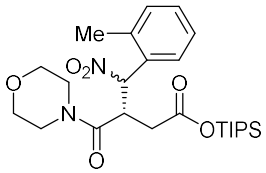
Following General Procedure 25, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(2-methylbenzylidene)azinate (61.4 mg, 0.2 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.40) afforded the title compound as a separable mixture of diastereomers (75:25 dr, major: 22.6 mg, 51%; minor: 7.4, 16%) as a colorless oil;

major diastereomer: $[\alpha]_D^{20}$ +95.0 (*c* 0.8, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 220 nm, 30 °C) t_R major: 14.2 min, t_R minor: 15.4 min, 96:4 er; ν_{max} (film) 2947, 2870 (C-H), 1736 (C=O), 1558, 1375 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.98 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.17−1.25 (3H, m, SiCH), 1.28 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 2.34 (1H, dd, *J* 17.9, 5.8, C*H*$_2$CO$_2$TIPS), 2.52 (3H, s, Ar-C*H*$_3$), 2.79 (1H, dd, *J* 17.9, 4.3, C*H*$_2$CO$_2$TIPS), 4.00 (1H, ddd, *J* 11.1, 5.8, 4.3, C*H*CO$_2$Et), 4.18–4.25 (2H, m,

$CO_2CH_2CH_3$), 6.44 (1H, d, *J* 11.1, C*H*NO_2), 7.22–7.30 (3H, m, ArH), 7.39–7.41 (1H, m, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 11.9 (Si*C*H$(CH_3)_2$, 14.1 ($CO_2CH_2CH_3$), 17.7 (SiCH(*C*$H_3)_2$), 19.7 (Ar-*C*H_3), 34.2 (*C*H_2CO_2TIPS), 43.7 (*C*HCO_2Et), 62.0 ($CO_2CH_2CH_3$), 84.9 (*C*HNO_2), 126.6 (CH_{Ar}), 127.2 (CH_{Ar}), 130.2 (CH_{Ar}), 131.0 (C_{Ar}), 131.7 (CH_{Ar}), 138.5 (CH_3-C_{Ar}), 170.7 (*C*O_2TIPS), 171.5 (*C*O_2Et); HRMS (NSI^+) $C_{23}H_{38}O_6NSi$ $[M+H]^+$, found 452.2467, requires 452.2463 (+0.9 ppm).

minor diastereomer: $[\alpha]_D^{20}$ −23.0 (*c* 0.5, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R minor: 8.7 min, t_R major: 13.6 min, 97:3 er; ν_{max} (film) 2947, 2870 (C-H), 1724 (C=O), 1557, 1373 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.89 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.06 (18H, d, *J* 7.5, SiCH(C$H_3)_2$), 1.25−1.31 (3H, m, SiCH), 2.46 (3H, s, Ar-CH_3), 2.71 (1H, dd, *J* 17.2, 3.3, CH_2CO_2TIPS), 3.03 (1H, dd, *J* 17.2, 9.8, CH_2CO_2TIPS), 3.87–3.97 (3H, m, 1H × C*H*CO_2Et, 2H × $CO_2CH_2CH_3$), 6.06 (1H, d, *J* 10.3, C*H*NO_2), 7.19–7.29 (3H, m, ArH), 7.52–7.54 (1H, m, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H$(CH_3)_2$, 13.7 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*$H_3)_2$), 19.5 (Ar-*C*H_3), 35.8 (*C*H_2CO_2TIPS), 45.6 (*C*HCO_2Et), 61.6 ($CO_2CH_2CH_3$), 86.8 (*C*HNO_2), 126.8 (CH_{Ar}), 127.0 (CH_{Ar}), 130.1 (CH_{Ar}), 131.0 (C_{Ar}), 131.1 (CH_{Ar}), 137.3 (CH_3-C_{Ar}), 170.4 (*C*O_2TIPS), 170.5 (*C*O_2Et); HRMS (NSI^+) $C_{23}H_{38}O_6NSi$ $[M+H]^+$, found 452.2463, requires 452.2463 (+0.0 ppm).

Triisopropylsilyl (*S*)-3-(morpholine-4-carbonyl)-4-nitro-4-(*o*-tolyl)butanoate (440)



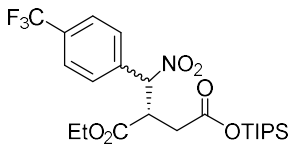
Following General Procedure 25, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(2-methylbenzylidene)azinate (61.4 mg, 0.2 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.40) afforded the title compound afforded the title compound as an inseparable mixture of diastereomers (26.6 mg, 54%; 65:35 dr) as a colorless oil; $[\alpha]_D^{20}$ +5.6 (*c* 0.8, $CHCl_3$); ν_{max} (film) 2945, 2866 (C-H), 1713 (C=O), 1636 (C=ON), 1551, 1360 (NO_2); HRMS (NSI^+) $C_{25}H_{41}O_6N_2Si$ $[M+H]^+$, found 493.2722, requires 493.2728 (−1.3 ppm);

major diastereomer: Chiral HPLC analysis, Chiralpak ADH (99:1 Petroleum ether : IPA, flow rate 1.0 $mLmin^{-1}$, 211 nm, 25 °C) t_R minor: 8.1 min, t_R major: 10.6 min, 94.5:5.5 er; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.03 (18H, dd, *J* 8.1, 3.3, SiCH(C$H_3)_2$), 1.24−1.33 (3H, m, SiCH), 2.48 (3H, s, CH_3), 2.68 (1H, dd, *J* 17.4, 2.9, CH_2CO_2TIPS), 3.18 (1H, dd, *J* 17.5, 10.9, CH_2CO_2TIPS), 3.11−3.22 (2H, m, CH_{morph}), 3.31−3.38 (2H, m, CH_{morph}), 3.57−3.71 (4H, m, CH_{morph}), 4.02 (1H, td, *J* 10.9, 2.9, C*H*CO_2TIPS), 6.03 (1H, d, *J* 11.1, C*H*NO_2), 7.26−7.34 (3H, m, CH_{Ar}), 7.60−7.62

(1H, m, CH_{Ar}); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH_3)$_2$, 17.8 (SiCH(*C*H_3)$_2$), 37.2 (*C*H_2CO_2TIPS), 41.5 (*C*HCON), 42.3 (*C*H_{morph}), 47.0 (*C*H_{morph}), 66.5 (*C*H_{morph}), 66.6 (*C*H_{morph}), 87.5 (*C*HNO_2), 125.8 (CH_{Ar}), 126.6 (CH_{Ar}), 130.2 (CH_{Ar}), 131.3 (CH_{Ar}), 131.6 (C_{Ar}), 138.1 (CH_3-C_{Ar}), 168.6 (*C*O_2TIPS), 171.3 (*C*ON);

minor diastereomer: Chiralpak ADH (99:1 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R major: 12.6 min, t_R minor: 20.1 min, 96:4 er; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.99 (18H, dd, *J* 7.5, 4.1, SiCH(C*H*$_3$)$_2$), 1.19–1.25 (3H, m, SiCH), 2.07 (1H, dd, *J* 17.5, 3.0, C*H*$_2CO_2$TIPS), 2.58 (3H, s, CH_3), 2.73 (1H, dd, *J* 17.5, 10.3, C*H*$_2CO_2$TIPS), 3.10–3.22 (2H, m, CH_{morph}), 3.58–3.62 (2H, m, CH_{morph}), 3.81–3.87 (2H, m, CH_{morph}), 3.94–3.97 (2H, m, CH_{morph}), 4.40 (1H, td, *J* 10.8, 3.1, C*H*CO_2TIPS), 6.20 (1H, d, *J* 11.1, C*H*NO_2), 7.26–7.34 (3H, m, C*H*$_{Ar}$), 7.47–7.49 (1H, m, C*H*$_{Ar}$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 11.9 (Si*C*H(CH_3)$_2$, 17.8 (SiCH(*C*H_3)$_2$), 35.5 (*C*H_2CO_2TIPS), 40.2 (*C*HCON), 42.9 (*C*H_{morph}), 47.3 (*C*H_{morph}), 66.8 (2×*C*H_{morph}), 87.5 (*C*HNO_2), 127.4 (CH_{Ar}), 130.3 (CH_{Ar}), 131.0 (C_{Ar}), 131.3 (CH_{Ar}), 131.6 (CH_{Ar}), 138.4 (CH_3-C_{Ar}), 170.7 (*C*O_2TIPS), 171.0 (*C*ON).

1-Ethyl 4-(triisopropylsilyl) (*S*)-2-(nitro(4-(trifluoromethyl)phenyl)methyl)succinate (441)



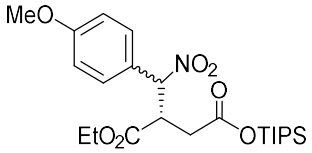
Following General Procedure 25, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(4- trifluoromethylbenzylidene)azinate (72.2 mg, 0.2 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.33) afforded the title compound as an inseparable mixture of diastereomers (27.8 mg, 55%, 85:15 dr) as a colorless oil; $[\alpha]_D^{20}$ +84.0 (*c* 0.3, $CHCl_3$); ν_{max} (film) 2951, 2870 (C-H), 1740, 1719 (C=O), 1560, 1325 (NO_2); HRMS (NSI$^+$) $C_{23}H_{35}F_3O_6NSi$ $[M+H]^+$, found 506.2189, requires 506.2180 (+1.8 ppm).

major diastereomer: Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 25 °C) t_R minor: 29.2 min, t_R major: 33.7 min, 86:14 er; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.02 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.22–1.30 (3H, m, SiCH), 1.29 (3H, t, *J* 7.5, $CO_2CH_2CH_3$), 2.23 (1H, dd, *J* 18.0, 5.3, C*H*$_2CO_2$TIPS), 2.88 (1H, dd, *J* 18.0, 4.4, C*H*$_2CO_2$TIPS), 3.91–3.98 (1H, m, C*H*CO_2Et), 4.21–4.28 (2H, m, $CO_2CH_2CH_3$), 6.21 (1H, d, *J* 10.9, C*H*NO_2), 7.57–7.60 (2H, m, ArH), 7.69–7.71 (2H, m, ArH); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F: –63.0 (C*F*$_3$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 11.9 (Si*C*H(CH_3)$_2$, 14.0 ($CO_2CH_2CH_3$), 17.7 (SiCH(*C*H_3)$_2$), 34.2 (*C*H_2CO_2TIPS), 44.0 (*C*HCO_2Et), 62.3 ($CO_2CH_2CH_3$), 89.0 (*C*HNO_2), 123.0 (q, $^1J_{CF}$ 236.1,

CF_3), 126.6 (q, $^3J_{CF}$ 3.7, *C*H_{Ar}-CF_3), 127.9 (CH_{Ar}), 131.2 (q, $^2J_{CF}$ 28.8, C_{Ar}-CF_3), 135.0 (C_{Ar}), 170.4 (*C*O_2TIPS), 171.6 (*C*O_2Et);

minor diastereomer: Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 25 °C) t_R major: 23.3 min, t_R minor: 42.1 min, >99:1 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.96 (3H, t, *J* 7.5, $CO_2CH_2CH_3$), 1.08 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.22−1.30 (3H, m, SiCH), 2.73 (1H, dd, *J* 17.4, 3.7, CH_2CO_2TIPS), 3.02 (1H, dd, *J* 17.4, 9.3, CH_2CO_2TIPS), 3.92–3.97 (1H, m, C*H*CO_2Et), 4.21–4.28 (2H, m, $CO_2CH_2CH_3$), 5.83 (1H, d, *J* 10.3, C*H*NO_2), 7.62–7.65 (2H, m, ArH), 7.74–7.75 (2H, m, ArH); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F: −63.0 (CF_3); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 14.0 ($CO_2CH_2CH_3$), 17.9 (SiCH(*C*H$_3$)$_2$), 34.2 (*C*H_2CO_2TIPS), 45.1 (*C*HCO$_2$Et), 61.9 ($CO_2CH_2CH_3$), 86.1 (*C*HNO_2).

1-Ethyl 4-(triisopropylsilyl) (*S*)-2-((4-methoxyphenyl)(nitro)methyl)succinate (442)



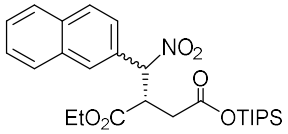
Following General Procedure 25, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(4-methoxybenzylidene)azinate (64.8 mg, 0.2 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.25) afforded the title compound as an inseparable mixture of diastereomers (37.9 mg, 81%, 85:15 dr) as a colorless oil; $[\alpha]_D^{20}$ +24.4 (*c* 0.5, $CHCl_3$); ν_{max} (film) 2947, 2868 (C-H), 1736, 1717 (C=O), 1558, 1516, 1373 (NO_2); HRMS (NSI$^+$) $C_{23}H_{41}O_7N_2Si$ $[M+NH_4]^+$, found 485.2685, requires 485.2678 (+1.4 ppm).

major diastereomer: Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 25 °C) t_R major: 21.3 min, t_R minor: 22.6 min, 99:1 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.01 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.21−1.28 (3H, m, SiCH), 1.25 (3H, t, *J* 7.5, $CO_2CH_2CH_3$), 2.28 (1H, dd, *J* 17.8, 5.8, CH_2CO_2TIPS), 2.78 (1H, dd, *J* 17.8, 4.3, CH_2CO_2TIPS), 3.81 (3H, s, OCH_3), 3.88–3.93 (1H, m, C*H*CO_2Et), 4.17–4.24 (2H, m, $CO_2CH_2CH_3$), 5.99 (1H, d, *J* 11.1, C*H*NO_2), 6.89–6.90 (2H, m, ArH), 7.33–7.35 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 14.1 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 34.4 (*C*H_2CO_2TIPS), 44.2 (*C*HCO$_2$Et), 55.5 (OCH_3), 62.0 ($CO_2CH_2CH_3$), 89.3 (*C*HNO_2), 114.8 (2×CH_{Ar}), 124.7 (C_{Ar}), 129.6 (2×CH_{Ar}), 132.7 (C_{Ar}-OCH_3), 170.6 (*C*O_2TIPS), 171.2 (*C*O_2Et);

minor diastereomer: Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 1.5 mLmin^{-1}, 211 nm, 25 °C) t_R major: 16.1 min, t_R minor: 17.5 min, 96:4 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.94 (3H, t, *J* 7.5, $CO_2CH_2CH_3$), 1.06 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.20−1.30 (3H, m, SiCH), 2.64 (1H, dd, *J* 17.4, 2.5, CH_2CO_2TIPS), 2.98 (1H, dd, *J* 17.4, 10.0,

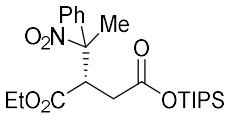
C*H*$_2$CO$_2$TIPS), 3.83 (3H, s, OCH$_3$), 3.88–3.93 (1H, m, C*H*CO$_2$Et), 4.17–4.24 (2H, m, CO$_2$C*H*$_2$CH$_3$), 5.61 (1H, d, *J* 10.5, C*H*NO$_2$), 6.93–6.95 (2H, m, ArH), 7.39–7.41 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 13.8 (CO$_2$CH$_2$*C*H$_3$), 17.7 (SiCH(*C*H$_3$)$_2$), 35.7 (*C*H$_2$CO$_2$TIPS), 46.2 (*C*HCO$_2$Et), 55.5 (OCH$_3$), 61.6 (CO$_2$*C*H$_2$CH$_3$), 91.1 (*C*HNO$_2$), 114.3 (2×CH$_{Ar}$), 124.7 (C$_{Ar}$), 129.8 (2×CH$_{Ar}$), 132.7 (*C*$_{Ar}$-OCH$_3$), 170.6 (*C*O$_2$TIPS), 171.2 (*C*O$_2$Et).

1-Ethyl 4-(triisopropylsilyl) (*S*)-2-(naphthalen-2-yl(nitro)methyl)succinate (443)



Following General Procedure 25, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(naphthalen-2-ylmethylene)azinate (64.8 mg, 0.2 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R$_f$ 0.27) afforded the title compound (30.2 mg, 62%, 94:6 dr) as a colorless oil; $[\alpha]_D^{20}$ +57.5 (*c* 0.6, CHCl$_3$); ν_{max} (film) 2947, 2870 (C-H), 1738 (C=O), 1715 (C=O), 1558, 1369 (NO$_2$); Chiral HPLC analysis, Chiralpak ADH (99:1 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t$_R$ minor: 22.9 min, t$_R$ major: 25.1 min, >99:1 er; ^{1}H NMR (500 MHz, CDCl$_3$) δ_H: 0.97 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.16–1.24 (3H, m, SiCH), 1.28 (3H, t, *J* 7.1, CO$_2$CH$_2$C*H*$_3$), 2.24 (1H, dd, *J* 18.0, 5.5, C*H*$_2$CO$_2$TIPS), 2.84 (1H, dd, *J* 18.0, 4.4, C*H*$_2$CO$_2$TIPS), 4.00–4.05 (1H, m, C*H*CO$_2$Et), 4.19–4.29 (2H, m, CO$_2$C*H*$_2$CH$_3$), 6.26 (1H, d, *J* 11.0, C*H*NO$_2$), 7.48–7.50 (1H, m, ArH), 7.52–7.57 (2H, m, ArH), 7.82–7.90 (4H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 11.9 (Si*C*H(CH$_3$)$_2$, 14.1 (CO$_2$CH$_2$*C*H$_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 34.4 (*C*H$_2$CO$_2$TIPS), 44.1 (*C*HCO$_2$Et), 62.1 (CO$_2$*C*H$_2$CH$_3$), 89.9 (*C*HNO$_2$), 123.7 (CH$_{Ar}$), 127.2 (CH$_{Ar}$), 127.6 (CH$_{Ar}$), 127.9 (CH$_{Ar}$), 128.4 (CH$_{Ar}$), 129.1 (CH$_{Ar}$), 129.8 (CH$_{Ar}$), 129.9 (C$_{Ar}$), 133.1 (C$_{Ar}$), 134.0 (C$_{Ar}$), 170.6 (*C*O$_2$TIPS), 171.1 (*C*O$_2$Et); HRMS (NSI$^+$) C$_{26}$H$_{38}$O$_6$NSi [M+H]$^+$, found 488.2465, requires 488.2463 (+0.4 ppm).

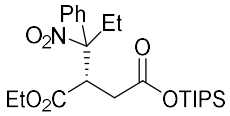
1-Ethyl 4-(triisopropylsilyl) (*S*)-2-(1-nitro-1-phenylethyl)succinate (446)



Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-phenylethylidene)azinate (46.1 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R$_f$ 0.43) afforded the title compound as a colorless oil (28.0 mg, 62%); $[\alpha]_D^{20}$ +32.5 (*c* 0.6, CHCl$_3$); ν_{max} (film) 2947, 2868 (C-H), 1730

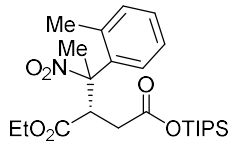
(C=O), 1549, 1464, 1371 (NO_2); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R major: 13.4 min, t_R minor: 14.6 min, 96:4 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.80 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.06 (18H, d, *J* 7.5, $SiCH(CH_3)_2$), 1.23–1.31 (3H, m, SiCH), 2.09 (3H, s, $C(Ph)CH_3$), 2.23 (1H, dd, *J* 17.1, 2.2, CH_2CO_2TIPS), 3.04 (1H, dd, *J* 17.1, 11.1, CH_2CO_2TIPS), 3.71–3.84 (2H, m, $CO_2CH_2CH_3$), 4.27 (1H, dd, *J* 11.1, 2.2, $CHCO_2Et$), 7.36–7.40 (5H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 13.6 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 20.5 ($C(Ph)CH_3$), 35.4 (CH_2CO_2TIPS), 50.3 ($CHCO_2Et$), 61.3 ($CO_2CH_2CH_3$), 93.6 (CNO_2), 125.6 (2×CH_{Ar}), 128.9 (2×CH_{Ar}), 129.5 (CH_{Ar}), 137.9 (C_{Ar}), 171.1 (CO_2TIPS), 171.1 (CO_2Et); HRMS (NSI$^+$) $C_{23}H_{38}O_6NSi$ $[M+H]^+$, found 452.2465, requires 452.2463 (+0.4 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(1-nitro-1-phenylpropyl)succinate (447)



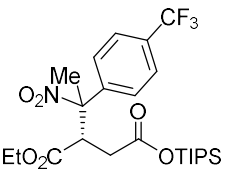
Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-phenylethylidene)azinate (48.2 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.38) afforded the title compound as a colorless oil (30.3 mg, 65%); $[\alpha]_D^{20}$ +22.4 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2945, 2868 (C-H), 1740 (C=O), 1549, 1464, 1369 (NO_2); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R major: 11.6 min, t_R minor: 20.1 min, 91:9 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.83 (3H, t, *J* 7.3, $C(Ph)CH_2CH_3$), 1.04 (18H, d, *J* 7.5, $SiCH(CH_3)_2$), 1.20 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.25–1.31 (3H, m, SiCH), 2.37 (1H, dq, *J* 14.7, 7.3, $C(Ph)CH_2CH_3$), 2.48 (1H, dq, *J* 14.7, 7.3, C(Ph)C*H*2CH3), 2.80 (1H, dd, *J* 18.0, 2.0, CH_2CO_2TIPS), 2.98 (1H, dd, *J* 18.0, 10.5, CH_2CO_2TIPS), 4.27 (1H, dd, *J* 10.5, 2.0, $CHCO_2Et$), 4.08–4.18 (2H, m, $CO_2CH_2CH_3$), 7.10–7.12 (2H, m, ArH), 7.10–7.12 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 9.4 ($C(Ph)CH_2CH_3$), 12.0 ($SiCH(CH_3)_2$, 14.0 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 32.0 (CH_2CO_2TIPS), 35.9 ($C(Ph)CH_2CH_3$), 47.9 ($CHCO_2Et$), 61.8 ($CO_2CH_2CH_3$), 98.4 (CNO_2), 126.3 (2×CH_{Ar}), 128.7 (CH_{Ar}), 128.9 (2×CH_{Ar}), 136.4 (C_{Ar}), 170.8 (CO_2TIPS), 172.0 (CO_2Et); HRMS (NSI$^+$) $C_{24}H_{40}O_6NSi$ $[M+H]^+$, found 466.2617, requires 466.2619 (–0.5 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(1-nitro-1-(*o*-tolyl)ethyl)succinate (448)



Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-(*o*-tolyl)ethylidene)azinate (56.0 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.63) afforded the title compound as a colorless oil (24.9 mg, 54%); $[\alpha]_D^{20}$ +21.8 (*c* 0.5, $CHCl_3$); ν_{max} (film) 2947, 2871 (C-H), 1722 (C=O), 1547, 1371 (NO_2); Chiral HPLC analysis, Chiralpak ODH (99:1 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R major: 10.8 min, t_R minor: 12.7 min, >99:1 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.76 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.07 (18H, dd, *J* 7.5, 3.6, $SiCH(CH_3)_2$), 1.25−1.32 (3H, m, SiCH), 2.12 (3H, s, $C(Ph)CH_3$), 2.29 (3H, s, Ar-CH_3), 3.07 (1H, dd, *J* 17.1,11.0, CH_2CO_2TIPS), 3.16 (1H, dd, *J* 17.2, 2.6, CH_2CO_2TIPS), 3.47–3.53 (1H, m, $CO_2CH_2CH_3$), 3.67–3.74 (1H, m, $CO_2CH_2CH_3$), 4.28 (1H, dd, *J* 11.0, 2.6, $CHCO_2Et$), 7.16–7.21 (4H, m, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 13.5 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 20.2 ($C(Ar)CH_3$), 24.3 (Ar-CH_3), 36.1 (CH_2CO_2TIPS), 47.5 ($CHCO_2Et$), 61.3 ($CO_2CH_2CH_3$), 92.8 (CNO_2), 126.2 (CH_{Ar}), 126.8 (CH_{Ar}), 129.2 (CH_{Ar}), 132.8 (CH_{Ar}), 136.6 (C_{Ar}), 137.3 (C_{Ar}-CH_3), 171.3 (CO_2TIPS), 171.5 (CO_2Et); HRMS (NSI^+) $C_{24}H_{39}O_6NSiNa$ $[M+Na]^+$, found 488.2428, requires 488.2439 (–2.2 ppm).

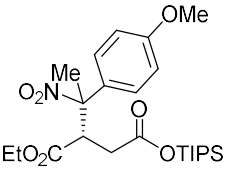
1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(1-nitro-1-(4-(trifluoromethyl)phenyl)ethyl)succinate (449)



Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-(4-(trifluoromethyl)phenyl)ethylidene)azinate (56.0 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.35) afforded the title compound as a colorless oil (31.9 mg, 61%); $[\alpha]_D^{20}$ +37.0 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2947, 2860 (C-H), 1728 (C=O), 1551, 1329 (NO_2); Chiral HPLC analysis, Chiralpak ODH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 220 nm, 30 °C) t_R major: 12.8 min, t_R minor: 22.4 min, 88:12 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.80 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.06 (18H, d, *J* 7.5, $SiCH(CH_3)_2$), 1.24−1.32 (3H, m, SiCH), 2.11 (3H, s, $C(Ph)CH_3$), 2.57 (1H, dd, *J* 17.2, 2.2, CH_2CO_2TIPS), 3.05 (1H, dd, *J* 17.2, 11.0, CH_2CO_2TIPS), 3.72–3.86 (2H, m, $CO_2CH_2CH_3$), 4.26 (1H, dd, *J* 11.0, 2.2, $CHCO_2Et$), 7.53–7.55 (2H, m, ArH), 7.64–7.66 (2H, m, ArH); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F: −63.0 (CF_3); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 13.5 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 20.3 ($C(Ar)CH_3$), 35.2 (CH_2CO_2TIPS), 50.2 ($CHCO_2Et$),

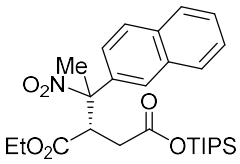
61.5 ($CO_2CH_2CH_3$), 93.0 (CNO_2), 121.5 (q, $^1J_{CF}$ 272.7, C_{Ar}-CF_3), 125.9 (q, $^3J_{CF}$ 3.6, CH_{Ar}-CF_3), 126.4 (CH_{Ar}), 131.9 (q, $^2J_{CF}$ 30.3, C_{Ar}-CF_3), 141.6 (C_{Ar}); 170.7 (CO_2TIPS), 170.9 (CO_2Et); HRMS (NSI^+) $C_{24}H_{36}O_6NF_3SiNa$ $[M+Na]^+$, found 542.2156, requires 542.2156 (−0.0 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(1-(4-methoxyphenyl)-1-nitroethyl)succinate (450)



Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-(4-methoxyphenyl)ethylidene)azinate (50.0 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.3) afforded the title compound as a colorless oil (32.2 mg, 67%); $[\alpha]_D^{20}$ +17.5 (*c* 1.4, $CHCl_3$); ν_{max} (film) 2253, 2160 (C-H), 1717 (C=O), 1555, 1458, 1373 (NO_2); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R major: 20.3 min, t_R minor: 24.9 min, 96:4 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.84 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.06 (18H, d, *J* 7.5, $SiCH(CH_3)_2$), 1.24–1.31 (3H, m, SiCH), 2.06 (3H, s, $C(Ph)CH_3$), 2.54 (1H, dd, *J* 17.1, 2.3, CH_2CO_2TIPS), 3.02 (1H, dd, *J* 17.1, 11.2, CH_2CO_2TIPS), 3.75–3.87 (2H, m, $CO_2CH_2CH_3$), 3.80 (3H, s, OCH_3), 4.29 (1H, dd, *J* 11.2, 2.3, $CHCO_2$Et), 6.86–6.88 (2H, m, ArH), 7.34–7.36 (2H, m, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 13.7 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 20.0 ($C(Ar)CH_3$), 35.3 (CH_2CO_2TIPS), 50.2 ($CHCO_2$Et), 55.5 (OCH_3), 61.3 ($CO_2CH_2CH_3$), 93.1 (CNO_2), 114.0 (2×CH_{Ar}), 127.3 (2×CH_{Ar}), 129.7 (C_{Ar}), 160.4 (C_{Ar}-OCH_3), 171.1 (CO_2TIPS), 171.1 (CO_2Et); HRMS (NSI^+) $C_{24}H_{39}O_7NSiNa$ $[M+Na]^+$, found 504.2381, requires 504.2388 (−1.4 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(1-(naphthalen-2-yl)-1-nitroethyl)succinate (451)

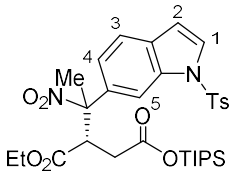


Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-(naphthalen-2-yl)ethylidene)azinate (53.6 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.37) afforded the title compound as a separable mixture of diastereomers (65:35 dr, major: 26.7 mg, 53%; minor: 14.4, 29%) as a colorless oil;

major diastereomer: $[\alpha]_D^{20}$ +39.3 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R major: 17.2 min, t_R minor: 22.3 min, 93:7 er; ν_{max} (film) 2945, 2868 (C-H), 1728 (C=O), 1547, 1369 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.58 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.06 (18H, dd, *J* 7.5, 1.8, $SiCH(CH_3)_2$), 1.24–1.31 (3H, m, SiCH), 2.21 (3H, s, $C(Ar)CH_3$), 2.64 (1H, dd, *J* 17.2, 2.2, CH_2CO_2TIPS), 3.10 (1H, dd, *J* 17.2, 11.0, CH_2CO_2TIPS), 3.62–3.68 (1H, m, $CO_2CH_2CH_3$), 3.71–3.78 (1H, m, $CO_2CH_2CH_3$), 4.39 (1H, dd, *J* 11.0, 2.2, $CHCO_2Et$), 7.49–7.54 (3H, m, ArH), 7.80–7.85 (4H, m, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 13.4 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 20.8 ($C(Ar)CH_3$), 35.4 (CH_2CO_2TIPS), 50.1 ($CHCO_2Et$), 61.3 ($CO_2CH_2CH_3$), 93.8 (CNO_2), 122.9 (CH_{Ar}), 125.2 (CH_{Ar}), 126.9 (CH_{Ar}), 127.3 (CH_{Ar}), 127.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.8 (CH_{Ar}), 132.8 (C_{Ar}), 133.4 (C_{Ar}), 135.2 (C_{Ar}), 171.1 (CO_2TIPS), 171.2 (CO_2Et); HRMS (NSI^+) $C_{27}H_{39}O_6NSiNa$ $[M+Na]^+$, found 524.2432, requires 524.2439 (−1.3 ppm).

minor diastereomer: $[\alpha]_D^{20}$ −10.0 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 $mLmin^{-1}$, 211 nm, 30 °C) t_R minor: 28.0 min, t_R major: 30.6 min, 88:12 er; ν_{max} (film) 2947, 2870 (C-H), 1732 (C=O), 1553, 1371 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.00 (18H, dd, *J* 7.5, 2.5, $SiCH(CH_3)_2$), 1.20−1.27 (3H, m, SiCH), 1.26 (3H, t, *J* 7.0, $CO_2CH_2CH_3$), 2.09 (1H, dd, *J* 17.1, 2.4, CH_2CO_2TIPS), 2.15 (3H, s, $C(Ar)CH_3$), 2.66 (1H, dd, *J* 17.1, 10.8, CH_2CO_2TIPS), 4.15–4.27 (2H, m, $CO_2CH_2CH_3$), 4.71 (1H, dd, *J* 10.8, 2.4, $CHCO_2Et$), 7.54–7.56 (2H, m, ArH), 7.76 (1H, dd, *J* 8.8, 2.2, ArH), 7.84–7.89 (3H, m, ArH), 8.02 (1H, d, *J* 2.2, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 14.1 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 19.0 ($C(Ar)CH_3$), 34.7 (CH_2CO_2TIPS), 48.7 ($CHCO_2Et$), 61.9 ($CO_2CH_2CH_3$), 92.5 (CNO_2), 123.3 (CH_{Ar}), 126.8 (CH_{Ar}), 127.1 (CH_{Ar}), 127.6 (CH_{Ar}), 127.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.3 (CH_{Ar}), 132.8 (C_{Ar}), 133.5 (C_{Ar}), 133.8 (C_{Ar}), 170.7 (CO_2TIPS), 171.0 (CO_2Et); HRMS (NSI^+) $C_{27}H_{39}O_6NSiNa$ $[M+Na]^+$, found 524.2432, requires 524.2439 (−1.3 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(1-nitro-1-(1-tosyl-1*H*-indol-6-yl)ethyl)succinate (452)

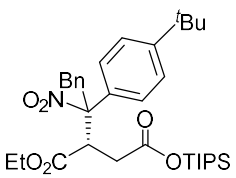


Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-(1-tosyl-1*H*-indol-5-yl)ethylidene)azinate (75.0 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (90:10 Petroleum ether : EtOAc, R_f 0.29) afforded the title compound as a separable mixture of diastereomers (65:35 dr, major: 28.5 mg, 44%; minor: 15.4, 24%) as a colorless oil;

major diastereomer: $[\alpha]_D^{20}$ +46.0 (*c* 0.3, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99:1 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R major: 37.4 min, t_R minor: 46.1 min, 94:6 er; ν_{max} (film) 2253, 2012 (C-H), 1722 (C=O), 1545, 1375 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.40 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.05 (18H, dd, *J* 7.5, 2.4, $SiCH(CH_3)_2$), 1.24–1.30 (3H, m, SiCH), 2.11 (Ar_{Ts}-CH_3), 2.34 (3H, s, $C(Ar_{ind})CH_3$), 2.57 (1H, dd, *J* 17.1, 2.2, CH_2CO_2TIPS), 3.03 (1H, dd, *J* 17.1, 11.2, CH_2CO_2TIPS), 3.51–3.67 (2H, m, $CO_2CH_2CH_3$), 4.39 (1H, dd, *J* 11.2, 2.2, $CHCO_2Et$), 6.64 (1H, dd, *J* 3.6, 0.8, H-2), 7.22–7.23 (2H, m, Ar-H), 7.35 (1H, dd, *J* 8.9, 2.1, H-4), 7.57 (1H, d, *J* 2.1, H-5), 7.60 (1H, d, *J* 3.6, H-1), 7.74–7.76 (2H, m, Ar-H), 7.94 (1H, d, *J* 8.9, H-3); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 13.2 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 20.3 ($C(Ar)CH_3$), 21.7 (Ar-CH_3), 35.3 (CH_2CO_2TIPS), 50.5 ($CHCO_2Et$), 61.1 ($CO_2CH_2CH_3$), 93.5 (CNO_2), 109.1 (C-1), 113.7 (C-5), 119.0 (C-4), 122.1 (C-2), 127.0 (2×CH_{Ar}), 127.6 (C-3), 130.1 (2×CH_{Ar}), 130.8 (C_{ind}), 132.9 (C_{ind}), 134.9 ($N=C(CH_3)Ar$), 135.1 (C_{Ar}), 145.4 (C_{Ar}-CH_3), 171.1 (CO_2TIPS), 171.1 (CO_2Et); HRMS (NSI$^+$) $C_{32}H_{45}O_8N_2SSi$ $[M+H]^+$, found 645.2658, requires 645.2660 (–0.4 ppm).

minor diastereomer: $[\alpha]_D^{20}$ –24.0 (*c* 0.6, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (98:2 Petroleum ether : IPA, flow rate 1.0 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 30.8 min, t_R major: 33.0 min, 90:10 er; ν_{max} (film) 2947, 2868 (C-H), 1734 (C=O), 1551, 1375 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.00 (18H, dd, *J* 7.5, 2.2, $SiCH(CH_3)_2$), 1.20–1.26 (3H, m, SiCH), 1.23 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 2.05 (1H, dd, *J* 17.0, 2.3, CH_2CO_2TIPS), 2.06 (3H, s, $C(Ar)CH_3$), 2.35 (3H, s, $C(Ar_{ind})CH_3$), 2.60 (1H, dd, *J* 17.1, 10.8, CH_2CO_2TIPS), 4.12–4.24 (2H, m, $CO_2CH_2CH_3$), 4.64 (1H, dd, *J* 10.8, 2.3, $CHCO_2Et$), 6.65 (1H, dd, *J* 3.6, 0.8, H-2), 7.23–7.26 (2H, m, Ar-H), 7.57 (1H, dd, *J* 9.0, 2.1, H-4), 7.61 (1H, d, *J* 3.6, H-1), 7.75–7.78 (2H, m, Ar-H), 7.78 (1H, d, *J* 2.1, H-5), 7.97 (1H, d, *J* 9.0, H-3); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 14.2 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 19.0 ($C(Ar)CH_3$), 21.8 (Ar-CH_3), 34.7 (CH_2CO_2TIPS), 48.9 ($CHCO_2Et$), 61.9 ($CO_2CH_2CH_3$), 92.4 (CNO_2), 109.1 (C-1), 114.0 (C-5), 120.1 (C-4), 122.8 (C-2), 127.0 (2×CH_{Ar}), 127.8 (C-3), 130.2 (2×CH_{Ar}), 131.1 (C_{ind}), 131.6 (C_{ind}), 135.1 ($N=C(CH_3)Ar$), 135.1 (C_{Ar}), 145.5 (C_{Ar}-CH_3), 170.7 (CO_2TIPS), 171.0 (CO_2Et); HRMS (NSI$^+$) $C_{32}H_{45}O_8N_2SSi$ $[M+H]^+$, found 645.2661, requires 645.2660 (+0.1 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(1-(4-(*tert*-butyl)phenyl)-1-nitro-2-phenylethyl)succinate (453)

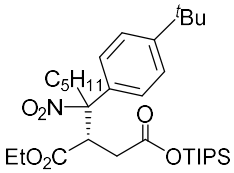


Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-(4-(*tert*-butyl)phenyl)-2-phenylethylidene)azinate (65.0 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.35) afforded the title compound as a separable mixture of diastereomers (60:40 dr, major: 28.3 mg, 49%; minor: 18.9, 32%) as a colorless oil;

major diastereomer: $[\alpha]_D^{20}$ +12.7 (*c* 1.0, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 11.4 min, t_R major: 15.5 min, 74:26 er; ν_{max} (film) 2255, 2162 (C-H), 1713 (C=O), 1549, 1373 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.01 (18H, d, *J* 7.5, SiCH(CH_3)$_2$), 1.22−1.32 (3H, m, SiCH), 1.29 (9H, s, (C(CH_3)$_3$), 1.31 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 2.87 (1H, dd, *J* 18.2, 1.9, CH_2CO_2TIPS), 2.98 (1H, dd, *J* 18.2, 9.9, CH_2CO_2TIPS), 3.62 (1H, d, *J* 13.2, CH_2Ph), 3.77 (1H, d, *J* 13.2, CH_2Ph), 4.02 (1H, dd, *J* 9.9, 1.9, CHCO$_2$Et), 4.25–4.29 (2H, m, $CO_2CH_2CH_3$), 6.69−6.72 (4H, m, 2×PhH, 2×ArH), 7.06−7.09 (2H, m, PhH), 7.14−7.16 (1H, m, PhH), 7.23−7.24 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 14.2 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 31.3 (C(*C*H$_3$)$_3$), 34.7 (*C*(CH$_3$)$_3$), 36.5 (*C*H$_2$CO$_2$TIPS), 45.0 (*C*H$_2$Ph), 46.0 (*C*HCO$_2$Et), 62.0 ($CO_2CH_2CH_3$), 98.4 (*C*NO$_2$), 125.4 (2×CH$_{Ar}$), 126.3 (2×CH$_{Ph}$), 127.3 (CH$_{Ph}$), 128.0 (2×CH$_{Ar}$), 131.3 (2×CH$_{Ph}$), 133.2 (C$_{Ar}$), 134.4 (C$_{Ph}$), 152.1 (C(CH$_3$)$_3$*C*$_{Ar}$); 171.2 (*C*O$_2$TIPS), 171.8 (*C*O$_2$Et); HRMS (NSI$^+$) $C_{33}H_{49}O_6NSiNa$ $[M+Na]^+$, found 606.3211, requires 606.3221 (−1.7 ppm).

minor diastereomer: $[\alpha]_D^{20}$ −16.1 (*c* 0.8, $CHCl_3$); Chiral HPLC analysis, Chiralpak ADH (99.5:0.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 30 °C) t_R minor: 20.9 min, t_R major: 27.0 min, 90:10 er; ν_{max} (film) 2965, 2868 (C-H), 1728 (C=O), 1549, 1369 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.02 (18H, dd, *J* 7.5, 2.4, SiCH(CH_3)$_2$), 1.23−1.28 (3H, m, SiCH), 1.25 (3H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.34 (9H, s, (C(CH_3)$_3$), 2.60−2.69 (2H, m, CH_2CO_2TIPS), 3.57 (1H, d, *J* 13.9, CH_2Ph), 3.93–4.06 (2H, m, $CO_2CH_2CH_3$), 4.13 (1H, dd, *J* 9.0, 4.6, CHCO$_2$Et), 4.26 (1H, d, *J* 13.9, CH_2Ph), 7.16−7.18 (2H, m, ArH), 7.28−7.30 (3H, m, PhH), 7.36−7.37 (2H, m, PhH), 7.39−7.40 (2H, m, ArH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H(CH$_3$)$_2$, 13.7 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 31.4 (C(*C*H$_3$)$_3$), 34.3 (*C*H$_2$CO$_2$TIPS), 34.8 (*C*(CH$_3$)$_3$), 42.8 (*C*H$_2$Ph), 47.0 (*C*HCO$_2$Et), 61.6 ($CO_2CH_2CH_3$), 98.5 (*C*NO$_2$), 125.3 (2×CH$_{Ar}$), 127.1 (2×CH$_{Ph}$), 128.0 (CH$_{Ph}$), 128.7 (2×CH$_{Ar}$), 130.5 (2×CH$_{Ph}$), 133.4 (C$_{Ar}$), 134.4 (C$_{Ph}$), 152.2 (C(CH$_3$)$_3$*C*$_{Ar}$); 170.4 (*C*O$_2$TIPS), 171.3 (*C*O$_2$Et); HRMS (NSI$^+$) $C_{33}H_{53}O_6N_2Si$ $[M+NH_4]^+$, found 601.3674, requires 601.3667 (+1.1 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(1-(4-(*tert*-butyl)phenyl)-1-nitrohexyl)succinate (454)



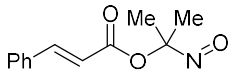
Following General Procedure 24, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(1-(4-(*tert*-butyl)phenyl)hexylidene)azinate (63.0 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.30) afforded the title compound as an inseparable mixture of diastereomers (48.8 mg, 87%; 60:40 dr) as a colorless oil; $[\alpha]_D^{20}$ +22.5 (*c* 0.6, $CHCl_3$); inseparable by chiral HPLC chiral GC; ν_{max} (film) 2959, 2870 (C-H), 1734 (C=O), 1547, 1369 (NO_2); HRMS (NSI^+) $C_{31}H_{57}O_6N_2Si$ $[M+NH_4]^+$, found 581.3978, requires 581.3980 (−0.4 ppm).

major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.89 (3H, t, *J* 6.8, $(CH_2)_3CH_3$), 1.03−1.05 (18H, m, $SiCH(CH_3)_2$), 1.14−1.20 (3H, m, $CO_2CH_2CH_3$), 1.14−1.20 (2H, m, $CH_2CH_2CHNO_2$), 1.24−1.30 (3H, m, SiCH), 1.31 (9H, s, $C(CH_3)_3$), 1.32−1.35 (4H, m, $(CH_2)_3CH_3$), 2.26−2.46 (2H, m, $CH_2CH_2CHNO_2$), 2.58 (1H, dd, *J* 17.3, 2.6, CH_2CO_2TIPS), 2.65 (1H, dd, *J* 17.3, 10.8, CH_2CO_2TIPS), 4.06–4.15 (2H, m, $CO_2CH_2CH_3$), 4.23 (1H, dd, *J* 10.8, 2.6, $CHCO_2Et$), 7.09−7.11 (2H, m, ArH), 7.36−7.38 (2H, m, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 14.0 $(CH_2)_3CH_3$), 14.1 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 22.4 ($(CH_2)_2CH_2CH_3$), 24.4 ($(CH_2)_2CH_2CH_3$), 31.3 ($C(CH_3)_3$), 32.0 ($(CH_2)_2CH_2CH_3$), 35.9 ($(CH_2)_2CH_2CH_3$), 34.7 ($C(CH_3)_3$), 38.7 (CH_2CO_2TIPS), 48.1 ($CHCO_2Et$), 61.7 ($CO_2CH_2CH_3$), 97.9 (CNO_2), 125.7 (2×CH_{Ar}), 125.9 (2×CH_{Ar}), 133.8 (C_{Ar}), 151.7 ($C(CH_3)_3C_{Ar}$); 171.0 (CO_2TIPS), 172.1 (CO_2Et);

minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.89 (3H, t, *J* 6.3, $(CH_2)_3CH_3$), 1.03−1.05 (18H, m, $SiCH(CH_3)_2$), 1.14−1.20 (3H, m, $CO_2CH_2CH_3$), 1.14−1.20 (2H, m, $CH_2CH_2CHNO_2$), 1.24−1.30 (3H, m, SiCH), 1.31 (9H, s, $C(CH_3)_3$), 1.32−1.35 (4H, m, $(CH_2)_3CH_3$), 2.39−2.51 (2H, m, $CH_2CH_2CHNO_2$), 2.81 (1H, dd, *J* 18.0, 2.1, CH_2CO_2TIPS), 2.95 (1H, dd, *J* 18.0, 10.3, CH_2CO_2TIPS), 4.05 (1H, dd, *J* 10.3, 2.1, $CHCO_2Et$), 4.06–4.15 (2H, m, $CO_2CH_2CH_3$), 7.01−7.03 (2H, m, ArH), 7.35−7.37 (2H, m, ArH); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 12.0 ($SiCH(CH_3)_2$, 13.9 $(CH_2)_3CH_3$), 14.1 ($CO_2CH_2CH_3$), 17.8 ($SiCH(CH_3)_2$), 22.5 ($(CH_2)_2CH_2CH_3$), 24.0 ($(CH_2)_2CH_2CH_3$), 31.3 ($C(CH_3)_3$), 32.0 ($(CH_2)_2CH_2CH_3$), 35.0 ($(CH_2)_2CH_2CH_3$), 34.7 ($C(CH_3)_3$), 37.3 (CH_2CO_2TIPS), 48.1 ($CHCO_2Et$), 61.6 ($CO_2CH_2CH_3$), 97.9 (CNO_2), 125.3 (2×CH_{Ar}), 127.0 (2×CH_{Ar}), 132.8 (C_{Ar}), 152.0 ($C(CH_3)_3C_{Ar}$); 170.7 (CO_2TIPS), 171.5 (CO_2Et).

7.5.4 Data for the nitroso side-product

2-nitrosopropan-2-yl cinnamate (428)

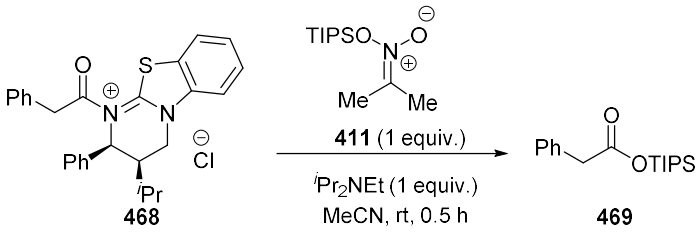


Following General Procedure 24, cinnamic anhydride (27.8 mg, 0.1 mmol), triisopropylsilyl propan-2-ylideneazinate (36.8 mg, 0.15 mmol), diisopropylethylamine (17 μL, 0.1 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.58) afforded the title compound (11.6 mg, 53%) as a colorless oil; ν_{max} (film) 1717 (C=O), 1636, 1568 (N=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.48 (6H, s, 2×CH_3), 6.58 (1H, d, *J* 15.8, PhCH=C*H*), 7.40–7.43 (3H, m, CH-Ph), 7.56–7.59 (2H, m, CH-Ph), 7.77 (1H, d, *J* 15.8, PhC*H*=CH); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.0 (2×*C*H_3), 117.7 (*C*H=CH-Ph), 121.1 (O*C*CH_3)$_2$), 128.4 (2×CH_{Ph}), 129.1 (2×CH_{Ph}), 130.8 (CH_{Ph}), 134.3 (C_{Ph}), 146.3 (*C*H=CH-Ph), 168.1 (CH=CH*C*O_2); HRMS (ESI$^+$) $C_{12}H_{13}O_3N_1Na$ [M+Na]$^+$, found 242.0786, requires 242.0788 (−0.8 ppm).

7.5.5 Mechanistic investigations

7.5.5.1 Catalyst turnover

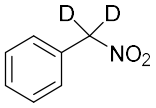
Triisopropylsilyl 2-phenylacetate (469)



Isothiouronium chloride salt **468** (21.3 mg, 0.05 mmol, 1 equiv.) was dissolved in acetonitrile (0.4 M). Triisopropylsilyl propan-2-ylideneazinate (12.3 mg, 0.05 mmol, 1 equiv.), in acetonitrile (0.6 M) and diisopropylethylamine (1 equiv.) were added to the reaction mixture and allowed to stir for 0.5 h at rt. The crude mixture was then concentrated *in vacuo*, and the residue purified by flash silica column chromatography (98:2 Petroleum ether : EtOAc, R_f 0.65) to afford the title compound (11.7 mg, 80%) as a colorless oil; ν_{max} (film) 2945, 2868 (C-H), 1717 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.00 (18H, d, *J* 7.4, SiCH(CH_3)$_2$), 1.20–1.29 (3H, m, SiCH), 3.64 (2H, s, C$H_2$$CO_2$TIPS), 7.23–7.33 (5H, m, CH-Ph); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.0 (Si*C*H$(CH_3)_2$, 17.8 (SiCH(*C*H_3)$_2$), 43.3 (*C*$H_2$$CO_2$TIPS), 127.0 (2×$CH_{Ph}$), 128.6 (2×$CH_{Ph}$), 129.5 (2×$CH_{Ph}$), 134.8 ($C_{Ph}$), 171.7 (*C*$O_2$TIPS); HRMS (ESI$^+$) $C_{17}H_{28}O_2SiNa$ [M+Na]$^+$, found 415.1745, requires 415.1751 (−1.9 ppm).

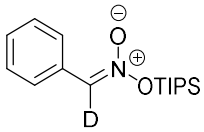
7.5.5.2 Synthesis of deuterated nitronates

(Nitromethyl-d_2)benzene (S73)



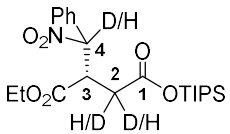
Following General Procedure 4, bromobenzene (0.26 mL, 2.5 mmol), Cs_2CO_3 (0.9 g, 2.75 mmol), powdered 4 Å molecular sieves (500 mg), $Pd_2(dba)_3$ (26 mg, 0.025 mmol) and XPhos (60 mg, 0.125 mmol) and nitromethane-d_3 (2.5 mL) afforded after SiO_2-chromatography (98:2 – 90:10 Petroleum ether : EtOAc, R_f 0.40) the title compound (167 mg, 48%) as a mixture of deuterated and protonated species as a light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.43–5.44 (2H, m, CHD), 5.45 (2H, s, CH_2), 7.44–7.47 (5H, m, ArH). Data in agreement with literature.[46]

Triisopropylsilyl (*E*)-(phenylmethylene-*d*)azinate (465)



Following General Procedure 23, triisopropylsilyl chloride (0.31 mL, 1.2 mmol) and DBU (0.19 mL, 1.26 mmol) were added sequentially to a stirred solution of the aryl nitromethane (167 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (5 mL) afforded after SiO_2-chromatography (100:0 – 95:5 Petroleum ether : EtOAc, R_f 0.45) the title compound (258 mg, 73%) with ~95% D-incorporation as a light yellow oil; ν_{max} (film) 2943, 2866 (C-H), 1690 (C=N), 1464 (C-H); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.14 (18H, d, *J* 7.4, SiCH(C*H*$_3$)$_2$), 1.33–1.43 (3H, m, SiCH), 7.31–7.34 (1H, m, ArH), 7.38–7.41 (2H, m, ArH), 7.87–7.89 (2H, m, ArH); ν_{max} (film) 2945, 2888 (C-H), 1682 (C=N), 1484 (C-H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.7 (Si*C*H(CH$_3$)$_2$), 18.1 (SiCH(*C*H$_3$)$_2$), 127.4 (2×CH_{Ar}), 128.7 (2×CH_{Ar}), 129.1 (CH_{Ar}), 129.3 (t, C(=N)D), 129.7 (C_{Ar}); HRMS (ESI$^+$) $C_{17}H_{30}O_2NSi$ $[M+H]^+$, found 308.2036, requires 308.2040 (−1.3 ppm).

1-Ethyl 4-(triisopropylsilyl) (2*S*)-2-(nitro(phenyl)methyl-*d*)succinate-3,3-d_2 (466)

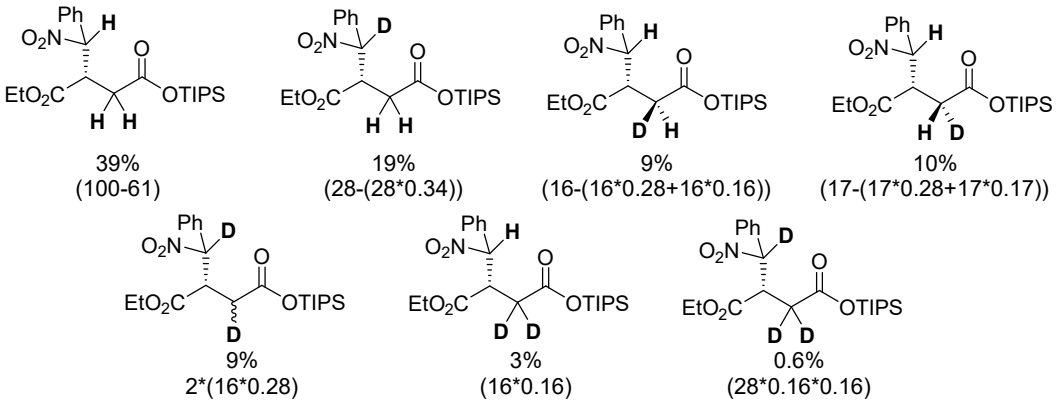


Following General Procedure 25, (*E*)-4-ethoxy-4-oxobut-2-enoic anhydride (27.2 mg, 0.1 mmol), triisopropylsilyl (*E*)-(phenylmethylene-*d*)azinate (60.0 mg, 0.2 mmol) and HyperBTM (6.2 mg, 0.02 mmol) in acetonitrile (0.5 mL) and subsequent chromatography (98:2 Petroleum ether : EtOAc, R_f 0.45) afforded the title compound as an inseparable mixture of diastereomers (28.3 mg, 54%, 85:15 dr) as a colorless oil; $[\alpha]_D^{20}$ −43.5 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2951, 2871 (C-H), 2253 (C-D), 2170 (C-D), 1734, 1717 (C=O), 1558, 1458, 1375 (NO_2); HRMS submitted.

major diastereomer: Chiral HPLC analysis, Chiralpak ADH (98.5:1.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 25 °C) t_R minor: 14.7 min, t_R major: 15.4 min, 98:2 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.00 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.21−1.28 (3H, m, SiCH), 1.25 (3H, t, *J* 7.5, $CO_2CH_2CH_3$), 2.23 (1H, dd, *J* 17.9, 5.6, C*H*$_2$CO$_2$TIPS), 2.79–2.84 (1H, m, C*H*(*D*)CO$_2$TIPS), 3.89–3.93 (1H, m, C*H*CO$_2$Et), 4.18–4.24 (2H, m, $CO_2CH_2CH_3$), 6.06–6.09 (1H, m, C*H*(*D*)NO$_2$), 7.38–7.46 (5H, m, ArH); ^{2}H NMR (77 MHz, $CHCl_3$) δ_D: 2.23 (br s), 2.82 (br s), 6.09 (br s); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 11.9 (Si*C*H(CH$_3$)$_2$, 14.1 ($CO_2CH_2CH_3$), 17.8 (SiCH(*C*H$_3$)$_2$), 34.1 (t, *J* 19.6, *C*H(D)CO$_2$TIPS) 34.3 (*C*H$_2$CO$_2$TIPS), 43.9–44.1 (*C*HCH(D)CO$_2$TIPS), 44.2 (*C*HCO$_2$Et), 62.0 ($CO_2CH_2CH_3$), 89.6 (*C*HNO$_2$), 128.1 (2×CH$_{Ar}$), 129.7 (2×CH$_{Ar}$), 130.5 (CH$_{Ar}$), 132.7 (C$_{Ar}$), 170.6 (*C*O$_2$TIPS), 171.1 (*C*O$_2$Et);

minor diastereomer: Chiralpak ADH (98.5:1.5 Petroleum ether : IPA, flow rate 0.5 mLmin^{-1}, 211 nm, 25 °C) t_R major: 14.2 min, t_R minor: 16.3 min, >99:1 er; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.90 (3H, t, *J* 7.6, $CO_2CH_2CH_3$), 1.06 (18H, d, *J* 7.5, SiCH(C*H*$_3$)$_2$), 1.21−1.28 (3H, m, SiCH), 2.66 (1H, dd, *J* 17.2, 3.4, C*H*$_2$CO$_2$TIPS), 3.01 (1H, dd, *J* 17.3, 9.9, C*H*(*D*)CO$_2$TIPS), 3.89–3.93 (1H, m, C*H*CO$_2$Et), 4.18–4.24 (2H, m, $CO_2CH_2CH_3$), 5.68–5.71 (1H, m, C*H*(*D*)NO$_2$), 7.39–7.45 (5H, m, ArH); ^{2}H NMR (77 MHz, $CHCl_3$) δ_D: 2.64 (br s), 3.01 (br s), 5.69 (br s); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 12.4 (Si*C*H(CH$_3$)$_2$, 13.7 ($CO_2CH_2CH_3$), 17.9 (SiCH(*C*H$_3$)$_2$), 35.3 (t, *J* 16.3, *C*H(D)CO$_2$TIPS), 35.5 (*C*H$_2$CO$_2$TIPS), 45.2–46.1 (*C*HCH(D)CO$_2$TIPS), 46.2 (*C*HCO$_2$Et), 61.6 ($CO_2CH_2CH_3$), 91.4 (*C*HNO$_2$), 128.3 (2×CH$_{Ar}$), 129.6 (2×CH$_{Ar}$), 130.4 (CH$_{Ar}$), 132.6 (C$_{Ar}$), 170.2 (*C*O$_2$TIPS), 170.4 (*C*O$_2$Et).

7.5.5.3 Calculation of the amount of each deuterated species



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