α,β-UNSATURATED ACYL AMMONIUM INTERMEDIATES IN ASYMMETRIC ORGANOCATALYSIS

AUTHOR

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

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α,β-Unsaturated Acyl Ammonium Intermediates in Asymmetric Organocatalysis

Emily Rose Tindale Robinson

2015

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To my family
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Abstract

This thesis details investigations into the generation and synthetic utility of \( \alpha,\beta \)-unsaturated acyl ammonium intermediates using isothioureas as Lewis base organocatalysts to generate a range of heterocyclic products.

Initial investigations focussed on the development of a Michael addition-lactonisation protocol utilising \( \alpha,\beta \)-unsaturated acyl ammonium intermediates (generated \textit{in situ} from HBTM 2.1 and \( \alpha,\beta \)-unsaturated homoanhydrides) and a range of 1,3-dicarbonyl nucleophiles. Products could be isolated as lactones or as ring-opened highly functionalised esters, giving good yields and excellent enantioselectivity. 1,3-Diketones were shown to generate a mixture of regioisomers and whereas 1,3-ketoesters afforded only a single regioisomer. A crystal structure of an \( \alpha,\beta \)-unsaturated acyl ammonium intermediate was obtained that clearly demonstrated steric blocking of the \( Si \)-face of the alkene by the catalyst stereodirecting groups, therefore it can be postulated that enantiocontrol in the addition occurs by selective nucleophilic addition from the \( Re \)-face.

\( \alpha,\beta \)-Unsaturated acyl ammonium species were then shown to participate in asymmetric annulation processes with benzazole nucleophiles to afford highly functionalised heterocyclic products, with both lactone and lactam formation observed. The relationship between nucleophile structure and process regioselectivity was investigated and it was demonstrated that benzothiazole and benzimidazole nucleophiles afforded preferential \( N \)-cyclisation to give lactams whilst benzoazoles exhibited \( O \)-cyclisation to form lactones. It was also possible to influence the regioselectivity by changing the electronic properties of the acyl group (\( R' \)). Due to the reactivity of this class of nucleophiles it was possible to access products with quaternary centres. Palladium-catalysed cross coupling reactions were also successful on 3-bromo substituted lactams, demonstrating the potential for further derivatising these interesting heterocyclic products.

Finally, a cascade protocol was developed that employed Michael-Michael-lactonisation steps to give tricyclic products from enone malonate nucleophiles and \( \alpha,\beta \)-unsaturated acyl ammonium intermediates (generated \textit{in situ} by addition of HBTM 2.1 into acid chlorides). Interestingly, the reaction showed higher enantioselectivity at elevated temperatures (70 °C) and moderate regioselectivity (1,4- vs. 1,2-addition), which could not be improved after extensive screening. A range of lactones was isolated in moderate yields and enantioselectivity.
Publications

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

Anhydrides as \( \alpha,\beta \)-unsaturated acyl ammonium precursors: isothiourea-promoted catalytic asymmetric annulation processes


Regioselectivity Switching in Isothiourea-Catalysed Annulations of Benzazoles: Synthetic and Computational Studies

Emily R. T. Robinson, Daniel M. Walden, Charlene Fallan, Paul Ha-Yeon Cheong, and Andrew D. Smith, *manuscript in preparation*
Abbreviations

Å Ångström(s) \((1 \times 10^{-10} \text{ m})\)
Ac Acetyl
APCI Atmospheric Pressure Chemical Ionization
app. Apparent
aq Aqueous
Ar Aromatic
atm Atmosphere
BEMP 2-\text{tert-}Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Bn Benzyl
Boc N-\text{tert-}Butoxycarbonyl
br Broad
BTM Benzotetramisole
Bu Butyl
Bz Benzoyl
\(c\) Concentration
C Celsius
cal Calorie(s)
CAN Ceric ammonium nitrate
cat. Catalyst
cm Centimetre(s)
COSY Correlation spectroscopy
d Doublet
DABCO 1,4-Diazabicyclo[2.2.2]octane
DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC Dicyclohexylcarbodiimide
DCE Dichloroethane
decom. Decomposition
DFT Density functional theory
DHPB 3,4-Dihydro-2H-pyrimido[2,1-b]benzothiazole
DMAP 4-Dimethylaminopyridine
DME Dimethoxy ethane
DMF Dimethylformamide
DMSO Dimethyl sulfoxide
dppf 1,1′-Bis(diphenylphosphino)ferrocene
dr Diastereoisomeric ratio
E Electrophile
EDCI 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG Electron donating group
ee Enantiomeric excess
EI Electron impact
equiv Equivalent molar quantity
er Enantiomeric ratio
ES Electrospray
ESI Electrospray ionisation
Et  Ethyl
EWG Electron withdrawing group
FID  Flame ionisation detector
FTMS Fourier Transform Mass Spectrometry
g  Gram(s)
GC  Gas chromatography
h  Hour(s)
HBTM Homobenzotetramisole
HetAr Heteroaryl
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  Isotopic
ID Ionisation detector
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
m Molar
M. S. 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
MTBD 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
o/n overnight
n Normal
n.r. No reaction
NBO Natural bond orbital
NBS N-Bromosuccinimide
NHC N-heterocyclic carbene
\(\nu_{\text{max}}\) Frequency
# Contents

Acknowledgements ........................................................................................................ iv
Abstract .......................................................................................................................... v
Publications .................................................................................................................... vi
Abbreviations .................................................................................................................. vii
Contents ........................................................................................................................... x

1. Introduction ................................................................................................................ 1
   1.1 Asymmetric Catalysis .......................................................................................... 1
   1.2 Lewis Base Organocatalysis ............................................................................. 3
      1.2.1 Iminium ion catalysis .............................................................................. 5
      1.2.2 Enamine catalysis ................................................................................... 6
      1.2.3 SOMO catalysis ..................................................................................... 7
      1.2.4 Acyl ammonium catalysis .................................................................... 9
      1.2.5 Ammonium enolate catalysis .................................................................. 11
      1.2.6 $\alpha,\beta$-Unsaturated acyl ammonium intermediates ......................... 15
      1.2.7 $\alpha,\beta$-Unsaturated acyl azolium intermediates ................................. 19
   1.3 Aims and Objectives ......................................................................................... 23

2. 1,3-Diketones and 1,3-Ketoesters as Nucleophiles ............................................... 24
   2.1 Project Aims ...................................................................................................... 24
   2.2 Reaction Optimisation ...................................................................................... 26
      2.2.1 Activation agent screening ..................................................................... 26
      2.2.2 Isothiourea screening .......................................................................... 29
      2.2.3 Reaction concentration effects ............................................................. 29
      2.2.4 Product isolation and ring-opening ....................................................... 30
      2.2.5 Base screening and catalyst loading ..................................................... 31
      2.2.7 Optimised reaction conditions ............................................................... 32
   2.3 Reaction Scope: Symmetrical Diketones ......................................................... 33
      2.3.1 Anhydride synthesis and scope ............................................................. 33
      2.3.2 Diketone scope .................................................................................... 35
   2.4 Use of Non-Symmetrical Dicarbonyl Nucleophiles .......................................... 37
2.4.1 Diketones ................................................................. 37
2.4.2 Ketoesters .............................................................. 38
2.5 Mechanistic Investigations .............................................. 39
  2.5.1 Postulated mechanism ............................................ 39
  2.5.2 Proposed stereochemical model .............................. 41
  2.5.3 Effect of E/Z anhydride configuration ...................... 44
2.6 Conclusions ............................................................... 45
3. Benzazoles as Nucleophiles ............................................. 47
  3.1 Introduction ............................................................. 47
    3.1.1 Benzazoles in medicinal chemistry ......................... 47
    3.1.2 Benzazoles in conjugate addition processes .............. 47
    3.1.3 Project aims ..................................................... 48
  3.2 2-Phenacylbenzothiazole: Initial Screening and Scope ........ 49
    3.2.1 Regioisomer formation and identification ................. 49
    3.2.2 Isothiourea screening ........................................ 51
    3.2.3 Solvent and temperature effects ........................... 51
    3.2.4 Recrystallisation .............................................. 52
    3.2.5 Anhydride scope .............................................. 53
  3.3 Exploring Regioselectivity Effects ................................ 56
    3.3.1 Influencing regioselectivity .................................. 56
    3.3.2 Nucleophile synthesis ........................................ 57
    3.3.3 Nucleophile effects on annulation regioselectivity .... 59
    3.3.4 Reaction scope: benzamide .................................. 62
    3.3.5 Reaction scope: benzoxazole ............................... 63
  3.4 Mechanistic understanding of regioselectivity .................... 64
    3.4.1 Proposed mechanism .......................................... 64
    3.4.2 Computational studies ........................................ 66
    3.4.3 Link between regioisomerism and enantioselectivity .... 70
    3.4.4 Direct recyclisation ......................................... 71
    3.4.5 Recyclisation in the presence of an external nucleophile 73
    3.4.6 Mechanistic implications of recyclisation investigations 75
3.5 Accessing Quaternary Centres ........................................................................... 76
  3.5.1 Anhydride synthesis....................................................................................... 76
  3.5.2 Anhydride scope ......................................................................................... 78
3.6 Product Derivatisations..................................................................................... 79
  3.6.1 Suzuki couplings ......................................................................................... 79
  3.6.2 Heck reactions ............................................................................................ 80
3.7 Conclusions ...................................................................................................... 82

4. Cascades from α,β-Unsaturated Acyl Ammonium Intermediates .................. 83
  4.1 Lewis Base Catalysed Cascade Processes......................................................... 83
    4.1.1 Iminium-initiated cascades ....................................................................... 83
    4.1.2 Enamine-initiated cascades ...................................................................... 86
    4.1.3 Cascades using α,β-unsaturated acyl ammonium/azolium intermediates .. 87
  4.2 Project Aims..................................................................................................... 90
  4.3 Reaction Optimisation....................................................................................... 92
    4.3.1 Initial results ............................................................................................. 92
    4.3.2 Determination of product configuration .................................................. 93
    4.3.3 Aims and procedures for reaction screening ........................................... 95
    4.3.4 Base screening .......................................................................................... 97
    4.3.5 Solvent mixtures ...................................................................................... 98
    4.3.6 Catalyst screening .................................................................................... 98
    4.3.7 Base additives .......................................................................................... 99
    4.3.8 Temperature screening ............................................................................ 100
    4.3.9 Effect of electrophiles ............................................................................. 102
    4.3.10 Catalyst loading ....................................................................................... 104
    4.3.11 Non-lithiated bases ................................................................................ 105
    4.3.12 Affecting lithium aggregation states ..................................................... 106
    4.3.13 Optimised Reaction Conditions .............................................................. 108
  4.4 Reaction Scope ................................................................................................ 109
    4.4.1 Enone-malonate synthesis via cross-metathesis ...................................... 109
    4.4.2 Cascade scope ......................................................................................... 110
  4.5 Conclusions ..................................................................................................... 112
5. Conclusions................................................................................................................. 114

6. Experimental ............................................................................................................. 115
   6.1 General Information................................................................................................. 115
   6.2 α,β-Unsaturated Acids .......................................................................................... 117
       General Procedure A: Knoevenagel Condensation................................................ 117
   6.3 α,β-Unsaturated Anyhydrides ............................................................................... 123
       General Procedure B: Anhydride Synthesis............................................................ 123
       (E)-3-(2-Chlorophenyl)acrylic anhydride (S1)....................................................... 127
   6.4 Nucleophiles ......................................................................................................... 134
       General Procedure C: Diketone Synthesis.............................................................. 134
       General Procedure D: Benzazole Synthesis with NaHMDS .................................. 136
       General Procedure E: Benzazole Synthesis via Diesters ....................................... 139
   6.5 Michael Addition-Lactonisation Products.............................................................. 142
       General Procedure F: Lactone formation............................................................... 142
       General Procedure G: Ring-Opened Products ...................................................... 150
       General Procedure H: Lactams and Lactones From Benzazoles ......................... 163
   6.6 Cascade Substrates ............................................................................................... 199
       General Procedure I: Enone-Malonate Synthesis .................................................. 199
   6.7 Cascade Products .................................................................................................. 203
       General Produre J: Michael-Michael-Lactonisation............................................... 203
   6.8 Misc ...................................................................................................................... 210

7. References .................................................................................................................. 219
1. Introduction

1.1 Asymmetric Catalysis

The development of chemical processes that proceed enantioselectively has become increasingly important as our understanding of the impact of chirality upon biological interactions has grown. Often one enantiomer of a drug can have greater therapeutic action, but if the other enantiomer shows no appreciable effect on the body the drug can be safely administered as a racemic mixture. However there are many cases where the unwanted enantiomer causes harm to the body and in these cases the racemic drug is unsafe for consumption.\textsuperscript{1,2}

Strategies for carrying out asymmetric synthesis include the use of reagents from the chiral pool, such as amino acids and sugars, which are naturally formed in high enantioselectivity. This can be highly efficient as the stereocentre is preserved rather than created, but synthetic pathways are limited to available substrates.\textsuperscript{3} It is also possible to generate and then resolve racemic mixtures by, for example, selective crystallisation of one enantiomer as a chiral salt. This opens up many synthetic possibilities however 50% material loss must be incurred to achieve the desired enantiomer in high selectivity.\textsuperscript{4} Chiral auxiliaries were developed as a further strategy to form stereocentres enantioselectively. A substrate is functionalised with a chiral functional group, which serves to direct the desired reaction in good diastereoselectivity and is subsequently removed. This strategy has proved to be highly useful although the overall efficiency can be low due to the requirement of additional protection and deprotection steps and the stoichiometric nature of chiral auxiliaries.\textsuperscript{5}

A further synthetic option is asymmetric catalysis, which aims to carry out reactions efficiently and enantioselectively using catalytic amounts of a chiral species to induce asymmetry. This circumvents the problems of loss of material inherent in resolving a racemic mixture, or the use of stoichiometric chiral auxiliaries. In nature, this is carried out by enzyme catalysis and many industrial processes have been developed which take advantage of the excellent selectivity that is achievable using biocatalysis.\textsuperscript{6} The major drawback of this method is high substrate specificity, which leads to reactions displaying either excellent reactivity and selectivity or no reactivity at all. This makes biocatalysis of limited value to synthetic chemists targeting new molecules or methodology.
1. Introduction

Enantioselective organometallic catalysis offers diverse synthetic options, with structurally diverse catalysts able to be designed and optimised for a particular process. Industrially there is a competition between the economics of large scale catalysis versus other methods of enantioenrichment; the efficiency of the catalysed reaction is often outweighed by the high cost of the catalyst. Despite such problems, many robust enantioselective catalytic organometallic processes have been developed and embraced by chemical industry, including the multi-tonne production of herbicide Metolachlor. Whilst it was initially marketed as a mixture of its four stereoisomers 1a–d (Figure 1) it was found that around 95% of the herbicidal activity came from two highly active stereoisomers (1a and 1b), enantiomers of one another.\(^7\)

![Figure 1: Stereoisomers of the herbicide Metolachlor](image)

An enantioselective synthesis of 1a was developed with the key step being the enantioselective reduction of imine 2 (Scheme 1). After extensive metal and ligand screening the optimum catalyst for this process was an iridium-Xyliophos complex.\(^8\) This catalyst achieved very high turnover rates of >200,000 TOF (h\(^{-1}\)), affording amine 3 in 100% conversion and 79% ee.\(^9\) Using this preparative method the final herbicide product can be prepared with an approximate 90% active isomer content, and the application required for the same herbicidal activity in the field was reduced to 65% of the original dose.\(^7\)

![Scheme 1: Enantioselective imine reduction in the synthesis of Metolachlor](image)

One of the main advantages of transition metal catalysts is high structural diversity which enables fine-tuning of catalytic activity by ligand alteration around different metal centres.
1. Introduction

As a result, catalytic systems have been developed that can carry out multiple reaction types with only small structural changes. These greatly open up synthetic possibilities with minimum investment in new catalysts and/or ligands. However, such metal catalysts can be expensive to make due to the high cost of the metals and/or ligands used and they are often unstable to air and moisture, making them difficult to handle.\(^1\) Of further concern is the potential difficulty encountered in removing metals from reaction mixtures due to the possible toxicity of metal residues.\(^1\)

1.2 Lewis Base Organocatalysis

An alternative to transition metal catalysis is organocatalysis, defined as “the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom.”\(^1\) In the development of organocatalysis, chemists hoped to harness the power of biocatalysis without the drawbacks of substrate specificity and also open up reaction conditions that are not compatible with enzymes.\(^1\) Many organocatalysts show good moisture and air tolerance and can be cheaper to prepare than transition metal catalysts. One of the earliest reported organocatalytic reactions is the Hajos-Parrish intramolecular aldol reaction (Scheme 2). (S)-Proline (6) catalyses the cyclisation of 5 by acting as a Lewis base, donating a lone pair of electrons to form an enamine intermediate 7, thus activating the ketone moiety. An intramolecular aldol reaction follows, forming cyclised product 8 in 97\% ee.\(^1\)

![Scheme 2: Asymmetric intramolecular aldol reaction](image)

Whilst it is agreed that the reaction proceeds through an enamine intermediate (7) the transition state of the Hajos-Parrish aldol reaction remains disputed. The general concensus is that it proceeds through a chair-type transition state (Figure 2), however it is unclear whether the transition state is stabilised through N–H---O (9a) or CO2–H---O (9b)\(^1\) interactions, or if it is a combination of multiple interactions (9c).\(^1\)
At the time, this result was considered a stand-alone example of organocatalysis and not part of a wider field. It was not until much later that proline-mediated enamine catalysis was revisited, and in 2000 List et al. demonstrated that (S)-proline was a successful catalyst in an intermolecular aldol process, giving product 12 in good yield and ee (Scheme 3). The reaction tolerates a wide range of substrates, but straight chain and α-acyloxy substituted aldehydes do not react.

To date, Lewis base organocatalysis remains the widest field within organocatalysis in terms of the reaction diversity it enables. Many different modes of activation within Lewis base organocatalysis have been investigated including enamine, iminium and SOMO (singly occupied molecular orbital) catalysis, which will be discussed in relation to MacMillan’s imidazolidinone catalysts (Figure 3). These can be considered to exhibit a “privileged” catalyst architecture as they can facilitate many reactions with high and predictable levels of enantioselectivity in mechanistically different ways. Ammonium enolate and acyl ammonium catalysis are also accessed using Lewis bases and will be discussed using the chemistry of isothiourea catalysts, which have been extensively investigated within the Smith group.
1.2.1 Iminium ion catalysis

MacMillan et al. first utilised imidazolidinone 15 to act as an enantioselective organocatalyst in the Diels-Alder reaction depicted in Scheme 4. Both endo and exo products (16a and 16b) were obtained in an excellent ee of 99% and 93% respectively. The reaction works well with a range of dienes and dienophiles giving good enantioselectivity, but the endo:exo ratios were consistently poor.

Scheme 4: Enantioselective organocatalytic Diels-Alder reaction

The proposed mechanism is detailed in Scheme 5. Condensation of the amine catalyst (15) with aldehyde 13 generates an iminium species (17) that is more electrophilic than the aldehyde starting material. The presence of the geminal dimethyl groups in catalyst 15 promotes formation of iminium 17 in good E/Z selectivity due to minimisation of steric interactions. The benzyl group efficiently blocks the Si-face of iminium 17, thus directing the reaction on the Re-face with high selectivity. Diels-Alder cycloaddition of 17 with diene 14, followed by iminium hydrolysis generates products 16a/b and reforms catalyst 15 (Scheme 5).

Scheme 5: Catalytic cycle for the enantioselective organocatalytic Diels-Alder reaction
This imidazolidinone catalyst motif has since been used to catalyse a wide range of reactions that proceed via an iminium intermediate including a variety of 1,4-nucleophilic additions to $\alpha,\beta$-unsaturated aldehydes.\textsuperscript{21,22}

The industrial utility of iminium catalysis has been recently demonstrated with the preparation of Telcagepant (24) on $>250$ kg scale by Merck.\textsuperscript{23,24} Telcagepant is a late-stage clinical candidate for the treatment of migraines,\textsuperscript{25} with a key step in its synthesis the asymmetric Michael addition of nitromethane to $\alpha,\beta$-unsaturated aldehyde 19 (Scheme 6). In this case, the Jørgensen-Hayashi catalyst (21) was the most efficient and could be used as a crude solution after TMS-protection of alcohol 20. Enantioselective addition of nitromethane followed by imine hydrolysis (facilitated by acid co-catalysts) afforded aldehyde 23 in high yield and excellent enantioselectivity. This key intermediate was further derivatised in four steps into Telcagepant 24 in an excellent 27% overall yield and in $>99.9\%$ ee.

![Scheme 6: Industrial scale application of iminium ion catalysis](image)

### 1.2.2 Enamine catalysis

Iminium intermediates (26) form enamines (27) upon $\beta$-deprotonation, giving two interconnected catalytic species with very different modes of activation (Scheme 7). Whilst in iminium ion catalysis the substrate is activated to nucleophilic attack by lowering of the LUMO energy relative to the parent carbonyl, enamine catalysis activates the substrate by raising the energy of the HOMO and thus increasing its nucleophilicity.
As enamine and iminium ion active species can interconvert it stands to reason that catalysts suitable for one mode of action should also work for the other. MacMillan’s imidazolidinone catalysts are also highly effective in enamine catalysis, such as the cross aldol reaction shown in Scheme 8. The cross-aldol reaction is promoted by dropwise addition of donor aldehyde 28 to a large excess of acceptor aldehyde 29. The initial addition product 31 reacts with a further equivalent of aldehyde 29 to form a hemiacetal 32, which prevents further addition and can be deprotected via in situ methanolysis to afford product 33 in good yield and high enantioselectivity. The imidazolidinone catalyst was successful in a variety of cross aldol reactions including those with α-acyloxy substitution, which were not tolerated in the corresponding (S)-proline-catalysed aldol process.  

1.2.3 SOMO catalysis

MacMillan then developed a third mode of catalytic activity, again connected to iminium and enamine intermediates. Upon single electron oxidation of enamine intermediate 27 a radical cation species 34 is generated, with its character somewhere between the nucleophilicity of enamine catalysis and the electrophilicity of iminium ion active species. This catalytic mode is defined as Single Occupied Molecular Orbital (SOMO) catalysis.
SOMO catalysis is highly successful at facilitating α-functionalisation of aldehydes, the first reported example being an α-allylation process (Scheme 10) that uses ceric ammonium nitrate (CAN) as an oxidant to generate the required SOMO intermediate. The reaction works well for a range of both aldehydes and allylsilanes, with good yields and enantioselectivity obtained in all cases.

The proposed mechanism for this transformation is detailed in Scheme 11. Initial enamine formation is followed by a one-electron oxidation using CAN to generate SOMO intermediate. Radical intermediate is obtained upon allyltrimethylsilane addition and is quenched with a further equivalent of CAN. Loss of trimethylsilane and imine hydrolysis affords product and reforms catalyst.
SOMO catalysis has subsequently been shown to be a highly versatile reaction mode, facilitating a wide range of other α-functionalisations including α-enolation, \(^\alpha\)-vinylation, \(^\alpha\)-chlorination and \(^\alpha\)-epoxidation.\(^\alpha\)

### 1.2.4 Acyl ammonium catalysis

The isothiourea moiety is found in biologically relevent compounds including the drugs Levaamisole 44 and Butamisole 45, used to treat parasitic worm infections in animals (Figure 4).\(^{31,32}\)

Birman \textit{et al.} first explored their use as Lewis base catalysts whilst investigating amidines and related structures as catalytic acylating agents in the kinetic resolution of secondary alcohols with acid anhydrides (Scheme 13).\(^{33,34}\) The Lewis base catalyst intercepts the anhydride, generating a chiral acyl ammonium species 47. Alcohol (±)-45 is preferentially acylated by 47 rather than the less reactive anhydride, and resolution is achieved by acylation of only one enantiomer of the alcohol. The racemic mixture is therefore separated into an enantioenriched alcohol ((\textit{S})-45) and an ester ((\textit{R})-46). The parameters reported are the reaction conversion (the percentage of ester 46 compared with alcohol 45), and the \(s\)-factor, which takes into account the relative rates of acylation of the two enantiomers of alcohol 45 and can be calculated from the enantioselectivity of the process.\(^{35}\) As conversion into the ester increases the ee of the parent alcohol is enhanced as the fast reacting enantiomer is used up. However if conversion is pushed too far the ee of the ester is compromised as more of the slow reacting alcohol enantiomer is acylated, therefore a balance must be struck if high ee of both substrates is to be attained.
1. Introduction

Scheme 12: Kinetic resolution of secondary alcohols

2-Phenyl-6-trifluoromethyl-dihydroimidazo[1,2-a]pyridine (CF₃-PIP, 48) was the first Lewis base catalyst investigated by Birman et al. for this process (Scheme 12). It gave a selectivity factor of 28 in the resolution of phenyl propanol which was improved by extending the π-system in the catalyst (Cl-PIQ, 49). Isothiourea catalysts were shown to be viable alternatives offering excellent selectivity in the process. Again, extending the π-system from tetramisole (TM, 50) to benzotetramisole (BTM, 51) proved important for enhanced selectivity and excellent results were obtained with analogues including homobenzotetramisole (HBTM, 52) and HBTM 2.1 (also known in the literature as HyperBTM). Other substrates that have been successfully resolved using isothiourea catalysis include a range of β-lactams, oxazolidinones, α-aryl acids and azlactones.

In addition to promoting intermolecular acyl transfer, isothioureas also carry out intramolecular carboxyl transfer processes. Smith et al. have developed an isothiourea-catalysed Steglich rearrangement (Scheme 13) in which O- to C- acyl transfer is achieved, forming quaternary carbon centres in high enantioselectivity. HBTM 2.1 53 was the optimal catalyst in this system, with Gröger et al. employing BTM 51 in a similar reaction which afforded low enantioselectivity. The reaction is tolerant of a wide variety of substrates including branched alkyl groups in the first example of the asymmetric rearrangement of an α-alkyl branched oxazoyl carbonate. Isothiourea-catalysed O- to C-carboxyl transfer has also been shown to work for furanly carbonates.
The oxazole substrate (54) is thought to first react with the catalyst to lose its carbonate group forming ion pair 56. Nucleophilic attack then occurs through C(4) onto the less hindered Re-face of the acyl ammonium species 56, forming product 55 and regenerating the catalyst 53.

1.2.5 Ammonium enolate catalysis

Isothioureas have also been used to form synthetically useful ammonium enolate intermediates.\textsuperscript{46} Formation of C1-ammonium enolates can proceed directly from ketenes (Figure 5, A), however the process encounters problems due to the highly unstable nature of the ketene starting materials 57 and is subject to substrate limitations.\textsuperscript{47} To date, isothioureas have not been used in conjunction with ketenes for the formation of enolates. An alternative method was developed by Romo \textit{et al.}, employing \textit{in situ} carboxylic acid activation using Mukaiyama’s reagent 61.\textsuperscript{48-51} Activated ester 60 then forms an acyl ammonium species (59) on reaction with a tertiary amine catalyst. Deprotonation of 59 affords the desired ammonium enolate (58) in a mild procedure starting from cheap and bench-stable carboxylic acids.
Romo et al. showed that this ammonium enolate formation strategy was compatible with isothiourea catalysis, employing HBTM (52) to catalyse the desymmetrisation shown in Scheme 15.\textsuperscript{52} In this case, tosyl chloride was used to “activate” carboxylic acid 63 via formation of a sulfonate ester. Addition of LiCl enhanced the yield and it is thought that the lithium cation chelates the substrate in the proposed pre-transition state assembly 64. Chelation was proposed to lock the conformation and possibly activates the ketone to nucleophilic addition.

Smith et al. then investigated the use of isothioureas in intramolecular Michael addition-lactonisation using pivaloyl chloride to activate carboxylic acid 66 \textit{in situ} (Scheme 16).\textsuperscript{53} The procedure showed high substrate tolerance with good results for aliphatic substrates, and aromatic substrates with both electron-withdrawing and donating substituents. High dr of up to 99:1 was observed and 90–99\% ee was achieved in all examples.

Intermolecular Michael addition-lactonisation also works well, with α-keto-\(\beta,\gamma\)-unsaturated esters (69) affording lactone products (70) in good yields (Scheme 17). The potential for
derivatisation of the products using *in situ* methanolysis was investigated and the ring-opened products (71) could be isolated in higher yields than the parent lactones (70).\(^{53}\)

![Scheme 17: Intermolecular variant of Michael addition-lactonisation process](image)

The proposed mechanism for the transformation is detailed in Scheme 18. Acyl ammonium 74 is formed *via* nucleophilic attack of isothiourea catalyst 53 onto activated acid 73. Enolate 75 is generated by deprotonation of the acyl ammonium intermediate, with recent studies suggesting that this is the rate-determining step and is carried out by the pivalate anion (with Hünig’s base presumably acting as a proton shuttle).\(^{54}\) Michael addition into the Michael-acceptor component 76 forms enolate 77, which cyclises to form lactone 78 and regenerate the catalyst.

![Scheme 18: Proposed mechanism for isothiourea-catalysed Michael addition-lactonisation](image)

To further understand the nature of enantiocontrol in the Michael addition-lactonisation process, computational studies were carried out on the reaction between phenylacetic acid 68 and trifluoroenone 79 (Scheme 19).\(^{54,55}\) Computational analysis of the transition state (80) demonstrates that enantiocontrol arises from the position of the stereodirecting
groups in the enolate intermediate. In the lowest energy conformation the bulkier isopropyl group occupies a pseudo-equatorial position and the phenyl group a pseudo-axial position to avoid 1,2-strain. This blocks the Si-face of the enolate thereby generating an (S)-stereocentre in the C–C bond forming step.

The catalyst conformation is further locked by an observed O→S attractive force, which prevents free rotation about the C(O)–N bond. The presence of oxygen to sulfur interactions is well documented in the literature: in a study of small molecular crystal structures, Stahl et al. showed that carbonyl groups display a strong preference for 1,5-oxygen to sulfur interactions. The effect has been exploited in the design of a variety of biologically active molecules, which has recently been extensively reviewed by Meanwell et al.\(^56\) One example is the following system developed by Nagao et al. who used a non-covalent O→S interaction to aid design of (acylamino)thiadiazoline derivatives as Angiotensin II receptor antagonists.\(^57\) X-ray crystallographic analysis of thiadiazole \(^82\) showed that its preferred conformer (\(^82\)b) exhibits an oxygen to sulfur attractive force (Figure 6). This holds it in a 5-membered ring and reduces the bond distance to 2.65 Å, significantly shorter than the sum of the Van der Waals’ radii (3.32 Å).

In the context of Lewis base catalysis, Birman et al. has suggested that the O→S interaction may provide isothiourea catalysts with enhanced activity compared with amidine analogues due to stabilisation of the acylated intermediate.\(^58\) Romo et al. observed that the interaction
may enhance enantioselectivity by helping to lock the conformation of the acylammonium species (Figure 7).\textsuperscript{52}

![Figure 7: Rotation in acylated amidines and isothioureas](image)

The nature of the $O\rightarrow S$ interaction is however not well understood. Recent computational studies by Romo et al. concerning the exact nature of this interaction will be discussed as part of mechanistic studies into the work described in this thesis (see section 2.5.2).

Recent developments in the field of ammonium enolate isothiourea catalysis have demonstrated that $N$-sulfonylketimines (84) can be used as Michael acceptors in related processes to generate dihydropyridones in good diastereo- and enantioselectivity.\textsuperscript{59} Use of thiophenyl acetic acid 83 as the ammonium enolate precursor enables the generation of synthetically useful pyridines 87 via exploitation of a facile elimination of thiophenol followed by $N$- to $O$-sulfonyl transfer (Scheme 20).\textsuperscript{60} A range of substitution patterns can be achieved and the retention of an $O$-tosyl group in the products allowed for a variety of further derivatisations to be performed including palladium-catalysed cross couplings and $S_N Ar$ substitutions.

![Scheme 20: Isothiourea-catalysed pyridine formation using $N$-sulfonyl imines as Michael acceptors](image)

### 1.2.6 $\alpha,\beta$-Unsaturated acyl ammonium intermediates

The advantage of any catalytic system can be seen in its generality. Ideally, one catalyst moiety will be able to activate a range of substrates in a variety of ways: this is well demonstrated by MacMillan's imidazolidinone catalysts that are capable of iminium ion, enamine, and SOMO catalysis (sections 1.2.1-1.2.3). Thus far isothiourea catalysts have been used for a variety of acyl transfers (Figure 8 (i)) and ammonium enolate transformations (ii). Further development of this catalyst system to include the use of $\alpha,\beta$-
unsaturated species in an asymmetric process (iii) is of high synthetic interest within the Smith group.

Figure 8: Isothiourea activation modes

The use of α,β-unsaturated acyl ammonium species in asymmetric organocatalysis has however not been widely explored. To the best of our knowledge prior to the beginning of this project the only example of the utilisation of a catalytic α,β-unsaturated acyl ammonium intermediate was demonstrated by Fu et al. (Scheme 21). Fu’s catalyst 90, a planar chiral PPY derivative, facilitates a cyclisation process between α,β-unsaturated acid fluoride 89 and a silylindene 88 to generate diquinanes (91). The annulated products are formed in good diastereoselectivity, however the enantioselectivity is good to modest and the chemistry was not demonstrated to form any other product scaffolds. Other Lewis base catalysts tested (quinidine and tertiary phosphines) did not generate the desired products and no attempts to improve the enantioselectivity were reported.

Scheme 21: Asymmetric [3+2] annulation catalysed by a planar chiral DMAP catalyst

The proposed mechanism is detailed in Scheme 22. Acylation of acid fluoride 89 generates α,β-unsaturated acyl ammonium species 92. The released fluoride anion adds to silicon, forming ion pair 93. In situ silicon deprotection generates a carbamion that can add into the α,β-unsaturated acyl ammonium affording adduct 94. The authors then propose the release
of ketene intermediate 95 that can cyclise in an ene-type process to give product 91, however the nature of this cyclisation process is unknown.

During the preparation of this thesis, but following our first publication in this area, Romo et al. reported the synthesis of N-heterocycles via dinucleophile addition into α,β-unsaturated acyl ammonium intermediates generated by acylation of α,β-unsaturated acid chlorides onto O-trimethylsilylquinine 98 (Scheme 23). Nucleophilic addition of amino esters formed 5-membered rings in good yields and enantioselectivity at –30 °C. It was also possible to generate 6-membered rings by extending the chain length of the amino ester starting materials. DBU was required to act as an acid scavenger, as without it the products were formed in <5% yield. Hünig’s base was also tested in this role however the conversion remained low. Using LiHMDS to deprotonate the amino ester is also crucial for reactivity and Romo postulates that the lithium chelates both the α,β-unsaturated acyl ammonium species and the nucleophile, thus lowering the energy of proposed transition state 100. The reaction scope was also expanded to include the use of 1,3-ketoesters as dinucleophiles, affording dihydropyranones in moderate to good yields, and in high enantioselectivity.
Romo et al. then showed that the \(\alpha,\beta\)-unsaturated acyl ammonium intermediate could participate in cycloadditions (Scheme 24). An isothiourea-catalysed Diels-Alder-lactonisation between 101 and 102 afforded a range of cyclised products in moderate to high yields, with excellent diastereo- and enantiocontrol.

Matsubara et al. recently demonstrated that chiral \(\alpha,\beta\)-unsaturated acyl ammonium intermediates could be successfully generated using bifunctional hydrogen-bonding catalyst 105. The tertiary amine group acts as a Lewis base to form the desired acyl ammonium intermediate, with the leaving group bound to the thiourea moiety (108). This can be delivered as a nucleophile with good enantiocontrol, followed by lactonisation to regenerate the catalyst. It was also possible to utilise external thiols in conjunction with bulky thioesters to further expand the utility of the methodology.
1. Introduction

1.2.7 α,β-Unsaturated acyl azolium intermediates

As there was limited understanding of the chemistry of α,β-unsaturated acyl ammoniums at the start of this work, initial inspiration was taken from the field of N-heterocyclic carbene (NHC) catalysis. The chemistry of α,β-unsaturated acyl azolium species has been more extensively investigated therefore it provided a good starting point for our own work.

Figure 9: α,β-Unsaturated acyl ammonium and azolium intermediates

The first example of a conjugate addition involving an α,β-unsaturated acyl azolium was developed by Lupton et al. in 2009 (Scheme 26).\textsuperscript{66} In situ deprotonation of the catalyst salt affords a free NHC catalyst that directly adds into enol ester \textit{109} to form an α,β-unsaturated acyl azolium intermediate in an ion pair with the enolate leaving group \textit{110}, which can act as a nucleophile to generate lactone product \textit{111}. The yield was good using achiral catalyst \textit{112}, but attempts to use chiral catalysts in the reaction were only moderately successful and treating starting material \textit{109} with 20 mol\% of catalyst \textit{113} gave product \textit{111} in a good yield but low ee.

Scheme 26: NHC-catalysed Michael addition-lactonisation from enol esters

One disadvantage of this procedure is the requirement to start with a substrate such as enol ester \textit{109}, which incorporates both the electrophilic and nucleophilic partners for the reaction. This could be synthetically limiting when using more complex reaction partners. Lupton therefore developed an direct method of generating α,β-unsaturated acyl azolium species by acylation of NHCs using acid fluorides \textit{114} (Scheme 27, A).\textsuperscript{67,68} Alternatively, Zeitler has reported that NHC addition to an alkynyl aldehyde \textit{119} followed by protonation...
gives allenol $117$ that rearranges to afford acyl azolium $116$ (B).$^{19}$ An alternative strategy uses aldehydes in the presence of stoichiometric oxidising agents (C).$^{70-73}$ NHC addition into an $\alpha,\beta$-unsaturated aldehyde $121$ generates the Breslow intermediate ($120$) which is oxidised to form the desired $\alpha,\beta$-Unsaturated acyl azolium intermediate $116$.

![Scheme 27](image)

Scheme 27: $\alpha,\beta$-Unsaturated acyl azolium formation via direct acylation or addition to alkynyl aldehydes

Using this oxidation strategy Studer et al. showed that NHC $123$ can catalyse the Michael addition-lactonisation between cinnamaldehyde ($13$) and 2,4-pentanedione ($122$).$^{70}$ In this case organic oxidant $124$ is used to oxidise the Breslow intermediate into an $\alpha,\beta$-unsaturated acyl azolium species. The reaction tolerates a variety of dicarbonyl nucleophiles and $\alpha,\beta$-unsaturated aldehydes, however substitution at the $\alpha$-position was not tolerated.

![Scheme 28](image)

Scheme 28: Development of NHC-catalysed Michael addition to $\alpha,\beta$-unsaturated aldehydes

Xiao et al. demonstrated that this reaction is amenable to asymmetric catalysis, generating lactone (R)-$129$ in high yield and stereoselectivity using either ynal addition or aldehyde addition-oxidation for acyl azolium formation (Scheme 30).$^{71,74}$ In both methods the use of molecular sieves was crucial for obtaining high yield and selectivity.
1. Introduction

Related work by You et al. (Scheme 30) screened other catalysts for the reaction and found that a combination of catalyst 131 (10 mol%) with NaBF₄ (5 mol%) as an additive achieved the highest selectivity, however the role of the additive has not been investigated.

Bode et al. carried out a similar annulation with a wide range of enol nucleophiles (Scheme 31) to give annulated products in good yields and moderate to excellent enantioselectivity. Bode has also shown that vinylogous amides are suitable nucleophiles in this process, affording dihydropyridone products, while Biju recently showed that pyrazolones were successful nucleophiles in this process.

The mechanism of these NHC-catalysed annulation processes is disputed. Studer et al. have carried out mechanistic studies which suggest that nucleophilic addition into the α,β-
unsaturated acyl azolium intermediate proceeds via 1,4-addition to generate an enolate intermediate. However, Bode et al. have also conducted mechanistic studies that they believe are indicative of 1,2-addition followed by 3,3-rearrangement. A recent computational collaboration between Bode and Shoenebeck showed that the two pathways are similar in energy and as they both generate the same enolate intermediate they are difficult to distinguish experimentally. However the enolate intermediate is formed, it is then agreed that tautomerisation followed by cyclisation forms the lactone product and regenerates the catalyst.

Scheme 32: Proposed catalytic cycle for NHC-catalysed Michael addition reaction

One of the major limitations of these NHC-catalysed reactions is the inability to use β-substituted α,β-unsaturated acyl azolium precursors. Recently, Xu et al. found that this could be circumvented by the use of saturated imidazolium catalysts (139). This NHC-precursor scaffold is more normally found in ligands or components of ionic liquids, but here enables access to anti-dihydropyranones in moderate to good dr, good yields and generally high enantioselectivity.

Scheme 33: Enantioselective NHC-catalysed Michael addition to α,β-unsaturated carbonyl species
1. Introduction

1.3 Aims and Objectives

Past work in the Smith group has demonstrated that ammonium enolate intermediates are competent Michael donors (Scheme 34, (A)). Elaboration of this methodology by reversal of the donor/acceptor roles via the introduction of an \( \alpha,\beta \)-unsaturated moiety into the catalyst-bound species (B) would be of high synthetic value. In this regard, the incorporation of dinucleophiles in the reaction would lead to highly functionalised enantioenriched motifs.

\[
\text{(A) Ammonium Enolate Reactivity}
\]

\[
\text{(B) \( \alpha,\beta \)-Unsaturated Acyl Ammonium Reactivity}
\]

Scheme 34: Lewis base catalysis utilising saturated (i) and \( \alpha,\beta \)-unsaturated (ii) substrates

NHCs have been demonstrated to be successful in such processes, however isothioureas may provide a useful alternative to NHCs. The current strategies to form acyl azolium species require highly reactive starting materials or expensive stoichiometric oxidants. In contrast the acid activation methodology developed by Romo and Smith enables direct isothiourea activation of bench-stable, commercially available carboxylic acids. Furthermore, NHC-catalysis must be performed under rigourously dry conditions whereas isothiourea catalysis has proven to be versatile in bench solvents under open flask conditions, providing further procedural advantages.

As MacMillan’s imidazolidinone catalysts have demonstrated, “privileged” catalyst architectures offer chemists a wide variety of modes of action, expanding the synthetic options open for the synthesis of a variety of product scaffolds. Through exploring the scope and mechanism of such modes we can continue to develop robust chemical processes that are attractive to both industry and academia. To this aim, the objectives of this work were to expand the applicability of isothioureas as Lewis base catalysts, by exploring the chemistry of \( \alpha,\beta \)-unsaturated acyl ammonium intermediates.
2. 1,3-Diketones and 1,3-Ketoesters as Nucleophiles

2.1 Project Aims

Over the last decade isothioureas have been developed as powerful Lewis base organocatalysts, having been employed in a number of asymmetric transformations (Figure 8). They were firstly explored as catalysts for acyl transfer reactions (Figure 8, (i)) including kinetic resolutions and C-acylations (see Section 1.2.4). Further development demonstrated the generation of ammonium enolate intermediates (ii) that participate in aldol and Michael addition-lactonisation processes (see Section 1.2.5). The chemistry of α,β-unsaturated acyl ammonium species (iii) however has been largely unexplored and had never been demonstrated before in isothiourea catalysis. Therefore at the outset of our research our aim was to use chiral isothiourea catalysts to generate α,β-unsaturated acyl ammonium intermediates that could be utilised in novel, enantioselective methodologies.

Taking inspiration from the chemistry of α,β-unsaturated acyl azolium species (as discussed in Section 1.2.7) the aim of this project was to develop an enantioselective isothiourea-catalysed Michael addition of dicarbonyl nucleophiles to α,β-unsaturated acyl ammonium intermediates. A hybrid catalytic cycle was proposed (Scheme 35) whereby the reaction is initiated by acylation of the catalyst with an activated acid to form an α,β-unsaturated acyl ammonium intermediate. Subsequent 1,4-addition (or 1,2-addition followed by 3,3-rearrangement) generates an ammonium enolate and forms a new C-C bond, setting the stereocentre. Proton transfer followed by lactonisation forms the product and regenerates the catalyst.
2. 1,3-Diketones and 1,3-Ketoesters as Nucleophiles

Successful demonstration of this reaction would provide the first example of an $\alpha,\beta$-unsaturated acyl ammonium intermediate participating in a Michael addition. Inspired by the research of Xiao$^71$ and You$^72$ a model reaction was selected for examination (Scheme 36). Xiao and You demonstrated that $\alpha,\beta$-unsaturated acyl azoliums could be accessed via NHC precursors 131 and 128, cinnamaldehyde 13 and stoichiometric organic oxidant 124. Our aim was to evaluate commercially available, bench-stable carboxylic acids and isothioureas as $\alpha,\beta$-unsaturated acyl ammonium precursors, eliminating the need for aldehyde synthesis and the use of expensive organic oxidants.

Scheme 35: Proposed mechanism for isothiourea-catalysed Michael addition-lactonisation of $\alpha,\beta$-unsaturated carboxylic acids

Scheme 36: Test reaction for optimisation studies
2.1,3-Diketones and 1,3-Ketoesters as Nucleophiles

Initial studies focussed on finding a suitable carboxylic acid activating agent to promote catalysis, followed by screening of chiral isothiourea catalysts to obtain acceptable levels of conversion and the best enantioselectivity in the process. This was followed by further fine tuning of base and solvent effects and investigation into product isolation methods to afford optimal reaction conditions, allowing exploration of the reaction scope and mechanism.

2.2 Reaction Optimisation

2.2.1 Activation agent screening

The first step in the proposed catalytic cycle (Scheme 35) is the formation of an α,β-unsaturated acyl ammonium species. To facilitate this first step, the carboxylic acid must be “activated” by introducing an effective leaving group. Previous work in the Smith group has demonstrated pivaloyl chloride as an effective activating agent, forming a mixed anhydride 146 in situ. However, in the model reaction (Scheme 37) pivaloyl chloride activation was ineffective and only starting material was returned.

Scheme 37: Use of pivaloyl chloride as an activating agent

One possible reason for the low reactivity observed was poor formation of mixed anhydride 146. To provide evidence of intermediate 146 methanol was used as a nucleophile (Scheme 38) in the synthesis of ester 147. “Unactivated” acid 143 does not esterify under these conditions therefore any formation of 147 must proceed through the mixed anhydride 146. After 3 h, analysis of the crude reaction mixture by $^1$H NMR showed conversion into ester 147 to be approximately 60%. This suggests modest formation of mixed anhydride 146, however since it was not possible to achieve conversion into lactone 145 via our organocatalysis this activation method was deemed unsuitable.
In order to find a more effective acid activation method, several *in situ* activating agents were investigated in the model reaction (Table 1). Consumption of the dicarbonyl was monitored by $^1$H NMR and calculated based upon the starting material to product ratio. In most cases unreacted starting materials were returned, however some success was obtained with both tosyl chloride and 4-methoxybenzoic anhydride. Increasing the quantity of activating agent had no effect on tosyl chloride activation, and with 4-methoxybenzoic anhydride a drop in conversion was observed at 2 equivalents and an increase at 1.2 equivalents to 62% was achieved.

<table>
<thead>
<tr>
<th>Activating Agent</th>
<th>Equivalents</th>
<th>Dicarbonyl Consumption (%)$^{[a]}$</th>
<th>Yield (%)$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivaloyl chloride</td>
<td>1.5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Mukaiyama reagent</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Benzoyl chloride</td>
<td>1</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Tosyl chloride</td>
<td>2</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>4-methoxybenzoic anhydride</td>
<td>1,2</td>
<td>53</td>
<td>42</td>
</tr>
</tbody>
</table>

Table 1: Screening of activating agents $^{[a]}$Calculated by $^1$H NMR, $^{[b]}$Isolated yield

To circumvent any problems of poor acid activation, pre-activated species were tested in the model reaction (Table 2). Despite the high reactivity of acid chlorides towards nucleophilic addition,$^{84}$ no product was formed when cinnamoyl chloride was employed.
Use of cinnamic anhydride in the model reaction provided the desired product 145 with 63% diketone consumption which was increased to 76% by using an excess of the anhydride.

<table>
<thead>
<tr>
<th>Activated Species</th>
<th>Equivalents</th>
<th>Dicarbonyl Consumption (%)</th>
<th>Yield (%)</th>
<th>[a]</th>
<th>Isolated yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinnamoyl chloride 148</td>
<td>1</td>
<td>0</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cinnamic anhydride 149</td>
<td>2</td>
<td>63, 76</td>
<td>8, 59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Comparison of pre-activation methods

[a]Calculated by ¹H NMR, [b]Isolated yield

Cinnamic anhydride 149 was initially synthesised from cinnamic acid 143 using N,N'-dicyclohexylcarbodiimide (DCC, 150 Scheme 39) as a coupling agent, however urea byproduct 152 coeluted with lactone 145 after the organocatalysis, making product purification difficult. Attempts to purify the anhydride by recrystallisation or trituration were unsuccessful so 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI.HCl, 151 Scheme 39) was investigated as an alternative coupling agent. The advantage of this reagent is that both the coupling agent and the urea byproduct 153 are water soluble, enabling purification by a simple water wash. The yield of anhydride obtained by this method was slightly reduced however it enabled isolation of organocatalysis product 145 in excellent purity.
2.2.2 Isothiourea screening

Using the optimal activation methods determined (A and B, Table 3), the chiral isothioureas (-)-tetramisole 50, (+)-benzotetramisole 51 and HBTM 2.1 53 (Table 3) were investigated. DHPB 144 afforded the product in the same yield for both activation methods, however the only chiral catalyst to give any conversion into product 145 was HBTM 2.1 53, with other chiral catalysts returning only unreacted starting materials. HBTM 2.1 53 gave excellent enantioselectivity (95% ee) in both cases, but a significantly higher yield was achieved using cinnamic anhydride (activation method B), hence this activation method was chosen for further reaction optimisation.

<table>
<thead>
<tr>
<th>Isothiourea Catalyst</th>
<th>Activation Method</th>
<th>Dicarbonyl Consumption (%)(^[a])</th>
<th>Yield (%)(^[b])</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>A</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>DHPB 144</td>
<td></td>
<td>B</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>TM 50</td>
<td></td>
<td>A</td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>76</td>
<td>59</td>
</tr>
<tr>
<td>BTM 51</td>
<td></td>
<td>A</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>HBTM 2.1 53</td>
<td></td>
<td>A</td>
<td>39</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>57</td>
<td>57</td>
</tr>
</tbody>
</table>

Table 3: Comparison of isothiourea catalysts \(^[a]\)Calculated by \(^1\)H NMR, \(^[b]\)Isolated yield

2.2.3 Reaction concentration effects

In an attempt to further increase conversion into desired product 145, the effects of reaction concentration were next investigated. A series of reactions using varying concentrations of 1,3-diphenyl-1,3-dipropanone 141 from 0.09 to 0.72 M was investigated (Table 4). A maximum conversion of 74% could be obtained using 1.2 equivalents of homoanhydride at a reaction concentration of 0.72 M, which could be further increased to 86% with 1.4 equivalents of homoanhydride at the same dicarbonyl concentration. Higher
concentrations could not be achieved due to poor solubility of the reactants and mobility causing the reaction to proceed inefficiently.

<table>
<thead>
<tr>
<th>Anhydride Equivalents</th>
<th>Dicarbonyl Concentration (M)</th>
<th>Dicarbonyl Consumption (%) [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>0.09</td>
<td>53</td>
</tr>
<tr>
<td>1.2</td>
<td>0.18</td>
<td>66</td>
</tr>
<tr>
<td>1.2</td>
<td>0.36</td>
<td>73</td>
</tr>
<tr>
<td>1.2</td>
<td>0.72</td>
<td>74</td>
</tr>
<tr>
<td>1.4</td>
<td>0.72</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 4: Effects of diketone concentration on dicarbonyl consumption [a] Calculated by 'H NMR

2.2.4 Product isolation and ring-opening

Throughout optimisation it was found that reaction yields were poorly reproducible, with isolated yields ranging from 27-63%. However conversion into product 145 (monitored by crude 'H NMR spectra) was consistently high, therefore product isolation and stability was investigated via a comparison of silica gel contact time. Two lactone purifications were carried out in tandem, comparing the speed at which eluent was passed through the column (Scheme 40). The “fast” column gave the product in a 54% yield; the “slow” column which involved longer contact time of the product on the silica gave a reduced 33% yield due to the apparent instability of the lactone.

Scheme 40: Lactone isolation and silica column stability

An alternative ring-opened product was targeted via in situ methanolysis of lactone 145 into ester 154. Ring-opening proceeded readily and afforded a chromatography-stable product ((S)-154) in high yield (Scheme 41). Whilst formally the absolute configuration of the stereocentre during the ring-opening changes from (R) to (S), no epimerisation occurs in this process and both lactone and ring-opened products were obtained in 95% ee.
The absolute configuration of the lactone product 154 was determined by comparison of its specific rotation to that quoted in the literature (Figure 11). X-ray crystallographic analysis of lactone 155 by You et al. determined the configuration to be (S). By analogy, You reported that lactone 154 must have the same absolute configuration at the stereogenic centre. The $[\alpha]_D^{20}$ measured for lactone 154 isolated in our investigations matches the value reported by You et al., so it follows that the product generated via isothiourea catalysis also contains an (R)-stereocentre.

![Scheme 41: Lactone isolation and methanolation](image)

**2.2.5 Base screening and catalyst loading**

Alternative bases were next examined to further improve conversion (Table 5). Triethylamine, MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, a hindered guanidine base) and $\text{K}_2\text{CO}_3$ all gave low conversion into product 154. Improved yields were obtained with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) however the enantioselectivity was compromised. In this case the reaction works well in the absence of an isothiourea catalyst, so the erosion of enantioselectivity is presumably due to competing Lewis base catalysis by DBU. When $\text{NEt}(\text{Pr}_2)$ was employed, lower catalyst loadings were tolerated but a modest drop in reaction conversion was observed. In contrast using PS-BEMP (2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene, loading of ~2.2 mmolg$^{-1}$) afforded 154 in increased yields and tolerated catalyst loadings as low as 5 mol% without any drop in yield. Further reductions to 1 mol% were successful but resulted
in reduced yield even at extended reaction times. Therefore further investigations were carried out using PS-BEMP as the base with 5 mol\% isothiourea catalyst loading.

<table>
<thead>
<tr>
<th>Base</th>
<th>Catalyst loading (mol%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEt$_3$</td>
<td>20</td>
<td>17$^{[a]}$</td>
<td>-</td>
</tr>
<tr>
<td>MTBD</td>
<td>20</td>
<td>0$^{[a]}$</td>
<td>-</td>
</tr>
<tr>
<td>K$_2$CO$_3$</td>
<td>20</td>
<td>10$^{[a]}$</td>
<td>-</td>
</tr>
<tr>
<td>NEt($i$Pr$_2$)</td>
<td>20</td>
<td>77$^{[b]}$</td>
<td>95</td>
</tr>
<tr>
<td>DBU</td>
<td>20</td>
<td>86$^{[b]}$</td>
<td>73</td>
</tr>
<tr>
<td>PS-BEMP</td>
<td>20</td>
<td>85$^{[b]}$</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>82$^{[b]}$</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>85$^{[b]}$</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>69$^{[b]}$</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>62$^{[b]}$</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 5: Base and catalyst loading optimisation. $^{[a]}$Diketone consumption calculated from crude NMR. $^{[b]}$Isolated yield

2.2.7 Optimised reaction conditions

The optimised reaction conditions are summarised in Scheme 42. The use of an excess of homoanhydride as a pre-activated carboxylic acid was crucial for both high yield and enantioselectivity. High concentration is important for increasing the reaction conversion, and a concentration of 0.72 M diketone is a good compromise between starting material consumption and mobility of the reaction mixture. Of the bases investigated, PS-BEMP was optimal as it allowed low catalyst loadings to be employed. Finally, in situ methanolysis generates highly functionalised esters that are more stable to column chromatography and improves product isolation. With the optimised reaction conditions established, a survey of the scope of the reaction was next investigated.
2.3 Reaction Scope: Symmetrical Diketones

2.3.1 Anhydride synthesis and scope

To probe the substrate scope and limitations of this reaction, a wide range of homoanhydrides was prepared according to the previously described EDCI coupling procedure (Scheme 43). A variety of β-aryl and β-alkyl α,β-unsaturated anhydrides were synthesised in order to explore steric and electronic effects in the Michael addition-lactonisation process, as well as the incorporation of heterocyclic substituents. The majority of anhydrides were accessed easily in CH₂Cl₂, however it was necessary to synthesise heterocyclic substrates 163 and 164 in THF to prevent the formation of polymeric material. The anhydrides were found to be stable in the freezer over the course of several months.

The range of homoanhydrides was then investigated under the optimised reaction conditions to examine the substrate scope of the Michael addition-lactonisation. Anhydrides with substituted aromatic groups were tolerated well (Scheme 44), with electron-withdrawing groups (165 and 166) giving high yields and good enantioselectivity. Electron-donating groups gave significantly lower conversion, with 4-methoxy substitution affording product 167 in a moderate 44% yield. This is possibly due to reduced electrophilicity in the electron rich α,β-unsaturated acyl ammonium intermediate.
Increasing the catalyst loading from 5 to 10 mol% led to an improvement in the yield, however a slight drop in enantioselectivity was observed. Substitution in the 2- (170) or 3- (168 and 169) position round the β-aryl ring was also tolerated, with little effect on the enantioselectivity of the process.

Pleasingly, the substrate scope was extended to include β-heterocyclic substituents (171 and 172, Scheme 45). The furanyl example gave a slightly lower yield, possibly due to the ring being slightly more electron-rich. Linear alkyl groups were also successful in the reaction, but β-branched alkyl anhydrides did not react under the reaction conditions. Alkyl substitution also resulted in lower ee than seen for aromatic substrates. Enantioselectivity could be increased by reducing the reaction temperature from 0 to –78 °C however a significant drop in yield was incurred in both cases. You et al. found that methyl substitution afforded only a 10% yield in their NHC-catalysed Michael addition-lactonisation process,\textsuperscript{72} so the use of isothioureas provides a significant advantage for these substrates.
2. 1,3-Diketones and 1,3-Ketoesters as Nucleophiles

Scheme 45: Heterocyclic and alkyl anhydrides in the Michael addition-lactonisation reaction

2.3.2 Diketone scope

We then turned our attention to alternative symmetrical dicarbonyl nucleophiles. First, a range of commercially available alkyl diketones was investigated (Scheme 46). Dimethyl substitution afforded product 176 in reasonable yield but low enantioselectivity, possibly due to reduced steric bulk leading to poor facial discrimination in the transition state. Branched (and hence more sterically demanding) alkyls were investigated, however they were not successful in the reaction and this is proposed to be due to hindrance of the nucleophilic addition. Isopropyl substitution afforded product 177 in a low yield contaminated with an unknown product. Further purification was unsuccessful and it proved impossible to obtain a pure sample for full characterisation. tert-Butyl substituted diketone displayed no reactivity and formation of product 178 was not observed.

Scheme 46: Alkyl diketones in the Michael addition-lactonisation reaction

To further investigate the scope of the reaction with regards to symmetrical diketones, a range of aryl diketones was prepared via LiHMDS deprotonation of aryl ketones and

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1 Carried out by Dr Carmen Simal
addition to aryl acid chlorides (Scheme 47). This procedure afforded symmetrical diketones 179-183 in modest yields.\(^a\)

These aryl diketones were subsequently examined in the Michael addition-lactonisation reaction (Scheme 48). Electron-poor diketones gave higher yields, possibly due to increased acidity of the \(\alpha\)-protons increasing the enolate concentration present. Equally this could explain the reduced enantioselectivity for electron poor nucleophiles due to enhanced background reaction rate. Use of diketone donors with electron-poor homoanhydrides improved both the yield and enantioselectivity, with 186 being obtained in 54% yield and 96% ee whilst 185 was obtained in a lower 40% yield and 90% ee.

To probe the scope of the isothiourea-catalysed reaction further, our attention turned to cyclic diketone 189 reported by Bode to be ineffective in the corresponding NHC-catalysed

\(^a\)Carried out by Dr Charlene Fallon
2.1,3-Diketones and 1,3-Ketoesters as Nucleophiles

process. Significantly, cyclic diketone 189 was successful in the isothiourea-catalysed process, however a short reoptimisation of solvent was required to increase the enantioselectivity. In CH₂Cl₂, the reactivity was good but the ee modest. Changing to THF increased the ee but led to a drop in enantioselectivity, however a 10:1 mixture of THF:CH₂Cl₂ afforded lactone 111 in good yield and enantioselectivity. This result further demonstrated the utility of our process in examples where NHC-catalysts are unsuccessful.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂Cl₂</td>
<td>82</td>
<td>74</td>
</tr>
<tr>
<td>THF</td>
<td>39</td>
<td>87</td>
</tr>
<tr>
<td>THF:CH₂Cl₂ (10:1)</td>
<td>80</td>
<td>86ⅲ</td>
</tr>
</tbody>
</table>

Table 6: Solvent effects observed for cyclic diketone annulation

2.4 Use of Non-Symmetrical Dicarbonyl Nucleophiles

2.4.1 Diketones

To further expand the scope, non-symmetrical diketones were examined. Initial investigations using 1-phenylbutane-1,3-dione 190 resulted in a 69:31 mixture of regioisomers 191a and 191b that were difficult to separate by chromatography (Scheme 49).ⅳ

Ring-opening of regioisomeric lactones 191a and 191b with methanol affords ester 192 in a 1:1 mixture of diastereomers that could not be separated (Scheme 50),ⅴ therefore ring-
opening to improve product isolation was not suitable for products generated from non-symmetrical nucleophiles.

![Scheme 50: Ring-opening of regioisomeric pairs](image)

### 2.4.2 Ketoesters

Ethyl benzoylacetate 193 was explored as a nucleophile in the optimised process, resulting in lactone 194 as a single regioisomer. Isolation of 194 proved difficult due to instability on silica gel. A number of chromatography conditions (quantity of silica, column eluents) were investigated and CH$_2$Cl$_2$ was identified as the optimum eluent with a short silica contact time.

![Scheme 51: Ethyl benzoylacetate as dicarbonyl nucleophile](image)

The high regio- and enantioselectivity obtained with ethyl benzoylacetate 193 led to examination of reaction scope using this nucleophile (Figure 12). Introduction of the ester functionality into the dicarbonyl increases the pKa of the α-protons, leading to lower consumption of starting material compared with 1,3-diphenyl-1,3-dipropionate 141 in all examples. Despite isolation problems, a range of lactones were successfully isolated in moderate yields and good enantioselectivity. Methyl substitution gave lower enantioselectivity with product 201 isolated in 65% ee. Heterocycles worked well, with thienyl 199 and furanyl 200 examples being isolated in good yield and high ee. Electron-withdrawing aryl substitution was highly successful in the process, however electron-donating groups were not tolerated. Several attempts were made to obtain the 4-methoxy substituted lactone however a combination of very low conversion and lactone hydrolysis meant isolation was unsuccessful.

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*Carried out by Dr Carmen Simal*
2.5 Mechanistic Investigations

2.5.1 Postulated mechanism

Inspired by related Lewis base-catalysed Michael-addition lactonisations, the catalytic cycle shown in Scheme 52 is proposed. The reaction is initiated by acylation of the catalyst with the homoanhydride to form an \( \alpha,\beta \)-unsaturated acyl ammonium intermediate. Two mechanistic pathways have then been suggested by the groups of Bode\(^\text{76,81}\) and Studer\(^\text{79}\) for related NHC-catalysed processes proceeding via \( \alpha,\beta \)-unsaturated acyl azolium intermediates (as discussed in Chapter 1, Section 1.2.7). If we assume that isothioureas behave similarly to NHCs in Lewis base catalysis, we can propose that the reaction could proceed via 1,2-addition of the nucleophile into the \( \alpha,\beta \)-unsaturated acyl ammonium intermediate followed by [3,3]-rearrangement to afford an ammonium enolate intermediate (as favoured by Bode). Alternatively, the same enolate could be formed directly via Michael addition of the nucleophile into the \( \alpha,\beta \)-unsaturated intermediate (as suggested by Studer). Since experimental and computational studies in the NHC literature have proved to be inconclusive, with the energies of the two pathways being very similar, it is undetermined which pathway is most likely for our isothiourea-catalysed process. From the ammonium

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\(^{\text{vi}}\) Carried out by Dr Carmen Simal

\(^{\text{vii}}\) Carried out by Dr Charlene Fallan
enolate, the product is formed via proton transfer and subsequent lactonisation; the product can then be ring-opened in situ with methanol to form highly functionalised esters.

In order to support this proposed mechanism, some control experiments were performed. It was possible to isolate α,β-unsaturated acyl ammonium 202 as a chloride salt by reacting cinnamoyl chloride with stoichiometric HBTM 2.1 at room temperature in CH₂Cl₂. The intermediate was formed as a precipitate that was isolated by filtration in a 77% yield. Intermediate 202 was then successfully employed as a precatalyst in the process (Scheme 53), which is consistent with the reaction proceeding via an α,β-unsaturated acyl ammonium intermediate.

Our attention then turned to work by Lupton et al. that demonstrated that α,β-unsaturated enol esters could be employed as nucleophile precursors in an NHC-catalysed conjugate addition (Scheme 54, A). Initial addition of NHC 113 to ester 109 generates an ion pair

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*Carried out by Dr Charlene Fallan*
(110) comprised of an \(\alpha,\beta\)-unsaturated acyl azolium electrophile and an enolate nucleophile. Product 111 was then formed in good yield but low ee. It is possible that in our process the nucleophile 141 could intercept the homoanhydride before the catalyst, however enol ester 203 did not rearrange under isothiourea catalysis\(^{ix}\) which is consistent with our proposal that the homoanhydride directly acylates HBTM 2.1 in the mechanism.

\[ \text{Scheme 54: Rearrangement of } \alpha,\beta\text{-unsaturated esters under Lewis Base catalysis}^{ix} \]

2.5.2 Proposed stereochemical model

To generate the observed (R)-lactone, the stereodetermining step in the mechanism must proceed \(\text{via}\) nucleophilic addition to the Si-face of the ketone or the Re-face of the olefin of the \(\alpha,\beta\)-unsaturated acyl ammonium ion in order to impart an (R)-stereocentre in the product (Scheme 55).

\[ \text{Scheme 55: Stereocentres induced during nucleophilic addition and lactonisation} \]

In order to analyse how the transition state induces preferential 1,2- or 1,4-addition to the back face as drawn, it is important to consider the conformation of the acyl ammonium species. Firstly it is assumed that the C-C(\(\text{O}\)) \(\sigma\)-bond adopts an \(s\text{-cis}\) conformation in order

\(^{ix}\) Carried out by Charlene Fallan
to minimise steric interactions between the substituents on the olefin and the

tetrahydropyrimidine portion of the isothiourea ring (Figure 13).

**Figure 13: Postulated non-bonding oxygen - sulfur interaction**

It is also thought that an oxygen to sulfur interaction exists, stabilising the species and
holding it in the *syn*-conformation shown in Figure 13. A study by Stahl *et al.*, using small
molecule crystal structures to determine conformational preferences, observed that many
species show a strong preference for 1,5-oxygen to sulfur interactions. The nature of the
interaction is not well understood but has been suggested to be an $n_\text{O} \rightarrow \sigma^*$ orbital
interaction. It could also simply be an electrostatic interaction between the oxygen and
sulfur atoms overcoming lone pair repulsion, but no evidence for this has yet been
reported. Recently, Romo in collaboration with Tantillo carried out computational
investigations into an isothiourea-catalysed Diels-Alder reaction also proceeding *via* an $\alpha,\beta$
unsaturated acyl ammonium intermediate (Scheme 56). Experimental results showed that
a single diastereomer of the product was obtained (103) in excellent enantioselectivity.
Computational calculations then showed that there was a large energy preference (>5
kcalmol$^{-1}$) for diene approach from the $\text{Re}$-face due to steric blocking by the (-)-BTM
catalyst on the $\text{Si}$-face (204), thus affording excellent stereocontrol in the process.

**Scheme 56: Isothiourea-catalysed Diels-Alder-lactonisation, with diene approach from the less hindered $\text{Si}$-face**

They also carried out natural bond orbital (NBO) analysis of the $\alpha,\beta$-unsaturated acyl
ammonium species to probe the orbital interactions responsible for the observed
conformation. While an oxygen to sulfur $n \rightarrow \sigma^*$ interaction did contribute to the stability of
the system, this effect was negated by the destabilising energy of lone pair repulsion
between oxygen and sulfur (Figure 14). However when the dihedral angle is 180°
unfavourable n→σ\textsubscript{C-H} interactions arise, which increase the energy of this conformation and leads to the observed syn-conformational lock.

Whatever the true nature of the O→S interaction, it enhances enantioselectivity in isothiourea-catalysed processes by locking the conformation of the acylated intermediate.\textsuperscript{52} This allows facial selectivity to arise from the positioning of the stereodirecting groups on the isothiourea catalyst. Isolated α,β-unsaturated intermediate 202 was analysed by X-ray crystallography (Figure 15), and the conformation of the catalyst in the solid state is thought to closely resemble the conformational preference in solution phase.

As seen in Figure 15 the 6-membered tetrahydropyrimidine ring adopts a pseudo half-chair conformation in order to reduce 1,2-interactions.\textsuperscript{87,89} The isopropyl group sits in an

\textsuperscript{a}Crystal obtained by Dr Charlene Fallan and analysed by Prof. Alexandra Slawin
equatorial position, locking the ring with the phenyl group sitting axially. The vertical positioning of the phenyl ring blocks the Si-face of the acylated catalyst, hence the nucleophilic addition occurs from the Re-face and installs an (R) stereocentre that is retained in the lactone product.

2.5.3 Effect of E/Z anhydride configuration

In order to investigate the effect of double bond geometry on the reaction a sample of cis-cinnamic acid was synthesised. Alkyne 205 was selectively reduced using Lindlar’s catalyst to give a reaction mixture containing 90% cis-alkene 206, 6% alkyne 205, and small quantities of the alkane 207 and trans-alkene 208. The reaction required two cycles to achieve improved conversion into alkene 206, giving material clean enough to take through to the next step without further purification.

$$\text{Ph} \equiv \text{CO}_2\text{Et} \xrightarrow{\text{H}_2\text{Lindlar cat. (3 mol% Pd)}} \text{Ph} \equiv \text{CO}_2\text{Et} + \text{Ph} \equiv \text{CO}_2\text{Et} + \text{Ph} \equiv \text{CO}_2\text{Et}$$

**Scheme 57:** Selective reduction of ethyl phenylpropiolate using Lindlar catalyst

cis-Ester 206 was then hydrolysed using lithium hydroxide, affording cis-cinnamic acid 209 in 89% yield (cis-geometry confirmed by matching 1H NMR data to the literature). cis-Anhydride 210 was generated using an EDCI coupling in a 56% yield, affording the product in an overall yield of 50% over 3 steps.

$$\text{Ph} \equiv \text{CO}_2\text{Et} \xrightarrow{\text{LiOH (3 equiv)}} \text{60 °C, 16 h} \xrightarrow{\text{EDCI.HCl (0.6 equiv)}} \text{Ph} \equiv \text{CO}_2\text{H} \equiv \text{Ph}$$

**Scheme 58:** Reduction and anhydride coupling of cis-ethyl cinnamate

Subjecting the cis-anhydride 210 to the optimised addition-lactonisation reaction conditions afforded the ring-opened product 154 in 41% yield (Scheme 59). HPLC analysis revealed that the use of the (Z,Z) anhydride favoured formation of the opposite (R)-enantiomer with low enantioselectivity.
2.1,3-Diketones and 1,3-Ketoesters as Nucleophiles

Scheme 59: Use of cis-cinnamic anhydride in the Michael addition-lactonisation reaction

A switch in enantioselectivity might be expected with a change of olefin geometry, however the reason for low enantioselectivity is not fully understood. If we assume that the s-cis conformation is retained in the (Z)-α,β-unsaturated acyl ammonium intermediate, we must consider the conformation that the phenyl group adopts (Figure 16). In the case of the (E)-intermediate it adopts a planar conformation, therefore facial selectivity is dictated only by the position of the catalyst stereodirecting groups. Whilst no crystal structure has been obtained for the (Z)-intermediate, it can be reasoned that the close proximity of the carbonyl group would prevent the phenyl group lying in the plane of the α,β-unsaturated system. This would provide further steric hindrance to nucleophilic addition and reduce the catalyst’s influence over facial selectivity. This therefore demonstrates the importance of (E,E)-geometry of the anhydride to obtain good enantioselectivity in the Michael addition-lactonisation process.

Figure 16: Conformations of α,β-unsaturated acyl ammonium species with E- and Z-configurations

2.6 Conclusions

A novel Michael addition-lactonisation process has been developed, demonstrating the first use of an α,β-unsaturated acyl ammonium intermediate in isothiourea organocatalysis. Screening of dinucleophiles demonstrated that 1,3-diphenyl-1,3-dipropanone afforded
comparable yields in our process to those reported by the groups of You\textsuperscript{72} and Xiaou\textsuperscript{71}.

Advantages of the isothiourea-catalysed system include the use of bench-stable, easily accessible starting materials. Increased enantioselectivity for electron-donating aryl groups is also obtained, alongside significantly better yields for alkyl substrates compared with NHC catalysis. The scope of the reaction has also been expanded with the first reports of electron-withdrawing aryl substituents and heterocycles in the reaction.

A variety of aryldiketones were successful in the reaction and the first successful use of electron-poor and heteroarene containing diketones was demonstrated. Ethyl benzoylacetate had also not been previously employed as a nucleophile in Michael addition-lactonisations with \( \alpha,\beta \)-unsaturated carbonyl species and was successful using a range of anhydrides with a selection of lactones being isolated in moderate to good yields and high enantioselectivity.

\( \alpha,\beta \)-Unsaturated acyl ammonium intermediate 202 was isolated by addition of HBTM 2.1 to cinnamoyl chloride. The acyl ammonium species was then successfully used as a precatalyst in the process which is consistent with the postulated mechanism. It was also possible to analyse the isolated \( \alpha,\beta \)-unsaturated acyl ammonium salt by X-ray crystallography. Assuming that the shape of the intermediate is similar in solid and solution phases, the configuration of the intermediate is consistent with our predicted stereochemical model.
3. Benzazoles as Nucleophiles

3.1 Introduction

3.1.1 Benzazoles in medicinal chemistry

The synthesis of benzazole-containing compounds is of high synthetic interest, primarily due to their biological activity. A search of PubChem, a database of molecules and their biological activities run by the National Centre for Biotechnology Information (a subsidiary of the National Institute of Health) in the USA, revealed 4,055 biologically active compounds containing a benzoxazole moiety (211), 10,323 containing benzothiazole (212) and 20,709 containing benzimidazole (213).\(^{31}\)

![Figure 17: Structures of benzazoles](image)

The medicinal uses of benzazoles have been the subject of several recent reviews which highlight the hugely diverse range of bioactivities displayed by these compounds. Benzothiazole, benzimidazole and benzoxazole-containing compounds are effective in a range of therapeutic treatments and have displayed impressive anti-bacterial, anti-fungal, anti-parasitic and anti-cancer properties. Due to their wide-ranging modes of action they are of great interest to medicinal chemists. This in turn makes them attractive targets for the development of, and incorporation into, new chemical methodologies.

3.1.2 Benzazoles in conjugate addition processes

A potentially versatile way of installing benzazoles is by conjugate addition of acyl benzazoles to Michael acceptors. Acyl benzazole nucleophiles have recently been shown by Lam et al. to be competent nucleophiles in a nickel-catalysed enantioselective Michael addition to nitroalkenes.\(^96\) The products were achieved in high yields, moderate to excellent dr and good enantioselectivity (Scheme 60).

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\(^{31}\) Search methodology: Structure search → substructure → input the relevant heterocycle → filters: bioactivity: active
Building upon work from Liso et al. that found that acyl benzazole can add to allyl malonates, Pittman Jr. et al. reported that acyl benzothiazole and benzoxazole nucleophiles undergo 1,4-addition to \( \alpha,\beta \)-alkynyl ester 219 (Scheme 61), generating intermediate diesters 220 which readily underwent *in situ* intramolecular cyclisation and double bond isomerisation to generate novel lactams 221 and 222 in good yields.  

To date, conjugate additions of acyl benzazoles remains an underexplored reaction. Development of new conjugate additions with this class of nucleophile is therefore of interest to install benzazole groups in novel, efficient and potentially enantioselective methodologies. This could, in turn, allow access to new molecular architectures for medicinal chemistry.

### 3.1.3 Project aims

With the aim to expand the scope of our isothiourea-catalysed Michael addition-cyclisation methodology beyond the use of 1,3-dicarbonyl nucleophiles (Chapter 2), we decided to investigate the nucleophilic addition of acyl benzazoles to \( \alpha,\beta \)-unsaturated acyl ammonium intermediates. The two processes reported by Lam and Pittman Jr. provide good precedent for benzazoles to act as competent Michael donors, suggesting that they may participate in isothiourea-catalysed Michael addition processes.
A potential complication of the targeted Michael addition-cyclisation is the regioselectivity of the cyclisation step (Scheme 62). We propose that 1,4-addition of nucleophile 223 to α,β-unsaturated acyl ammonium intermediate 224 would generate intermediate 225, which may promote catalyst turnover through both N- and O-cyclisation affording lactam 226a or lactone 226b. Both products are interesting and novel heterocycle-containing molecular classes, and we aimed to develop reaction conditions to promote selective formation of either of the heterocyclic cores. To investigate the postulated regiodivergence we proposed to synthesise a variety of benzazole nucleophiles, changing both the electronic properties of the acyl and heterocyclic moieties, then use them in conjunction with α,β-unsaturated acyl ammonium intermediates to form a range of heterocyclic products in good enantioselectivity.

Scheme 62: Potential regiodivergence in the Michael addition-cyclisation process

### 3.2 2-Phenacylbenzothiazole: Initial Screening and Scope

#### 3.2.1 Regioisomer formation and identification

2-Phenacylbenzothiazole (227) was employed in a model reaction (Scheme 63) utilising related conditions to those developed for 1,3-dicarbonyl nucleophiles (as discussed in Chapter 2). Homooanhydride 149 (1.4 equivalents) was dissolved in CH₂Cl₂ at 0 °C, then nucleophile 227, base and catalyst (HBTM 2.1, 5 mol%) were added and the flask stirred at 0 °C to room temperature overnight. It was possible to use NEt(Pr)₂ as base instead of the more expensive PS-BEMP without losing reactivity at low catalyst loadings. Two regioisomers (228a and 228b) were identified, which were distinguishable in the crude ¹H NMR spectrum. The regioisomeric ratio was measured by ¹H NMR as 88:12, and the isomers were readily separated by column chromatography although only a small quantity of the minor isomer was isolated.
The identity of the two isomers was determined by $^{13}$C ($^1$H) NMR spectroscopy (Figure 18). Whilst the lactone and lactam $^{13}$C signals have similar chemical shifts (166.6 and 167.9 ppm), a characteristic ketone signal (191.2 ppm) could be confidently assigned in the spectrum of the major isomer (228a). This signal is absent in the spectrum of the minor isomer 228b therefore it was reasoned that lactamisation must be the major cyclisation pathway.

Further evidence for the structure of 228a was gained by X-ray crystallographic analysis (Figure 19), which clearly shows the novel tricyclic heterocycle structure. It is interesting to note that the observed O→S distance in the crystal structure is 2.574 Å, significantly shorter than the Van der Waals’ radii (4.144 Å). This is consistent with our previous observations of an attractive O→S interaction in the acyl ammonium intermediate, and provides further evidence of its ubiquity where oxygen and sulfur exist in a 1,5-relationship.
During sample preparation an enantioenriched sample of the major isomer 228a separated into racemic crystals and enantiopure non-crystalline material. The crystals obtained provide good evidence of the formation of N-cyclised lactam 228a but as it was not possible to access suitable crystals of enantiopure material we were unable to prove the absolute stereochemistry. The absolute configuration of the products has therefore been assumed to be analogous to previous work (Section 2.2.5).

### 3.2.2 Isothiourea screening

Initial reaction screening using isothiourea HBTM 2.1 53 afforded N-cyclised product 228a in moderate enantioselectivity (64% ee). Alternative isothiourea catalysts were tested to see if increased selectivity could be achieved (Table 7), however both tetramisole (TM 50) and benzotetramisole (BTM 51) displayed poor conversion, lower regioselectivity and reduced enantioselectivity. This is consistent with results obtained with dicarbonyl nucleophiles (Section 2.2.2).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Regioisomeric ratio (228a:228b)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHPB 144</td>
<td>92 : 8</td>
<td>82</td>
<td>-</td>
</tr>
<tr>
<td>HBTM 2.1</td>
<td>92 : 8</td>
<td>75</td>
<td>64</td>
</tr>
<tr>
<td>TM 50</td>
<td>78 : 22</td>
<td>-</td>
<td>40&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BTM 51</td>
<td>88 : 12</td>
<td>-</td>
<td>45&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Table 7: Catalyst screening<sup>a</sup>major regioisomer 228a, <sup>b</sup>samples obtained by preparative TLC

### 3.2.3 Solvent and temperature effects

A solvent screen was then carried out, and showed that the reaction did not require anhydrous solvents and proceeded well in all bench solvents tested including acetone and THF (Table 8). Chlorinated solvents afforded the lowest ee although the reason for this is unknown. Test reactions indicated that no significant background reaction was taking place, suggesting that an alternative solvation effect is responsible. A maximum ee of 84% was achieved in THF with a small drop in regioselectivity from 92:8 (CH<sub>2</sub>Cl<sub>2</sub>) to 89:11...
(THF). The rr could not be improved by reaction dilution or cooling the reaction to -78 °C therefore bench grade THF/0 °C were chosen as the optimum reaction conditions.

### Table 8: Solvent and temperature screening

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Regioisomeric ratio (228a:228b)</th>
<th>Yield (%) (0 °C)</th>
<th>ee (%) (0 °C)</th>
<th>ee (%) (-78 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH2Cl2</td>
<td>92 : 8</td>
<td>75</td>
<td>64</td>
<td>66[b]</td>
</tr>
<tr>
<td>THF</td>
<td>89 : 11</td>
<td>87</td>
<td>84</td>
<td>84[b]</td>
</tr>
<tr>
<td>Acetone</td>
<td>85 : 15</td>
<td>-</td>
<td>82[b]</td>
<td>81[b]</td>
</tr>
<tr>
<td>Toluene</td>
<td>89 : 11</td>
<td>-</td>
<td>82[b]</td>
<td>81[b]</td>
</tr>
<tr>
<td>EtOAc</td>
<td>88 : 12</td>
<td>-</td>
<td>81[b]</td>
<td>82[b]</td>
</tr>
<tr>
<td>Et2O</td>
<td>93 : 7</td>
<td>-</td>
<td>81[b]</td>
<td>80[b]</td>
</tr>
<tr>
<td>1,4-dioxane</td>
<td>88 : 12</td>
<td>-</td>
<td>77[b]</td>
<td>-</td>
</tr>
<tr>
<td>MeCN</td>
<td>90 : 10</td>
<td>-</td>
<td>73[b]</td>
<td>-</td>
</tr>
<tr>
<td>CHCl3</td>
<td>95 : 5</td>
<td>-</td>
<td>53[b]</td>
<td>-</td>
</tr>
</tbody>
</table>

[a]major regioisomer 228a, [b]sample obtained via preparative TLC

### 3.2.4 Recrystallisation

The racemic form of the major regioisomer (228a) was significantly more crystalline than the enantiopure form, and we were able to exploit this effect to enhance the product ee (Table 9). After product isolation the ee of 228a was 83%. Upon recrystallisation from ethyl acetate the racemic form crystallised preferentially, giving a solid on filtration with 5% ee. Concentrating the liquors gave 228a as a solid with 97% ee. The increased crystallinity of the racemic material is further demonstrated by a significant difference in the melting points of the two samples, the racemic sample melting at 192-194 °C and the enantiopure at 168-171 °C.
3. Benzazoles as Nucleophiles

<table>
<thead>
<tr>
<th>Sample</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>mp (˚C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>228a No recrystallisation</td>
<td>78</td>
<td>83</td>
<td>-</td>
</tr>
<tr>
<td>228a Recrystallisation solid</td>
<td>8</td>
<td>5</td>
<td>192-194</td>
</tr>
<tr>
<td>228a Recrystallisation filtrate</td>
<td>67</td>
<td>96</td>
<td>168-171</td>
</tr>
<tr>
<td>228b No recrystallisation</td>
<td>12</td>
<td>90</td>
<td>178 (dec)</td>
</tr>
</tbody>
</table>

Table 9: Enhancement of ee by recrystallisation

3.2.5 Anhydride scope

Following the determination of the optimum reaction conditions the scope of the reaction with respect to 2-phenacylbenzothiazole was investigated. We wanted to investigate both steric and electronic effects by testing a variety of aryl and alkyl α,β-unsaturated anhydrides. A wide range of cheap, commercially available carboxylic acids are available as anhydride precursors, but to further widen the scope a number of non-commercially available acids were synthesised via a Knoevenagel condensation between malonic acid 229 and aryl aldehydes, affording acids 230-233 in good yields without the need for chromatographic purification (Scheme 64).

When mesitaldehyde (234) was subjected to the same reaction conditions however, the only product formed was non-decarboxylated product 235 (Table 10) with a conversion of 89% as measured by 1H NMR. Increasing the temperature (to facilitate decarboxylation) saw low conversion (10%) to decarboxylated acid 236, suggesting that the reaction conditions favour starting materials at elevated temperature.
An alternative synthetic route to 236 from Aitken et al. was employed, condensing mesitaldehyde 234 with ethyl acetate in a sodium metal mediated aldol reaction (Scheme 4) that afforded mesitylcinnamic acid 236 in a moderate 52% yield over the two steps.

With these acids in hand, the corresponding homoanhydrides were prepared via EDCI coupling. The scope of the reaction was then investigated under the previously optimised conditions (Scheme 67). The products were isolated by column chromatography, and in most cases the regioisomers were readily separated. In the cases of 4-CF₃ substitution (238a/238b) and 2- or 3-Br substitution (240a/240b, 241a/241b) the regioisomers coeluted and could not be separated. For these examples the crude rr (determined by ¹H NMR) and the regioisomeric mixture obtained after purification do not necessarily match due to the minor O-cyclised isomer being more sensitive to silica chromatography. In all of these cases, the regioisomeric mixture could be fully separated by chiral HPLC so ee values could be calculated for each regioisomer.
3. Benzazoles as Nucleophiles

Use of an electron withdrawing group led to a slight reduction in the regioselectivity but regioisomers 238a/238b were obtained in good yield and enantioselectivity. 4-methoxy substitution was also tolerated and gave 239a/239b in moderate yields. 2-Bromocinnamic anhydride led to a moderate yield, possibly due to reduced reactivity of the sterically bulky Michael-acceptor. Unusually, 2-bromo minor isomer 240b was formed in significantly lower ee (31%) than the corresponding major regioisomer 240a, and the reason for this is not currently understood (for further discussion see Sections 3.4.2-3.4.5). Mesitylcinnamic anhydride was inactive in the process and it is thought that double ortho-substitution provides too much steric blocking for nucleophilic addition to take place. Pleasingly, 3-bromo-substitution gave good yields and enantioselectivity for both regioisomers 241a/241b.

The reaction scope was extended to incorporate heterocyclic substituents (Scheme 67), which were successful however 3-furyl and thiophenyl substitution gave reduced yields of 243a/243b and 244a/244b in comparison to aryl substituents. In these cases, the crude $^1$H NMR spectra were complex and it is thought that poor yields are due to both reduced reactivity and increased byproduct formation leading to problematic purification. Alkyl
substitution was well tolerated and did not lead to a drop in enantioselectivity (which was observed in reactions with 1,3-diketone nucleophiles, see Chapter 2). Ester substitution products 246a/246b were successfully formed however were isolated in low ee.

Scheme 67: Reaction scope with 2-phenacyl benzothiazole

3.3 Exploring Regioselectivity Effects

3.3.1 Influencing regioselectivity

To probe the nature of regioselectivity in the Michael addition-cyclisation process a range of alternative nucleophiles were targeted. The first aim was to change the electronic properties of the acyl group to investigate the relationship between nucleophile structure and regioselectivity. It was reasoned that conjugated ester and amide groups may disfavour O-cyclisation to give single regioisomers similar to the observations made with diketone and ketoester nucleophiles (Figure 20). Conversely, it was hoped that an electron poor acyl group may increase the proportion of O-cyclisation.

Figure 20: Regioselectivity for benzothiazole and dicarbonyl nucleophiles
We were also interested in the effects of changing the heterocycle from benzothiazole to benzoxazole and benzimidazole (Figure 21). In the case of benzothiazole we propose that O-cyclisation is disfavoured due to the presence of an O→S interaction between the heterocycle and the acyl group which must be broken to allow O-cyclisation. In contrast, benzoxazole and benzimidazole nucleophiles do not form O→S interactions which could significantly change the relative energies of the cyclisation pathways and thus alter the regioselectivity of the process.

![Diagram showing cyclisation pathways for benzothiazole and benzoxazole/ benzimidazole nucleophiles.](image)

**Figure 21: Regioselectivity for benzothiazole and dicarbonyl nucleophiles**

### 3.3.2 Nucleophile synthesis

Initial work towards the synthesis of 2-phenacylbenzothiazole (227) concentrated on a reported Claisen condensation between 2-methylbenzothiazole (247) and ethyl benzoate (248) using n-butyl lithium as the base.\(^{100}\) The reaction was carefully repeated a number of times, however the reaction was capricious: it failed approximately half the time and the reason for this is unknown. It is thought that the deprotonation step was successful each time since a marked colour change from pale yellow to dark brown was observed. When successful, the yield of the reaction ranged between 22 and 60%, and when unsuccessful only starting material was returned. The use of 2-methylbenzimidazole in this condensation afforded 249 in a moderate 36% yield, but methylbenzoxazole did not produce the desired product 250, with predominantly starting material returned.

![Scheme 68: Synthesis of nucleophiles via Claisen condensation](image)
Lozinskii et al. reported that nucleophilic addition of dimethylbenzimidazole 251 into benzoyl chloride 252 was successful, using triethylamine as a mild base (Scheme 69).\textsuperscript{101} The reaction initially forms a double addition ester 253, which must be subsequently hydrolysed to afford the desired acylbenzazole 249.

![Scheme 69: Synthesis of nucleophiles via an ester formation-hydrolysis strategy](image)

Using this strategy, 2-phenacyl benzimidazole 254, benzothiazole 227 and benzoxazole 250 were synthesised in moderate yields (Figure 22). Benzoxazole 250 was formed by room temperature hydrolysis in MeOH/KOH due to product instability at higher temperatures. In contrast it was necessary to carry out the hydrolysis into 255 in a 1:1 mixture of n-butanol and DMF at reflux overnight due to low ester solubility.

![Figure 22: Benzazole yields for the ester formation-hydrolysis strategy](image)

An alternative strategy was to switch the nucleophile/electrophile roles of the heterocycle and acyl partner in a simple NaHMDS mediated coupling reported to achieve a wide range of products in good yields.\textsuperscript{102} This route generated amide and ester substituted benzothiazoles 256 and 257 in very good yields (Scheme 70). Attempts to use this method to install electron withdrawing aryl groups have however been unsuccessful, with 4-fluoroacetophenone returning only unreacted starting materials and 4-nitroacetophenone decomposing upon addition of NaHMDS. Problems of double nucleophilic addition were encountered in the addition to 2-chlorobenzoxazole. Alongside the desired amide 258 a large quantity of 259 was formed leading to very difficult chromatographic separation. To reduce the formation of the double addition product reagent addition order, reaction temperature, and dilution were investigated. The best way to minimise double addition was through slow dropwise addition of the chlorinated heterocycle at -78 °C. This improved the ratio of single to double addition products from 0.8 : 1 to 2.5 : 1, which enabled some separation by chromatography leading to a 258 in a moderate yield of 34%.
3. Benzazoles as Nucleophiles

In summary, a range of benzothiazole nucleophiles incorporating a range of electron donating and withdrawing acyl groups, as well as benzoazole and benzimidazole-containing nucleophiles, has been successfully synthesised (Table 11).

<table>
<thead>
<tr>
<th>X</th>
<th>R</th>
<th>Product</th>
<th>Method</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Ph</td>
<td>227</td>
<td>B</td>
<td>51</td>
</tr>
<tr>
<td>S</td>
<td>PhNO₂</td>
<td>255</td>
<td>A</td>
<td>78</td>
</tr>
<tr>
<td>S</td>
<td>NMe₂</td>
<td>256</td>
<td>B</td>
<td>99</td>
</tr>
<tr>
<td>S</td>
<td>O'Bu</td>
<td>257</td>
<td>B</td>
<td>88</td>
</tr>
<tr>
<td>O</td>
<td>Ph</td>
<td>250</td>
<td>A</td>
<td>67</td>
</tr>
<tr>
<td>O</td>
<td>NMe₂</td>
<td>258</td>
<td>B</td>
<td>34</td>
</tr>
<tr>
<td>NH</td>
<td>Ph</td>
<td>254</td>
<td>A</td>
<td>65</td>
</tr>
<tr>
<td>NMe</td>
<td>Ph</td>
<td>249</td>
<td>A</td>
<td>55</td>
</tr>
</tbody>
</table>

Table 11: Summary of synthetic methods used to generate benzazole nucleophiles

3.3.3 Nucleophile effects on annulation regioselectivity

With a range of benzazole nucleophiles in hand, tests were carried out to determine their reactivity and regioselectivity in annulation processes with cinnamic anhydride using the previously optimised conditions. Firstly we investigated the effects of changing the acyl group on the benzothiazole-containing nucleophile (Scheme 71). Azaarylamide 256 and azaarylester 257 afforded N-cyclised products 260 and 261 regioselectively and in good yields, which is consistent with our observations using ketoester nucleophiles. We believe
that conjugated acyl groups disfavour the formation of the lactonisation intermediate (as conjugation must be broken), thus reducing O-cyclisation. It is also possible that the increased donor capabilities of the ester and amide groups could increase the strength of the O→S interaction in the precyclisation intermediate, further stabilising the lactamisation intermediate and potentially enhancing the regioselectivity. In comparison, 4-nitrophenacylbenzothiazole 255 led to the formation of 262a/262b with a greater proportion of O-cyclisation (75:25 rr) compared with the parent phenyl substituted nucleophile (88:12 rr). The electron withdrawing acyl group could lower the energy of the lactonisation intermediate by providing additional charge stabilisation, thus increasing the proportion of O-cyclisation.

We then investigated the effects of changing the heterocycle moiety. Interestingly 2-phenacylbenzoxazole 250 gave a complete switch in regioselectivity compared with benzothiazole, with almost exclusively O-cyclised product 263 observed. It was not possible to force benzoxazole N-cyclisation by the use of benzoxazole-amide nucleophile 258 (only starting materials were returned).
Initial investigations into benzimidazole reactivity showed that 2-phenacylbenzimidazole 254 showed good activity, forming a 1:1 mixture of two products that could not be separated by chromatography. Mass spectrometry analysis of the mixture identified a single product mass which suggests a mixture of regioisomers or tautomers. $^1$H NMR analysis (Figure 23) shows two spin systems: spin system A can be attributed to product 265c, a tautomeric form of N-cyclised product 265b. Spin system B is likely to be either 265a or 265b, however it has not been possible to confidently assign spin system B as the NMR spectra could not be sufficiently separated for conclusive analysis.
To simplify the NMR spectra for further analysis the reaction was repeated with crotonic anhydride (Scheme 74). In this case 266 was isolated as an 80:20 mixture of regioisomers (which could be confidently assigned by $^1$H and $^{13}$C NMR), with N-cyclised isomer 266 formed in 4:1 dr. The major diastereomer was confirmed by NOE analysis. Due to the complex mixture it was not possible to measure the enantioselectivity of the process due to poor separation of the 6 peaks in the chiral HPLC spectrum.

Attempts to use protected benzimidazoles in this reaction proved unsuccessful (Scheme 75) and this is possibly because the resulting lactams 267/268 cannot tautomerise to the preferred product configuration (cf. tautomer 266).

**3.3.4 Reaction scope: benzamide**

The scope of the reaction utilising azaaryl amide 256 was further investigated, since selection of this nucleophile in the annulation process allows for regioselective formation of N-cyclised products (Scheme 76). Unlike the phenacylbenzothiazole series (Scheme 67) recrystallisation was not required to enhance the ee as all products were formed in excellent enantioselectivity. Furthermore no O-cyclisation was observed in any of the reaction mixtures. Electron-withdrawing substitution was successful and afforded 269 in good yield and high ee, whilst 4-methoxy substitution (270) led to a moderate drop in yield due to lower reactivity of electron rich Michael acceptors. 2- and 3-bromo substitution was well tolerated with a lower yield observed for 2-substitution, possibly due to increased steric hindrance. 2-Furyl substituted 273 was accessed in a good yield but the introduction of 3-
furyl and 3-thiophenyl groups led to reduced yields of 274 and 275. As observed in the phenacyl benzothiazole series this is thought to be due to a combination of lower reactivity and difficult purification. Methyl substitution was successful in the reaction, giving a small drop in enantioselectivity. Pleasingly, product 277 containing an ester moiety was obtained in good yield and high ee.

Scheme 76: Reaction scope with azaaryl amide, anhydride screening

### 3.3.5 Reaction scope: benzoxazole

To further investigate the scope of this reaction, 2-phenacylbenzoxazole was explored as a nucleophile under the optimised conditions (Scheme 77). Use of this heterocycle affords O-cyclisation in excellent selectivity, with only a small amount of the N-cyclised product visible in the crude $^1$H NMR spectrum (typically ≤ 3%); in each case the minor regioisomer was not isolated by column chromatography. The use of an electron withdrawing aryl group on the homoanhydride gave reduced yields, whereas 4-methoxy substitution gave 279 in good yield. This is the reverse of the trend observed for N-cyclisation. 2-Bromo substitution was not tolerated and returned starting materials, this is possibly due to steric hindrance being too high for addition of benzoxazole nucleophile 250. 3-Bromo
3. Benzazoles as Nucleophiles

substitution however worked well in the process and 280 was isolated in good yield and excellent enantioselectivity. As has been observed with other nucleophiles 2-furyl substitution was well tolerated however 3-furyl and thiophenyl groups give reduced yield. Lactone 282 was isolated in a particularly low yield and this is thought to be partly a problem in the isolation of the product. Use of fumarate anhydride demonstrated reduced enantio- and regioselectivity with 285a/285b isolated as an inseparable mixture of regioisomers in modest ee. This is the only example where significant amounts of N-cyclisation was observed for the benzoxazole series.

Scheme 77: Reaction scope with 2-phenacyl benzoxazole, anhydride screening [a]regioisomeric ratios calculated from crude 1H NMR spectrum

3.4 Mechanistic understanding of regioselectivity

3.4.1 Proposed mechanism

The proposed mechanism (Scheme 78) is modelled closely on the mechanism discussed in Chapter 2. We believe that pre-cyclisation intermediates 288a and/or 288b (conformers of one another) are generated via nucleophilic addition into α,β-unsaturated acyl ammonium species 286 followed by proton transfer. It is thought that the regioselectivity of the process is related to the relative energies of the lactamisation and lactonisation pathways.
In the benzothiazole case, an oxygen to sulfur interaction was observed in the X-ray crystal structures for both the $\alpha,\beta$-unsaturated acyl ammonium intermediate 202 and the $N$-cyclised product 228a, with reduced atom distances compared with the Van der Waals’ radii (Scheme 79). We therefore propose that a similar interaction is present in intermediates 289 and 290a. This could provide additional stabilisation to $N$-cyclisation intermediate 290a compared to $O$-cyclisation intermediate 290b for benzothiazole-containing nucleophiles.
3. Benzazoles as Nucleophiles

3.4.2 Computational studies

To probe these proposals computational studies have been carried out examining the nature of the two cyclisation pathways in collaboration with the Cheong group at Oregon State University. In the determination of the intermediates along the cyclisation pathways conformational searches were carried out manually and exhaustively, with calculations implemented in Gaussian09. It was found that the O→S interactions postulated in Scheme 79 are observed and provide a significant 4-5 kcal mol\(^{-1}\) stabilisation energy; it is proposed that these interactions are maintained throughout the cyclisation pathways. The pre-cyclisation intermediate for O-cyclisation (Figure 24) shows a 2.0 kcal mol\(^{-1}\) preference for nucleophilic addition anti- to the stereodirecting groups. This suggests that the stereodirecting groups provide efficient steric blocking for both Michael addition and lactonisation steps in this case.

![Figure 24: anti-conformation of O-cyclisation (benzothiazole)](image)

\[ \Delta G^\ddagger = 10.7 (\Delta \Delta G^\ddagger = 0.0) \]

Surprisingly in the N-cyclisation pathway the expected nucleophilic attack anti- to the catalyst stereodirecting groups is higher in energy than syn-addition (1.5 kcal mol\(^{-1}\) difference, Figure 25). The calculated syn-lactamisation intermediate appears to be additionally stabilised by a π-stacking interaction between the benzothiazole ring and the phenyl substituent on the catalyst. Interestingly anti-lactamisation is 0.4 kcal mol\(^{-1}\) higher in energy than anti-lactonisation. This suggests that there may be other stabilising interactions at play in the O-cyclisation mechanism.

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\(^{\text{xii}}\) All computational work carried out by Daniel Walden

\(^{\text{xiii}}\) Diagrams provided by Daniel Walden
3. Benzazoles as Nucleophiles

The partial reaction coordinate was also calculated (Figure 26) and showed that lactonisation proceeds via a stepwise mechanism, with formation of a tetrahedral intermediate prior to catalyst release. For the lactamisation pathway however no tetrahedral intermediate could be located and it is therefore thought that it proceeds via a concerted asynchronous transition state.

The N-cyclised product was calculated to be both the kinetic and thermodynamic product. Not only is the cyclisation pathway lower in energy than the corresponding lactonisation mechanism, but the final lactam product is additionally stabilised both by an O→S interaction and a non-classical hydrogen bond between the lactam carbonyl group and the adjacent aryl ring. Pleasingly, the interatomic distances predicted computationally closely match those measured in the lactam crystal structure (Figure 27).

Diagrams provided by Daniel Walden
Using all the computed parameters it was possible to calculate a predicted $\text{rr}$ for the process of 87:13. This directly matches the experimental results (88:12 $\text{rr}$, Scheme 80).

The calculations were repeated for the same annulation process with 2-phenacyl benzoxazole as the nucleophile. It was hoped that this would give insight into the reasons for the complete switch in regioselectivity using this heterocycle. Experimentally, almost exclusive $O$-cyclisation is observed for this nucleophile. The lowest energy pre-cyclisation intermediate found was an $anti$-lactonisation intermediate (Figure 28), which is consistent with our experimental results. The transition state conformation closely resembles that of $O$-cyclisation using the benzothiazole nucleophile (Figure 24) but it is 3.6 kcalmol$^{-1}$ lower in energy.

---

**Figure 27:** Conformation of $N$-cyclised lactam and stabilising interactions displayed in A: computed structure and B: X-ray structure of 228a$^{**}$

**Figure 28:** $anti$- conformation of $O$-cyclisation (benzothiazole)$^{**}$

$^{**}$ Diagrams provided by Daniel Walden
In the benzoazoxole case, \textit{N}-cyclisation \textit{syn}- to the stereodirecting groups proved significantly higher in energy than \textit{anti}-addition (Figure 29). Nucleophilic attack \textit{anti}- to the stereodirecting groups appears to place the heterocyclic ring in a flat conformation orthogonal to the carbonyl group. This is in contrast to the benzothiazole case which had a more flattened angle of attack, and is 0.8 kcal mol\(^{-1}\) higher in energy despite additional stabilisation from an O\(\rightarrow\)S interaction (Figure 25).

Calculation of the partial reaction coordinate for benzoxazole cyclisation showed that both lactonisation and lactamisation proceed via stepwise mechanisms, with tetrahedral intermediates identified for each pathway. The lactam is both the kinetic and thermodynamic product, with the \textit{O}-cyclisation pathway lower in energy than \textit{N}-cyclisation for all identified intermediates.

From these calculated transition state energies the computed \textit{rr} for the benzoazoxole annulation process is close to 99:1, which is consistent with the experimental results (Scheme 81).

\textsuperscript{xvi} Diagrams provided by Daniel Walden
3. Benzazoles as Nucleophiles

Scheme 81: Comparison of experimental and computed regioisomeric ratios (benzoxazole)

3.4.2 Link between regioisomerism and enantioselectivity

During the investigation into the reaction scope, several unusual results were observed: regioisomeric pairs 262a/262b and 240a/240b were obtained in significantly different ee (Scheme 82). This was unexpected because it is thought that the two regioisomers are generated from common intermediate 295 in which the stereocentre configuration has already been set.

Scheme 82: Different ee for regioisomeric pairs \( \text{ene} \) measured from mixture of regioisomers

To investigate this effect, mechanistic studies were carried out using 4-nitro substituted regioisomers 262a/262b as they were separable by chromatography. It was hoped that useful information about the link between enantioselectivity and regioselectivity might be gained by carrying out ring-opening of products 262a/b followed by recyclisation of acid 292 to see if any change in enantioselectivity occurs (Figure 31 (a)). A crossover experiment in the presence of an external nucleophile should also give information about any reversibility in the process (Figure 31 (b)).
Racemic acid (±)-292 was synthesised via gram-scale organocatalytic formation of the two regioisomers 262a and 262b using (±)-HBTM 2.1 as the catalyst, followed by in situ methanolysis to form methyl ester 293. The addition of DMAP was essential to ring open the N-cyclised regioisomer whereas the O-cyclised isomer ring-opened more readily. Ester hydrolysis under basic conditions led to decomposition, but heating ester 293 in concentrated HCl afforded acid (±)-292 in a 70% yield over three steps on gram-scale (Scheme 83). Enantioenriched acid was synthesised in the same way in an 83% overall yield. The acid could not be separated by chiral HPLC but the enantioenriched ester 293 was found to have an 83:17 er. For these investigations er rather than ee is reported in order to give a clearer picture of any change in the enantiomeric ratios during recyclication.

3.4.3 Direct recyclication

Racemic acid 292 was recycliced via in situ activation by pivaloyl chloride followed by deprotonation with NEt(iPr)2 and cyclisation with a variety of isothiourea catalysts (Table 12). The regioisomeric ratio was measured by 1H NMR analysis and the ee of the major
isomer measured by chiral HPLC after isolation by chromatography. The ee of the minor isomers could not be measured due to significant product degradation. With no catalyst present the major N-cyclised product 262a is formed racemically with a higher N- to O-cyclisation ratio than in the catalysed reaction. In the presence of (2S,3R)-HBTM 2.1, however, we were excited to observe that non-zero ee could be achieved by cyclising racemic acid (±)-292 under asymmetric catalysis. Cyclisation resulted in 42% ee for major regioisomer 262a with a greater proportion of O-cyclisation (Table 13).

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Starting material configuration</th>
<th>Catalyst</th>
<th>( r_{bb}^{(b)} ) (262a:262b)</th>
<th>er (262a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1 dr, 50:50 er(^{(a)})</td>
<td>–</td>
<td>96:4</td>
<td>51:49</td>
</tr>
<tr>
<td>2:1 dr, 50:50 er(^{(a)})</td>
<td>(2S,3R)-HBTM 2.1</td>
<td>85:15</td>
<td>71:29</td>
</tr>
</tbody>
</table>

Table 12: Recyclisation of racemic ring-opened acid \(^{(a)}\)Measured for methyl ester 293, \(^{(b)}\)calculated from the crude \(^1\)H NMR

The recyclisation process was repeated using an enantioenriched acid (Table 13). When cyclisation occurred in the absence of any catalyst it again generated 262a racemically. Enantiopure (2S,3R)-HBTM 2.1 formed N-cyclised product 262a in 90:10 er, and interestingly the same er was obtained using both (±)-HBTM 2.1 and achiral isothiourea DHPB.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Starting material configuration</th>
<th>Catalyst</th>
<th>( r_{bb}^{(b)} ) (262a:262b)</th>
<th>er (262a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1 dr, 83:17 er(^{(a)})</td>
<td>–</td>
<td>71:29</td>
<td>49:51</td>
</tr>
<tr>
<td>2:1 dr, 83:17 er(^{(a)})</td>
<td>(2S,3R)-HBTM 2.1</td>
<td>80:20</td>
<td>90:10</td>
</tr>
<tr>
<td>2:1 dr, 83:17 er(^{(a)})</td>
<td>(±)-HBTM 2.1</td>
<td>75:25</td>
<td>91:9</td>
</tr>
<tr>
<td>2:1 dr, 83:17 er(^{(a)})</td>
<td>DHPB</td>
<td>79:21</td>
<td>90:10</td>
</tr>
</tbody>
</table>

Table 13: Recyclisation of enantioenriched ring-opened acid \(^{(a)}\)Measured for methyl ester 293, \(^{(b)}\)calculated from the crude \(^1\)H NMR
Based upon the recyclisation of enantioenriched acid (3S)-292, we have proposed a mechanism for the observed results (Scheme 84). In the non-catalysed case racemisation could be achieved by a slow rate of cyclisation combined with a relatively fast rate of retro-Michael addition. This leads to erosion of the er before cyclisation takes place, giving the cyclised products in reduced er. Since a variety of Lewis base catalyst (racemic, asymmetric and achiral) gave the same result of retention of er from starting material to cyclised product, we can postulate that the cyclisation rate is now fast with all catalysts tested. The retro-Michael is now relatively slow, and so does not have an opportunity to erode the er prior to cyclisation.

3.4.2 Recyclisation in the presence of an external nucleophile

A crossover experiment was carried out where racemic acid 292 was cyclised in the presence of external nucleophile 227 and (2S,3R)-HBTM 2.1 (53) (Scheme 85). This was undertaken to conclusively demonstrate whether the cyclisation exhibits reversibility. The only source of a cinnamic acid precursor is acid (±)-292 therefore any formation of crossover products 228a/228b must arise from reaction reversibility. We were interested in both the ratio and the er of the four potential products (which are distinguishable by 1H NMR spectroscopy).
Scheme 85: Recyclisation in the presence of an external nucleophile to show reversibility

![Scheme 85](image)

Analysis of the crude reaction mixture showed the presence of all four products (as labelled in Figure 32) suggesting that the reaction has a degree of reversibility. Assuming that all of acid 292 cyclised, the mixture of products contained a total of 12% crossover products 228a and 228b. It was possible to isolate 228a and 262a, the N-cyclised regioisomers for both nucleophiles and calculate the er for both species. Crossover lactam 228a was isolated in high er because the addition of the crossover nucleophile takes place under predominantly asymmetric catalytic control. 262a was isolated in low but non-racemic er, which is consistent with prior observations.

![Figure 32](image)
3. Benzazoles as Nucleophiles

3.4.5 Mechanistic implications of recyclisation investigations

This study has shown that recyclisation of a racemic acid under asymmetric catalysis leads to regioisomers of enhanced ee. It has also shown that the reaction is somewhat reversible and that cyclisation of the enantioenriched acid under asymmetric, racemic and achiral catalysis afforded products with the same enhanced ee. During these recyclisation experiments we directly accessed diastereomeric intermediates cis- and trans-294 (Scheme 86, with cis- and trans- referring to the relative configuration of the newly formed C-C bond to the catalyst stereodirecting groups) which are also accessed via nucleophilic addition of 255 to α,β-unsaturated acyl ammonium 202 followed by proton transfer.

Crossover experiments have shown that the nucleophilic addition is somewhat reversible ($k_1/k_1^\dagger$ and $k_2/k_2^\dagger$) therefore the ratio of intermediates cis-294 to trans-294 could change over time. Resubmission of the lactam and lactone products to the reaction conditions however did not lead to a change in the ee, suggesting that reversibility is not the sole cause of ee differences between the generated regioisomers. Also to consider is the possibility that the two diastereomeric intermediates cis- and trans-294 could cyclise at different rates: if $k_N \neq k'_N$ or $k_O \neq k'_O$ then different ratios of the four products would be obtained, giving a different er values for the major and minor regioisomers. Unfortunately due to the complex nature of the cyclisation mechanism it is not possible to say with certainty what the root causes are of the regioisomeric differences in ee.

Scheme 86: Reversibility and cyclisation rates affording $N$- and $O$-cyclised products
3. Benzazoles as Nucleophiles

3.5 Accessing Quaternary Centres

3.5.1 Anhydride synthesis

It was hoped that the strong reactivity of benzazole nucleophiles might enable an annulation process with trisubstituted anhydrides to access interesting heterocyclic molecules bearing quaternary centres. 3-Methylbut-2-enolic acid was commercially available and in order to extend our investigation further a range of non-commercially available acids were targeted. A Horner-Wadsworth-Emmons reaction with phosphonate 295 followed by ester hydrolysis generated acids 296 and 297 in moderate yields but unfortunately trifluoromethylated acid 298 could not be formed under a variety of Horner-Wadsworth-Emmons or Wittig protocols tested.\(^{105}\)

![Scheme 87: Synthesis of trisubstituted anhydrides](image)

An alternative procedure to form 298 was employed from Tarrant and Taylor,\(^ {106}\) which initially afforded β-hydroxy acid 300 upon condensation of 1,1,1-trifluoroacetone (299) with malonic acid (229) (Scheme 88). To dehydrate this intermediate it was necessary to heat hydroxyacid 300 in 50% aqueous sulfuric acid for 14 hours at 200 °C in distillation apparatus. As the unsaturated acid formed it was distilled across into a collecting flask, giving 298 as a colourless oil after aqueous extraction in 31% yield.

![Scheme 88: Condensation of trifluoroacetone with malonic acid](image)

Whilst the \((E)\)- and \((Z)\)- isomers of 298 were readily identifiable by \(^1\)H and \(^19\)F NMR the configuration of the major isomer could not be confirmed by standard NOESY spectra due to long-range \(CH \rightarrow CH_3\) coupling, which gave positive results for both isomers in the mixture. A heteronuclear-NOESY experiment was therefore carried out (HOESY, Figure...
3. Benzazoles as Nucleophiles

33). After irradiating a specific $^{19}$F frequency a $^1$H spectrum was immediately run. Enhancement of a $^1$H peak after $^{19}$F irradiation indicates that the proton and fluorine are close in space. After irradiation of the CF$_3$ group of the major isomer ($\delta_F$ -71.45 ppm) a $^1$H signal enhancement was observed for the $\alpha$-proton of the major isomer only. This NOE result therefore indicates that the major isomer has the (E)-configuration.

Geranic and neric acids ([(Z)-303 and (E)-303]) were also targeted because as (E/Z)-isomers of one another they could give information about the effects of (E/Z)-geometry on the isothiourea-catalysed annulation process. Initially it was hoped that geraniol ([(Z)-301]) and nerol ([(E)-301]) could be oxidised into the corresponding carboxylic acids using a Jones oxidation, however this resulted in (E/Z)-isomerisation. Instead, a two-step method was employed (Scheme 89) with manganese dioxide giving aldehydes ([(Z)-302] and (E)-302) in good yields followed by Pinnick oxidation to afford the carboxylic acids ([(Z)-303] and (E)-303). The (E/Z)-ratio was unchanged throughout the two step procedure.

![Scheme 89: Two-step oxidations of geraniol (Z)-301 and nerol (E)-301](image)

*Measured by $^1$H NMR analysis,*

*[^][b]Measured by GC analysis*
3. Benzazoles as Nucleophiles

3.5.2 Anhydride scope

An initial test reaction between 3-methylbut-2-enoiic anhydride (304) and 2-phenacylbenzothiazole 227 afforded achiral N-cyclised product 305 in good yield, with no observed O-cyclisation in the crude $^1$H NMR (Scheme 90). This is the first time that a quaternary centre has been accessed using our isothiourea-catalysed Michael addition-cyclisation protocol.

Scheme 90: Annulation process utilising dimethyl substituted anhydride

Unfortunately when a range of other anhydrides were tested no reactivity was observed (Scheme 91). Further screening with alternative benzazole nucleophiles was met with failure, and it is not understood why the process shows such a high degree of specificity.

Scheme 91: Unsuccessful trisubstituted anhydrides in annulation process

The use of trifluoromethylated anhydride 309 however successfully generated cyclised product 310 bearing a chiral, quartenary trifluoromethylated centre. Interestingly this is the only case yet investigated where a significant amount of 1,2-addition product was also observed. The 1,4- and 1,2-addition products (310 and 311) were isolated in a 7:3 mixture after column chromatography which could be subsequently separated by trituration with Et$_2$O to give 1,2-addition product 311 as a solid and 1,4-addition product 310 as a yellow oil upon concentration of the trituration liquors. Pleasingly, whilst 310 was isolated in a modest yield (28%) it was formed in excellent ee (96%).
3. Benzazoles as Nucleophiles

3.6 Product Derivatisations

In order to demonstrate the synthetic utility of the annulation products obtained by this isothiourea-catalysed methodology, derivatisation of brominated lactam 272 and lactone 280 was investigated. These compounds were successfully synthesised regioselectively on a gram-scale in excellent enantioselectivity using the previously optimised conditions (Figure 34). The 3-bromo substitution was thought to be a useful synthetic handle for palladium-catalysed coupling reactions, making them relevant to pharmaceutical screening protocols.

3.6.1 Suzuki couplings

The first coupling reaction investigated was a Suzuki coupling employing methoxyboronic acid 312 with palladium acetate as a catalyst (conditions from Martinez et al.). Initially, tri(o-tolyl)phosphine was used as the ligand (Table 14) however this afforded product 313 in only 44% yield. Switching to dppf increased the yield to 70% and it is thought that the increased bulk of the ligand improves the efficiency of reductive elimination.
### 3. Benzazoles as Nucleophiles

#### 3.6.2 Heck reactions

A Heck reaction was then attempted between lactam 272 and methyl acrylate 315, using conditions from Baccanari et al.\textsuperscript{109} Heating at 100 °C overnight in a sealed tube using acetonitrile as the solvent afforded product 316 in a 43% yield, with the rest of the mass returned as starting material. In order to increase reaction conversion the process was repeated in DMF and heated at 125 °C. This increased the yield to 89% (alongside 11% unreacted starting material). The enantioselectivity of 316 could not be measured \textit{via} chiral HPLC due to poor visualisation of the enantiomers. Despite many attempts, it was not
possible to obtain a reliable HPLC spectrum showing the desired peaks. It is assumed however that the Heck reaction is unlikely to have changed the enantioselectivity since the Suzuki coupling resulted in no erosion of enantioselectivity at high temperatures.

In the case of lactone 280 (Table 16) similar problems were encountered when heating the reaction at 100 °C in acetonitrile, with 66% starting material returned plus 33% of the desired coupled product 317a. When the reaction was repeated at 125 °C, N-cyclised regioisomer 317b was unexpectedly isolated in 11% yield. This suggests that the elevated temperature leads to process reversibility and allows access to the higher energy N-cyclisation pathway. Again, the products did not behave as expected on chiral HPLC and so no enantioselectivity has been measured.
3. Benzazoles as Nucleophiles

3.7 Conclusions

Nucleophiles containing benzazole heterocycles have been shown to be useful and interesting reagents in a Michael addition-cyclisation procedure proceeding via an \( \alpha,\beta \)-unsaturated acyl ammonium intermediate. A wide range of examples has been synthesised showing good reactivity with a range of alkyl, aryl and heterocyclic \( \alpha,\beta \)-unsaturated homoanhydrides. These nucleophiles could cyclise both through the carbonyl moiety and through the N-heterocycle, and it was possible to selectively form one regioisomer through judicious choice of nucleophile. Furthermore, it was possible to generate quaternary centres in high enantioselectivity.

The cyclisation mechanism was investigated and it is thought that regioselectivity relies on the relative energies of cyclisation pathways. Computational work showed that for benzothiazole substrates the pre-lactamisation intermediate was especially stabilised by retention of O→S interactions and by \( \pi-\pi \) stacking between the benzothiazole ring and the catalyst stereodirecting group. For benzoxazole species however, \( N- \) and \( O- \) cyclisation both proceed \textit{anti} to the stereodirecting groups with \( O- \) cyclisation calculated as being lower in energy. It is thought that relative cyclisation rates and reaction reversibility might be responsible for some of the regioisomeric pairs displaying different ee.

It was then shown that 3-bromosubstituted annulation products could be derivatised using pharmaceutically relevant palladium-catalysed coupling reactions. This was very successful for an \( N- \) cyclised product, but showed limited suitability for the \( O- \) cyclised lactone tested due to lactone instability. Given the medicinal interest in benzazole containing compounds,\(^{92-95}\) it is hoped that in the future it may be possible to submit our novel benzazole-containing compounds to biological testing, to ascertain if they have any useful bioactivity.
4. Cascades from α,β-Unsaturated Acyl Ammonium Intermediates

4.1 Lewis Base Catalysed Cascade Processes

Cascade reactions proceed via a sequence of chemical processes that generate several intermediates, each one more thermodynamically stable than the last, until a product is achieved that is stable to the reaction conditions. The use of cascades in natural product synthesis has long been considered a “gold standard” in the field, as complex product architectures can be elegantly and efficiently achieved. This in turn has driven the development of increasingly efficient and therefore economical synthetic methods for the production of target molecules for the pharmaceutical and fine chemicals industries.

Historically, the development of organocatalysis was driven by a desire to mimic the chemistry of enzyme catalysis using small molecules, and since many complex biosyntheses are facilitated by enzyme-catalysed cascade processes the development of cascade-promoting organocatalysis is of great interest to the synthetic community. Lewis base catalysis is a versatile way of achieving cascade reactions, with most published work exploiting the interconnected nature of enamine and iminium intermediates. This field has been recently been reviewed by Song and Wang, and representative examples of iminium and enamine initiated cascades will be shown here to demonstrate how chemical complexity is built from simple principles.

4.1.1 Iminium-initiated cascades

Nucleophilic addition reactions into an α,β-unsaturated iminium intermediate (323) can take advantage of the nucleophilicity of the resultant enamine (324) to carry out a second chemical process. This was first demonstrated by MacMillan et al. in an efficient γ-arylation, β-chlorination process (Scheme 93). The use of low temperature and EtOAc as solvent was important to achieve high stereoselectivity. A variety of aryl nucleophiles could be installed in this way, including furans, thiophenes and indoles.
Using this cascade design it is also possible to form cyclic substrates by reacting an imine intermediate with a tethered nucleophile-electrophile system. This has been exploited by Brenner-Moyer et al. in the formation of fused bicyclic products (328) from cyclic unsaturated β-dicarbonyl substrates 326 (Scheme 94).\textsuperscript{116,117} The reaction is believed to proceed via initial 1,4-addition of the malonate moiety into an iminium intermediate. The resultant enamine 327 undergoes a second 1,4-addition to afford ring closure, followed by hydrolysis to afford the products in high diastereo- and enantioselectivity.

MacMillan et al. demonstrated that iminium-iminium cascades were also viable catalytic pathways in the synthesis of complex molecular architectures (Scheme 95).\textsuperscript{113} Tetracycle 332 was formed in excellent enantioselectivity from the addition of vinyllindole 329 to propargyl aldehyde 330. The mechanism is thought to proceed via an initial [4+2] cycloaddition. The cascade can then afford two processes: ring closure via amine addition to the α,β-unsaturated iminium moiety and methylselenide elimination. The authors propose that methylselenide elimination occurs first, however this leads to a dicationic intermediate that has not been directly observed.
The authors were especially interested in the generation of scaffold 332 because it is a common architecture present in several natural product families including Strychnos, Aspidosperma and Kopsia. Excitingly, it was possible to further elaborate organocascade product 333 (synthesised in both enantiomeric forms) to form six indole alkaloids 334-339 (Figure 35). The alkaloids were made using short synthetic sequences, many shorter than had been previously achieved, highlighting the utility of organocascade processes in the efficient formation of complex architectures.
4. Cascades from α,β-Unsaturated Acyl Ammoniums

4.1.2 Enamine-initiated cascades

Many reported enamine-initiated cascades have been designed to proceed via enamine-iminium-enamine protocols, as first demonstrated by Enders et al. in a 3-component cascade, forming four contiguous stereocentres (Scheme 96). Enamine-catalysed Michael-addition to nitroalkene 341 is followed by iminium-catalysed Michael addition to α,β-unsaturated aldehyde 13. Finally, ring closure affords aldol product 342 which undergoes hydrolysis and elimination to give cyclohexene 343 in moderate yield but with excellent stereocontrol.

Recent work by Melchiorre et al. has shown that oxindoles such as 345 can act in a similar Michael-Michael-Aldol process to give spirooxindoles 346 in high diastereo- and enantioselectivity (Scheme 97, A). This work was then developed further to accomplish the formation of six contiguous stereocentres in a reaction that imparts impressive molecular complexity from relatively simple starting materials (Scheme 97, B). Both A and B undergo an enamine-catalysed [1,4]-addition as before, but only A can proceed via a second [1,4]-addition due to the presence of a blocking group at the β-position of the α,β-unsaturated aldehyde in system B. Instead, [1,6]-addition occurs in this case to give a dienamine intermediate that can carry out ring closure. Unlike in reaction A, the cyclohexane formed is not amenable to the elimination of water so is isolated as alcohol 348 with all six newly-formed stereocentres retained. Pleasingly, this procedure was also amenable to the formation of spirocyclic benzofuranones.
4. Cascades from α,β-Unsaturated Acyl Ammoniums

4.1.3 Cascades using α,β-unsaturated acyl ammonium/azolium intermediates

Recent work has demonstrated that α,β-unsaturated acyl ammonium and azolium species can be used as intermediates in cascade reactions. The first example was reported by Studer et al. who treated an external nucleophile with a tethered dielectrophile in the presence of an NHC catalyst in a Michael-Michael-lactonisation (MML) process (Scheme 98).[121] An α,β-unsaturated acyl azolium intermediate is generated in situ by oxidation of the Breslow intermediate (see Section 1.2.7 for more details). Diketone addition to the α,β-unsaturated acyl azolium species then affords enolate 350, which can undergo an intramolecular Michael addition followed by lactonisation to form tricyclic product 351/352 and regenerate the catalyst. Alkyl diketones afforded higher diastereoselectivity than aryl diketones, but excellent enantioselectivity was observed for all examples.

Scheme 97: Formation of spirocyclic oxindoles via organocascade catalysis

An alternative to this tethering strategy (Figure 36, A) is to react a simple α,β-unsaturated acyl species with a tethered nucleophile-electrophile (Figure 36, B). This gives access to

Scheme 98: NHC-catalysed Michael-Michael-lactonisation organocascade via addition of an external nucleophile
different product architectures and enables the use of commercially available $\alpha,\beta$-unsaturated acyl ammonium/azolium precursors.

Romo et al. were the first to use this tethering method in a Michael-Aldol-lactonisation (MAL) process (Scheme 99). Commercially available $\alpha,\beta$-unsaturated acid chlorides were employed in this transformation to generate complex cyclopentanes 355 in good yields and high diastereo- and enantioselectivity. The dicarbonyl portion of the nucleophile 353 acts as a Michael donor to generate intermediate 354, which is set up to do an Aldol reaction followed by lactonisation to give the products. The reaction requires a lithiated base (LiHMDS or $t$-butyllithium) and the authors postulate that the lithium is required to chelate enolate 354 in order to facilitate the cyclisation process. Initial Michael addition anti to the stereodirecting groups on the isothiourea catalyst gives good stereocontrol, with the proposed cyclisation transition state (354) alleviating 1,3-allylic strain between $R^3$ and the enolate. This gives a high level of stereocontrol over the cyclisation step and the reaction affords a single diastereomer in all examples.

Studer et al. then showed that this MAL cascade was amenable to NHC catalysis, with isolation of either cyclopentanes (357) or cyclopentenes (358) depending on the substrate.
used.\textsuperscript{123} The two reactions proceed via the same mechanism but CO\textsubscript{2} is eliminated more readily in aryl-substituted examples thus none of the cyclopentane was observed, only the eliminated cyclopentene product in these cases. LiCl was used as an additive to speed up the reaction and also to enhance enantioselectivity.

\textbf{Scheme 100: Oxidative NHC-catalysed Michael-Aldol-lactonisation organocascade via α,β-unsaturated aldehydes}

This elimination of CO\textsubscript{2} was also observed by Biju \textit{et al.} who investigated an MAL reaction between α-bromoenal 359 and the same ketoester 356 under NHC-redox catalysis.\textsuperscript{124} The authors only investigated the use of aryl ketones in the MAL process therefore only cyclopentenes 358 were isolated. Compared with Studer’s work the yield of 358 is slightly lower however the enantioselectivity is enhanced even in the absence of the LiCl additive, using the same NHC catalyst (128).

\textbf{Scheme 101: NHC-catalysed Michael-Aldol-lactonisation organocascade via α-bromoenals}

Hui \textit{et al.} have recently used α-bromoenals in a Michael-Mannich-lactamisation cascade, affording complex tricyclic products 362 in good yields and excellent diastereo- and enantioselectivity.\textsuperscript{125} The malonate portion of the nucleophile-electrophile substrate 360 initiates a Michael addition into an α,β-unsaturated acyl azolium species, affording enolate 361 that undergoes ring closure via an intramolecular Mannich reaction. Lactamisation from the pendant amine then releases the catalyst and generates the product.
4. Cascades from α,β-Unsaturated Acyl Ammoniums

4.2 Project Aims

The utility of the α,β-unsaturated acyl ammonium intermediate is still relatively underexplored and we hoped to further investigate the chemistry that these intermediates can undergo. Combining the chemistry developed within this thesis and the MAL chemistry initiated by Romo et al. we aimed to access an isothiourea-catalysed MML cascade (Scheme 103) utilising tethered Michael donor-acceptor substrates and α,β-unsaturated acyl ammonium intermediates.

A tethered nucleophile-electrophile would initiate the cascade by adding into the α,β-unsaturated acyl ammonium intermediate, forming an enolate that can undergo an intramolecular Michael addition to form a 5-membered ring. Finally, lactonisation would form a 5,6-bicyclic product and regenerate the catalyst (Scheme 104).

A related process has been demonstrated by Li et al. who used NHC catalysis to generate spirocyclic products via an MML cascade in moderate dr (Scheme 105).
Unfortunately in this process they were unable to achieve any enantioselectivity, with a wide range of chiral NHC catalysts trialled affording 0% ee. This process was therefore thought to be a good challenge for isothiourea catalysis, to investigate whether it is possible to achieve enantioselectivity in a novel MML cascade reaction.

Scheme 105: NHC-catalysed Michael-Michael-Lactonisation process

In Li’s process the second (intramolecular) Michael-addition is thought to be highly diastereoselective, therefore the low diastereoselectivity must arise from poor facial control over the initial nucleophilic addition (Figure 37). The use of a symmetrical nucleophile would remove this complication and therefore dicarbonyl nucleophile-electrophiles were targeted for our isothiourea-catalysed process.

Symmetrical dicarbonyl nucleophiles containing an enone Michael acceptor such as 366 have been demonstrated in a Lewis base-catalysed Michael-Michael cascade in work by Wang et al. (Scheme 106). The enone-malonate acts as a Michael donor in the absence of base, forming enamine 368 that can undergo a second Michael addition followed by hydrolysis to give cyclopentane products 369 containing 3 contiguous stereocentres. The process works well for electron poor and electron rich aryl enals 367, giving high yields and excellent diastereo- and enantioselectivity at moderate catalyst loading (10 mol%). This
gave us confidence that enone-malonates would be suitable for testing in an isothiourea-catalysed MML cascade.

4. Cascades from \(\alpha,\beta\)-Unsaturated Acyl Ammoniums

4.3 Reaction Optimisation

4.3.1 Initial results

Initial screening of the MML reaction utilised reaction conditions similar to those reported by Romo et al. for their MAL cascade.\(^{122}\) Enone-malonate \(370\) (synthesised via cross-metathesis between 2-allyl diethylmalonate and methylvinyl ketone) was chosen as the model nucleophile-electrophile component and cinnamoyl chloride \(148\) was used as the \(\alpha,\beta\)-unsaturated acyl ammonium precursor. Enone-malonate \(370\) was first deprotonated by addition of LiHMDS, followed by addition of Hünig’s base and isothiourea catalyst (HBTM 2.1). The acid chloride was added last as a solution in \(\text{CH}_2\text{Cl}_2\) and the reaction stirred overnight. Two products were observed in the crude \(^1\text{H}\) NMR spectrum which were separable by chromatography and identified as 1,2-addition product \(371b\) and 1,4-addition cascade product \(371a\) (Scheme 107). Moderate regioselectivity (76:24 \(371a:b\)) and poor enantioselectivity (38% ee, \(371a\)) was achieved, however we were pleased to generate the desired product.

The two products can be formed via the mechanisms proposed in Scheme 108. In the 1,2-addition pathway, deprotonated enone-malonate \(372\) can add to either the acid chloride \(148\)
or the α,β-unsaturated acyl ammonium intermediate 202 to afford the undesired 1,2-addition product 371b. Alternatively, 1,4-addition of the enone-malonate can afford enolate intermediate 373 that is set up to carry out an intramolecular 1,4-addition followed by lactonisation to afford the cascade product 371b.

Scheme 108: Proposed 1,2 (371b)- and 1,4 (371a)-addition mechanisms

4.3.2 Determination of product configuration

MML product 371a was obtained as a single diastereomer and to determine the configuration a 1H NOE analysis was carried out. A suitable 1H NMR solvent had to be determined as in CDCl₃ the bridgehead protons signals (B and D, Figure 38) overlap. The spectrum is further complicated by the presence of diastereotopic ethyl ester groups, one of which splits again into a diastereotopic pair giving three complex signals which obscure the protons of interest. After screening several deuterated solvents it was found that deuterated benzene afforded full separation of the bridgehead signals B and D, with partial overlap between F and the ester groups. This was sufficient signal separation to carry out NOE analysis. Proton assignments were made for both the CDCl₃ and C₆D₆ spectra by 2D NMR analysis including COSY and HSQC.
Irradiation of protons B and D showed signal enhancement for one another, along with the ortho-protons on the phenyl ring (Figure 39). Proton E also showed an NOE interaction with the phenyl ring but no NOEs were observed between proton E and either B or D. This suggests that protons B and D, which do exhibit NOEs, are cis- to one another whereas proton E is on the opposite face.

To date it has not been possible to obtain an absolute configuration for the 1,4-addition product \(371a\). It is an oil and therefore cannot be analysed by X-ray crystallography, and suitable derivatisations to known compounds have not been identified. Based upon our understanding of Michael addition into \(\alpha,\beta\)-unsaturated acyl ammoniums, we believe that the initial intermolecular Michael addition proceeds from the Re-face at the \(\beta\)-carbon, generating enolate \(375\) (Scheme 109). The subsequent intramolecular Michael addition also occurs from the Re-face to minimise steric interactions with the stereodirecting groups of the catalyst. We believe that the \(syn\)-ring junction is formed due to lithium chelation of the enolate and enone oxygen atoms. This is consistent with the Heathcock model which states that a closed transition state (where \(Li^+\) can transfer from one enolate to another) is
favoured compared to an open transition state (where enolate and enone groups are in an anti-conformation and metal transfer does not occur).\textsuperscript{127} Whilst transition state 375b also conforms to the Heathcock model a steric clash can be envisaged between the enone moiety and the catalyst. We therefore believe that the intramolecular Michael addition proceeds \textit{via} intermediate 375a, leading to \textit{syn}-ring junction. Based upon the assumption that initial Michael addition installis an (R)-stereocentre at C(7), we therefore believe that the final product obtained has a (4a$S$, 7$R$, 7$aR$) configuration.

Scheme 109: Stereochemical outcomes of proposed transition states

4.3.3 Aims and procedures for reaction screening

1,4-Addition product 371a was obtained in poor yield and this was thought to be due in part to lactone instability to chromatography. To ensure result reproducibility, it was decided to compare ratios of 1,2- and 1,4-addition products from the crude $^1$H NMR spectra throughout the screening process (A, Figure 40). This was carried out by comparison of the integration of C(7)$H$ (B, Figure 40) to either an olefinic proton or the CH$_2$ signal of the 1,2-addition product (C, Figure 40). This choice depended on which areas of the crude $^1$H NMR spectra were cleanest, but as demonstrated in A the same results are obtained using either method. Samples of 371a for chiral HPLC analysis were prepared by preparative TLC to increase throughput.
The two main problems to be addressed during optimisation were the regioselectivity (76:24 1,4-:1,2-addition) and enantioselectivity of the process (36% ee). In order to gain more information about the two problems the reaction was repeated at 0% and 100% catalyst loading (Table 17). With no catalyst present (0 mol%), 1,2-addition product 371a was generated in good regioselectivity (65:10) suggesting that the background reaction accounts for the poor regioselectivity of the process but only has minimal impact on the enantioselectivity of 371a. At 100 mol% catalyst loading the reaction proceeded to form only 1,4-addition product 371a in low 45% ee, suggesting that the isothiourea-catalysed addition process promotes excellent regioselectivity but is not very enantioselective.
4.3.4 Base screening

Firstly, alternative bases were screened to see if this had an effect on the regio- or enantioselectivity of the MML process (Table 18). Using LiHMDS with cinnamic anhydride as the electrophile afforded an improved 1,2:1,4-addition ratio, however the enantioselectivity was reduced to 18% and unexpectedly the opposite enantiomer was formed in excess. The use of NaHMDS afforded only 1,2-product 74 with cinnamoyl chloride and returned only starting material with cinnamic anhydride, while PS-BEMP afforded no conversion into product with either electrophile. The reason for the base-specificity of the MML process is not understood, but matches the observations of Romo et al. during the optimisation of their MAL process. The optimisation was therefore continued using LiHMDS/cinnamoyl chloride.

Table 17: Initial MML screening

<table>
<thead>
<tr>
<th>Catalyst loading (mol%)</th>
<th>SM (370)</th>
<th>1,2 (371b)</th>
<th>1,4 (371a)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>x</td>
<td>24</td>
<td>76</td>
<td>38%</td>
</tr>
<tr>
<td>0</td>
<td>25</td>
<td>26</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>100</td>
<td>x</td>
<td>x</td>
<td>100</td>
<td>45%</td>
</tr>
</tbody>
</table>

Table 18: Base and electrophile screening

<table>
<thead>
<tr>
<th>Base</th>
<th>SM (370)</th>
<th>1,2 (371b)</th>
<th>1,4 (371a)</th>
<th>ee (%)</th>
<th>SM (370)</th>
<th>1,2 (371b)</th>
<th>1,4 (371a)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiHMDS</td>
<td>x</td>
<td>24</td>
<td>76</td>
<td>38%</td>
<td>21</td>
<td>14</td>
<td>65</td>
<td>18% (ent)</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>✔</td>
<td>✔</td>
<td>x</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
<td>x</td>
<td>-</td>
</tr>
<tr>
<td>PS-BEMP</td>
<td>✔</td>
<td>✔</td>
<td>x</td>
<td>-</td>
<td>✔</td>
<td>✔</td>
<td>x</td>
<td>-</td>
</tr>
</tbody>
</table>
4.3.5 Solvent mixtures

In Romo’s MAL procedure a mixture of CH$_2$Cl$_2$/THF is employed to give optimum enantioselectivity. An investigation into the relationship between solvent mixture composition and selectivity was carried out (Table 19). We started at a 30:70 mixture of CH$_2$Cl$_2$/THF in line with Romo’s observations, but found that increasing the proportion of CH$_2$Cl$_2$ in the reaction solvent afforded worse regio- and enantioselectivity. In contrast the selectivity was increased at higher THF content, with the best enantioselectivity obtained at 89-100% THF content and the best regioselectivity of 74:14 afforded in 100% THF. We therefore removed CH$_2$Cl$_2$ from the reaction mixture, and proceeded with THF as the reaction solvent.

<table>
<thead>
<tr>
<th>CH$_2$Cl$_2$ (%)</th>
<th>THF (%)</th>
<th>SM (370)</th>
<th>1,2 (371b)</th>
<th>1,4 (371a)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>5</td>
<td></td>
<td>75</td>
<td>25</td>
<td>8%</td>
</tr>
<tr>
<td>80</td>
<td>20</td>
<td></td>
<td>41</td>
<td>59</td>
<td>8%</td>
</tr>
<tr>
<td>60</td>
<td>40</td>
<td></td>
<td>32</td>
<td>68</td>
<td>15%</td>
</tr>
<tr>
<td>40</td>
<td>60</td>
<td></td>
<td>37</td>
<td>63</td>
<td>25%</td>
</tr>
<tr>
<td>30</td>
<td>70</td>
<td></td>
<td>24</td>
<td>76</td>
<td>38%</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
<td></td>
<td>40</td>
<td>60</td>
<td>40%</td>
</tr>
<tr>
<td>11</td>
<td>89</td>
<td></td>
<td>42</td>
<td>58</td>
<td>49%</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>12</td>
<td>14</td>
<td>74</td>
<td>49%</td>
</tr>
</tbody>
</table>

Table 19: Probing CH$_2$Cl$_2$:THF solvent mixtures. [a] ee not determined, complex $^1$H NMR and HPLC spectrum

4.3.6 Catalyst screening

Alternative isothiourea catalysts were then tested in the reaction. BTM 51 afforded higher enantioselectivity (58% ee), however the amount of 1,4-addition was significantly decreased with both BTM 51 and TM 50. Enhancement of the 1,2-addition reaction is due to increased background reaction, which could occur if the $\alpha$$\beta$-unsaturated acyl ammonium intermediates with other isothioureas are less reactive, or if the intermediate is at a lower
concentration in solution. As HBTM 2.1 afforded significantly better regio- and enantioselectivity we continued with HBTM 2.1 as the isothiourea catalyst.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>SM (370)</th>
<th>1,2 (371b)</th>
<th>1,4 (371a)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBTM 2.1 53</td>
<td>12</td>
<td>14</td>
<td>74</td>
<td>49%</td>
</tr>
<tr>
<td>BTM 50</td>
<td>13</td>
<td>59</td>
<td>29</td>
<td>58%</td>
</tr>
<tr>
<td>TM 51</td>
<td>15</td>
<td>70</td>
<td>15</td>
<td>45% (ent)</td>
</tr>
</tbody>
</table>

Table 20: Isothiourea screening

4.3.7 Base additives

The MAL procedure developed by Romo et al. uses a second base (NEt(Pr)2) as an acid scavenger. An investigation into the use of alternative base additives in our MML process was carried out (Table 21). With no additional base, the ratio of 1,2:-1,4-addition is reduced to 50:50 compared with the use of NEt(Pr)2 (14:74) and the ee is lower (20%). Use of two equivalents of LiHMDS gave a messy reaction mixture with no discernable product peaks in the crude 1H NMR spectrum, as did DBU. Lower ee was observed with NEt3, PBEMP and Cs2CO3 (21-43% ee). K2CO3 and K2HPO4 gave very similar enantioselectivity to NEt(Pr)2, however the 1,2:-1,4-addition ratio was reduced (57 and 60% 1,4-addition product content compared with 74% for NEt(Pr)2) therefore we continued with NEt(Pr)2 as the base additive.
4. Cascades from α,β-Unsaturated Acyl Ammoniums

The next parameter to be investigated was reaction temperature. Unexpectedly, at lower temperature the enantioselectivity was significantly reduced, with 1,4-addition product obtained in only 2% ee at -78 °C. This was unexpected, as low temperatures (and thus more rigid transition states) are more usually associated with enantioselective catalysis. Increasing the temperature to 20 °C increased the ee to 60%, which could be further improved by heating the reaction. At 70 °C 371a was obtained in 76% ee, so we decided to continue with this reaction temperature.
We have previously observed that the background reaction affords 1,2-addition regioselectively, so does not significantly impact the enantioselectivity of the 1,4-addition process. Changes in ee upon changing the temperature are therefore not simply due to altering the relative rates of both 1,2- and 1,4-addition reactions. It also cannot be related to changes in acyl ammonium concentration as the 1,4-addition product is only generated via this intermediate, so the selectivity should be independent of concentration. We do not currently understand the nature of this trend, and hope to be able to clarify the reasons through modelling in future work.

At the higher temperatures starting material degradation was observed, so to get a better picture of the material recovery the screening proceeded using an internal standard (1,4-dinitrobenezene) to give $^1$H NMR yields of each species at the end of the reaction (Table 23). Repeating the reaction at 70 °C in THF (with fresh LiHMDS to ensure good starting material conversion) gave 1,4-addition product 371a in 51% $^1$H NMR yield and 71% ee.

The enantioselectivity could be further improved by heating the solvent above its boiling point in a sealed tube, however this gave worse material recovery due to increased degradation at the very high temperatures. Using dioxane as solvent/co-solvent also increased the ee, with more degradation observed giving lower $^1$H NMR yields of the
desired product 371a (35-36%). A compromise was therefore sought, and 70 °C in THF was chosen as the optimal combination.

Slow electrophile addition was investigated, but while the ratio of 1,2:1,4-addition was improved, greater starting material degradation was observed over the longer reaction time and the overall yield of the 1,4-MML product 371a was reduced. Diluting the reaction led to enhanced reaction times and greater starting material degradation, with no change in the ratio of regioisomers.

### 4.3.9 Effect of electrophiles

The use of alternative electrophiles to cinnamoyl chloride was next investigated in order to determine whether they afforded different ratios of 1,2:1,4-addition. Of the electrophiles tested only homoanhydride 149 afforded any product, but unfortunately, the 1,2:1,4- ratio was reduced and the enantioselectivity significantly lower using this activation method. All other activated acids tested afforded no product formation, but considerable degradation of the diester starting material was observed. Imidazole amide 378, recently demonstrated in our lab to be suitable for the generation of ammonium enolate intermediates in Michael addition-lactonisation processes,xvii also returned only starting material. α-Substituted acid

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xvii Carried out by Claire Young, unpublished results
4. Cascades from α,β-Unsaturated Acyl Ammoniums

chlorides 379 and 380 were hoped to reduce the rate of 1,2-addition by steric blocking at the α-position, however they demonstrated no reactivity.

Also tested was the effect of acid chloride equivalents on the reaction (Table 25). At increased equivalents of acid chloride the amount of 1,2-addition remained almost constant (17-22% 1H NMR yield), but the amount of 1,4-addition product fell from 34% to 17% at three equivalents of 148. At a higher reaction temperature of 120 °C increased enantioselectivity was achieved, with 371a formed in 86% ee using 2 or 3 equivalents of acid chloride 148 but at reduced 1H NMR yields (27-28%). Lower total material recovery at higher acid chloride equivalents and higher temperatures suggests that byproduct formation and degradation pathways are more significant. At lower equivalents of cinnamoyl chloride,
the starting material conversion was significantly reduced (results not shown), so we maintained 1.4 equivalents of 148 at 70 °C as the optimum conditions.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Acid chloride (equiv)</th>
<th>SM (370)[a]</th>
<th>1,2 (371b)[a]</th>
<th>1,4 (371a)[a]</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 °C</td>
<td>1.4</td>
<td>20</td>
<td>18</td>
<td>34</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>17</td>
<td>22</td>
<td>25</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>18</td>
<td>19</td>
<td>17</td>
<td>81</td>
</tr>
<tr>
<td>120 °C</td>
<td>1.4</td>
<td>12</td>
<td>17</td>
<td>22</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
<td>18</td>
<td>27</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>16</td>
<td>20</td>
<td>28</td>
<td>86</td>
</tr>
</tbody>
</table>

Table 25: Acid chloride equivalents [a]H NMR yield using 1,4-dinitrobenzene as internal standard

4.3.10 Catalyst loading

Next to be investigated was the effect of the catalyst loading on the selectivity of the reaction. Unsurprisingly, at lower catalyst loading the rate of 1,4-addition is slower therefore more 1,2-addition is observed. Whilst it was hoped that higher catalyst loading would result in the reverse effect, no appreciable increase in the ratio of 1,2-:1,4- products was observed even at very high catalyst loadings of 50 mol%, therefore the catalyst loading remained at 20 mol%.
4. Cascades from α,β-Unsaturated Acyl Ammoniums

Table 26: Catalyst Loading $^1$H NMR yield using 1,4-dinitrobenzene as internal standard

<table>
<thead>
<tr>
<th>Catalyst loading (mol%)</th>
<th>SM (370)[a]</th>
<th>1,2 (371b)[a]</th>
<th>1,4 (371a)[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>14</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>20</td>
<td>&lt;5</td>
<td>23</td>
<td>51</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
<td>17</td>
<td>40</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>13</td>
<td>37</td>
</tr>
</tbody>
</table>

4.3.11 Non-lithiated bases

The role of Li$^+$ in the MML process is not fully understood, but it is thought to be essential for chelating the transition state of the intramolecular Michael addition step (375, Scheme 110). In the absence of Li$^+$, 1,2-addition is favoured because the transition state (381) does not rely on chelation to preorganise the proposed transition state assembly.

The role of the base additive (NEt(Pr)$_2$) remains mysterious: without it, the catalyst appears to not turn over with the $^1$H NMR yield of the 1,4-MML product approximately matching the catalyst loading (20 mol% gave 371a in 24% $^1$H NMR yield, Table 27). The remainder of the starting material is either returned unchanged or can go on to form the 1,2-addition product. Turnover is achieved by addition of an organic base such as NEt(Pr)$_2$, or an
inorganic base. Cs$_2$CO$_3$ was retested at 70˚C due to its success at 0˚C, giving comparable results to NEt($i$Pr)$_2$ (42%, 76% ee).

Also tested were a range of non-lithiated bases, using LiCl as an additive to provide the required Li$^+$ ions for chelation. NEt($i$Pr)$_2$ afforded only 12% 371a, with very poor starting material conversion (61% remaining) suggesting that deprotonation is inefficient. KHMDS and NaHMDS afforded worse conversion to 371a (31% and 19% $^1$H NMR yields respectively) and strong organic base PS-BEMP also afforded poor regioselectivity. The ees for these reactions were not determined due to the reduced conversions.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>1st Base (1 equiv)</th>
<th>2nd Base (1.4 equiv)</th>
<th>Additive (1 equiv)</th>
<th>SM (370)[a]</th>
<th>1,2 (371b)[a]</th>
<th>1,4 (371a)[a]</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiHMDS</td>
<td>-</td>
<td>-</td>
<td>29</td>
<td>18</td>
<td>24</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>NEt($i$Pr)$_2$</td>
<td>-</td>
<td>&lt;5</td>
<td>23</td>
<td>51</td>
<td>71</td>
</tr>
<tr>
<td>Cs$_2$CO$_3$</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>20</td>
<td>42</td>
<td>76</td>
</tr>
<tr>
<td>NEt($i$Pr)$_2$</td>
<td>-</td>
<td>LiCl</td>
<td>61</td>
<td>14</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>KHMDS</td>
<td>NEt($i$Pr)$_2$</td>
<td>LiCl</td>
<td>31</td>
<td>20</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>NEt($i$Pr)$_2$</td>
<td>LiCl</td>
<td>21</td>
<td>17</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>PS-BEMP</td>
<td></td>
<td></td>
<td>23</td>
<td>25</td>
<td>34</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 27: Base screening $^1$H NMR yield using 1,4-dinitrobenzene as internal standard

4.3.12 Affecting lithium aggregation states

Lithium is well known to form a range of coordinated species when solvated, with different coordination numbers achieved when different ligands are applied.$^{128,129}$ The aggregation state, and thus the chelation ability, of Li$^+$ is therefore strongly affected by solvation and the ratio of ligands present in the system. In our MML process there are a large number of competing ligands including THF, NEt($i$Pr)$_2$ and a range of enolate intermediates therefore gaining insight into the specific Li-aggregation in this system is too complex for simple analysis. We can however potentially affect the Li-aggregation by changing the ratio of LiHMDS to NEt($i$Pr)$_2$ in the system (Table 28). Interestingly, changing the ratio of LiHMDS to NEt($i$Pr)$_2$ from 1:0.3 to 1:3 made no appreciable difference to the ratios of
products obtained (39-41% 371a, 72-74% ee). Catalytic NEt(Pr)₂ (0.3 equivalents) was sufficient to fulfil its role in the system, but the minimum cut-off was not further investigated since no improvement in selectivity was observed. Catalytic LiHMDS was also tested in the reaction although this resulted in very poor conversion into both 1,2- and 1,4-products 371b and 371a (6% and 18% respectively).

\[
\begin{align*}
\text{LiHMDS} & \quad \text{NEt}^2(\text{Pr})_2 \quad \text{SM} (370) [a] \\
1 & & 0 & 29 & 18 & 24 & 82 \\
0.3 & & 12 & 17 & 40 & 74 \\
1 & & 14 & 18 & 39 & 74 \\
3 & & 16 & 19 & 41 & 72 \\
0.3 & & 1 & 64 & 6 & 18 & 80 \\
\end{align*}
\]

Table 28: Effect of changing the ratio of LiHMDS to NEt(Pr)₂. [H] NMR yield using 1,4-dinitrobenzene as internal standard

The coordinating ability of the solvent was then investigated (Table 29). LiHMDS was added as a solution in toluene to remove competing ligation from THF. Using this LiHMDS solution, conversion into product was reduced even when using THF as the main reaction solvent. Because conversions were so low these reactions were not analysed by chiral HPLC so the product ee has not been recorded. If toluene was used as the reaction solvent, no conversion into any products was observed and this solvent effect is possibly hampering reactivity in the other reactions even when very small quantities of toluene are used. None of the reactions showed any improvement in 1,2:1,4-selectivity, therefore no change was made to the reaction solvent used.
4. Cascades from α,β-Unsaturated Acyl Ammoniums

Table 29: Solvent screening [1H] NMR yield using 1,4-dinitrobenzene as internal standard

<table>
<thead>
<tr>
<th>Solvent</th>
<th>SM (370)[a]</th>
<th>1,2 (371b)[a]</th>
<th>1,4 (371a)[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>9</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>MeCN</td>
<td>4</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>DCE</td>
<td>&lt;5</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>DMF</td>
<td>19</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>EtOAc</td>
<td>9</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Toluene</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

4.3.13 Optimised Reaction Conditions

After a thorough screening process, it appears that the most important factor in controlling the enantioselectivity of the process is the reaction temperature, with elevated temperatures significantly enhancing the ee of the products. A compromise of 70 °C in THF was chosen as at higher temperatures greater product degradation was observed. A second base (NEt(Pr)2) is used to aid catalyst turnover, and HBTM 2.1 was the best catalyst in this system. It is possible that other avenues of investigation may further improve the regioselectivity of the process, but until now a 7:3 ratio of 1,4-:1,2- addition is the highest achieved, giving 1,4-addition product 371a as a single diastereomer in 71% ee.
4.4 Reaction Scope

4.4.1 Enone-malonate synthesis via cross-metathesis

In order to investigate the scope of the MML process with respect to the nucleophile-electrophile reactant, an optimisation of the starting material synthesis was carried out. It was not possible to generate the enone-malonate starting materials via ozonolysis/Wittig procedures due to the unstable nature of intermediate aldehydes, leading to no formation of the desired products. Grubbs II-catalysed cross metathesis between allylester \(382\) and methyl vinyl ketone \(383\) afforded the desired product \(370\), but the conversion was low so a range of alternative catalysts developed by the Nolan group \(^{130}\) were tested to try and improve the efficiency of the reaction.\(^{xviii}\) These catalysts have been shown to be highly effective in cross-metathesis processes however in our reaction M20 \(385\) and M31 \(387\) gave poor conversion to product \(370\) (12-27%, Scheme 112). M23 \(386\) and M2 \(388\) afforded higher conversions of 41% and 56% respectively on a 0.5 mmol scale. However when the M2-catalysed reaction was scaled up to 15 mmol the conversion dropped to 39%. No competing homocoupling of allyl ester \(382\) was observed and the reaction did not tolerate lower catalyst loadings. Increased and decreased equivalents of methyl vinyl ketone \(383\) were also investigated however no improvement to the conversion was achieved.

![Scheme 112: Screening of metathesis catalysts](image)

In order to investigate the scope of the MML process we hoped to synthesis a range of enone-dicarbonyl starting materials, varying both the steric and electronic properties to ascertain their effects on the cascade process. The cross-metathesis reaction enabled access to a range of enone-malonates in moderate yields (19-23%, Scheme 113), with the

\(^{xviii}\) Catalysts M2, M20, M23 and M31 were kindly donated by Prof S. P. Nolan and are commercially available from Umicore.
incorporation of sterically small (methyl) and large (iso-propyl) substituents, as well as dibenzyl malonate. 2- Allyl-1,3-diketones were also investigated however product 392 could not be isolated as it showed a high tendency to perform intramolecular 1,4-addition, giving 392 and rearranged product 393 as a mixture upon purification.

Attempts to couple allyl malonates with phenyl vinyl ketone was unfortunately unsuccessful, with starting materials returned unreacted under the cross-metathesis conditions. To date therefore we have not been able to prepare a wider variety of enone-dicarbonyl starting materials for use in the MML cascade, but it is hoped that the scope could be improved in future work by investigation of alternative synthetic pathways.

4.4.2 Cascade scope

A preliminary investigation into the scope of the reaction has been carried out using the enone-malonates synthesised via cross metathesis (Scheme 114). Annulation with cinnamoyl chloride afforded bicyclic products 371a and 394-398a in moderate regioselectivity (61:39 to 77:23). Upon repetition of the reaction with diethyl enone-malonate on a larger scale we observed increases in both the yield of 371a (32% to 41%) and its ee (71% to 82%) compared with the results obtained during reaction screening, with no change in the regioisomeric ratio (68:32).
It was generally possible to separate the major 1,4-cascade products from the side products by chromatography (generated via 1,2-addition), however the 1,2-products coeluted with the enone-malonate starting materials. In most cases the starting material was fully converted during the reaction time however the use of bulky isopropyl substituted enone-malonate gave a slower reaction, which afforded 1,4-product 396a, 1,2-product 396b and starting material 389 in a 51:22:16 crude mixture. Upon purification, this afforded 396a in a moderate 44% yield and 396b in 36% as a 7:3 mixture with the starting material. Extending the reaction time increased degradation products and did not increase the yields of either 1,4- or 1,2-addition products.

Use of a methyl ester group led to increased 1,4-:1,2-addition ratio (77:23 394a:b) and gave an increased yield of 1,4-addition product 394a (63%) with no significant drop in ee (71%). This was pleasing because previous results with methyl substituted 1,3-diketones afforded annulation products in decreased ee (Section 2.3.2). Benzyl substitution was well tolerated, with the results for 395a/395b closely matching those of other linear alkyl malonates.

We then investigated the use of alkyl substituted Michael acceptors by using commercially available crotonoyl chloride (R² = Me) as the α,β-unsaturated acyl ammonium precursor. Dimethylmalonate 1,4-addition product 397a was isolated in 56% yield, which closely matches the results obtained with cinnamoyl chloride (394a, 63%). This was also observed for dibenzylmalonate substituted products 398a/398b which were obtained in identical regioisomeric ratios (77:23) and yields (398b, 54%) compared with the phenyl-substituted product 395a/398b. Excitingly, the methyl substituted products 397a and 398a were isolated in much higher 90% ee compared with phenyl substituted products 394a/395a (70-72% ee). In future work, the scope of this reaction will be extended to further explore the relationship between steric/electronic effects and enantioselectivity. From the preliminary results seen here, we can be confident that the process is robust for a variety of substituents, and especially high enantioselectivity can be obtained for alkyl examples.
4. Conclusions

As part of our efforts to explore the chemistry of α,β-unsaturated acyl ammonium intermediates we have successfully demonstrated the first Lewis base-catalysed Michael-Michael-lactonisation process, utilising enone-malonates as Michael donor-acceptor species alongside α,β-unsaturated acyl ammonium intermediates generated in situ from addition of HBTM 2.1 into α,β-unsaturated acid chlorides. Pleasingly, the cyclised products were formed as single diastereomers, suggesting that stereocontrol is excellent for both inter- and intramolecular Michael additions.

Interestingly, enhanced enantioselectivity at elevated temperatures was observed and we were able to carry out an enantioselective organocatalytic cascade process at high temperatures of 70 °C in THF. We also demonstrated the importance of Li⁺ ions for efficient conjugate addition, which is proposed to be due to important chelation interactions in the intramolecular Michael addition transition state. HBTM 2.1 afforded both the best regio- and enantioselectivity in this system, with other isothioureas tested (BTM and TM) giving poor regioselectivity due to enhanced background reactions.
The reaction scope has demonstrated that a range of enone-malonates successfully participates in the cascade reaction, affording 1,4-addition products in moderate regioselectivity, yields and enantioselectivity. Increased steric bulk reduces starting material conversion, but regio- and enantioselectivity remained unchanged. “Small” alkyl groups demonstrated increased regioselectivity, but again the enantioselectivity was similar across the range.

In future work, we aim to expand the scope of the reaction to include a wider range of enone-malonates and to further investigate the effects of changing the sterics and electronics of the α,β-unsaturated acid chloride component. In order to expand the scope, we also hope to improve the starting material synthesis. The cross-metathesis is low yielding and has shown high substrate specificity, which limits the synthetic possibilities of the reaction. Alternative strategies such as Tsuji-Trost coupling of malonates to allyl acetates could be investigated, which if successful could provide a reliable method to generate the starting materials in increased yields.
5. Conclusions

At the outset of this work, the chemistry of α,β-unsaturated acyl ammonium intermediates was underexplored, with only one process reported by Fu et al. exploiting Lewis base catalysis to afford diquinane products in low ee (Section 1.2.6). We set out to further explore the potential of these catalytic intermediates in a range of 1,4-additions, in order to broaden the applicability of a potentially important catalytic intermediate.

We have successfully developed Michael addition-cyclisation processes employing a wide range of nucleophiles including 1,3-diketones, 1,3-ketoesters and 2-acylbenzazoles, accessing novel heterocyclic products in excellent ee. The origin of the enantioselectivity in our Michael addition-cyclisation process was explored by examination of the crystal structure of the α,β-unsaturated acyl ammonium intermediate, and insight into the relative energies of N- and O- cyclisation pathways for annulation of cinnamic anhydride with 2-phenacyl benzothiazole and benzoxazole was gained by computational work (carried out in collaboration with the Paul Ha Yeon Cheong). Given the precedent for biological activity demonstrated by benzazole containing compounds, we hope that future work will enable evaluation of the bioactivity of the heterocycles we have accessed.

We then went on to demonstrate that α,β-unsaturated acyl ammonium intermediates can participate in complex chemical cascades. A Michael-Michael-lactonisation process was developed, which showed an interesting relationship between enantioselectivity and temperature. The reactions were performed at 70 °C for optimum enantioselectivity, and to the best of our knowledge this is the first organocatalytic reaction to require such elevated temperatures to improve ee. In a preliminary reaction scope a range of enone-malonates were employed in the cascade process giving access to tricyclic lactone products in moderate yields and good enantioselectivities.

Since we embarked upon this research the field of α,β-unsaturated acyl ammonium catalysis has grown rapidly, with work by Romo and Matsubara successfully utilising this intermediate in a diverse range of Michael additions to access novel products. As the field of organocatalysis continues to grow, the ability to exploit a wide range of catalytic intermediate is crucial for accessing different product architectures. As part of this growth, the development of α,β-unsaturated acyl ammonium intermediates in catalysis provides an important expansion of the chemistry that we can access, and thus the products we can obtain.
6. Experimental

6.1 General Information

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

For moisture sensitive reactions, solvents (THF, CH₂Cl₂, toluene, hexane and Et₂O) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and -78 °C were obtained using ice/water and CO₂(s)/acetone baths respectively. Temperatures of 0 °C to -50 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reflux conditions were obtained using a DrySyn heating mantle equipped with a contact thermometer. In vacuo refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC₂ 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 F₂₅₄ silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO₄ solution. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

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

Infrared spectra ($\nu_{\text{max}}/\text{cm}^{-1}$) were recorded on a Shimadzu IRAffinity-1 using a Pike
attenuated total reflectance (ATR) accessory. Only the characteristic peaks are quoted.

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

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

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

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter or
Optical Activity AA-1000 polarimeter, operating at the sodium D line with a 100 mm path
cell at rt.
6.2 α,β-Unsaturated Acids

**General Procedure A: Knoevenagel Condensation**

To a solution of the corresponding aldehyde (1 equiv) in pyridine (1.5 M), was added malonic acid (1.2 equiv) and piperidine (0.12 equiv) at room temperature. The reaction mixture was heated at 85 °C for 18 h. After cooling to room temperature the solution was acidified using 6 M HCl affording the carboxylic acid as a precipitate which was isolated by filtration. The acid was purified by column chromatography or recrystallisation as required.

**(E)-2-Bromocinnamic acid (230)**

The title compound was prepared according to General Procedure A from 2-bromobenzaldehyde (3.49 mL, 30.0 mmol), malonic acid (3.75 g, 36.0 mmol and piperidine (0.35 mL, 3.60 mmol) in pyridine (20 mL) to give the carboxylic acid 230 as a white solid which was washed with hexane; no further purification needed (6.78 g, 99%); mp 217–219 °C {Lit. 131 217.5–218.5 °C}; δH (300 MHz, DMSO-d6) 6.57 (1H, d, J 15.9, ArCH=CH2), 7.32 – 7.39 (1H, m, J 7.6, 1.8, ArC(5)H), 7.40 – 7.47 (1H, m, ArC(4)H), 7.71 (1H, dd, J 7.9, 1.4, ArC(3)H), 7.84 (1H, d, J 15.9, ArCH=CH2), 7.90 (1H, dd, J 7.8, 1.8ArC(6)H), 12.64 (1H, br, s, COOH). Data in agreement with the literature.131

**(E)-3-Bromocinnamic acid (231)**

The title compound was prepared according to General Procedure A from 3-bromobenzaldehyde (3.49 mL, 30.0 mmol), malonic acid (3.75 g, 36.0 mmol) and piperidine (0.35 mL, 3.60 mmol) in pyridine (20 mL) to give the carboxylic acid 231 as a white solid which was washed with hexane; no further purification needed (6.45 g, 95%); mp 176–178 °C {Lit. 132 175–176.3 °C}; δH (300 MHz, DMSO-d6) 6.61 (1H, d, J 16.0, ArCH=CH2), 7.37 (1H, t, J 7.9, C(5)H), 7.56 (1H, d, J 16.1, ArCH=CH2), 7.57 – 7.62 (1H,
6. Experimental

118

m, C(4)H), 7.71 (1H, dt, J 7.8, 1.3, ArC(6)H), 7.94 (1H, t, J 1.8, ArC(2)H), 12.52 (1H, s, COOH). Data in agreement with the literature.132

(2E)-3-(Thiophen-3-yl)prop-2-enoic acid (232)

The title compound was prepared according to General Procedure A from thiophene-3-carbaldehyde (2.59 mL, 30.0 mmol), malonic acid (3.75 g, 36.0 mmol) and piperidine (0.35 mL, 3.60 mmol) in pyridine (20 mL) to give the carboxylic acid 232 as an off-white solid, no further purification needed (4.33 g, 94%); mp 148–150 °C {Lit.133 151 °C}; δH (300 MHz, CDCl3) 6.27 (1H, d, J 15.9, ArCH=CH), 7.32 (1H, ddd, J 5.1, 1.4, 0.4, ArC(4)H), 7.36 (1H, ddd, J 5.1, 2.9, 0.6, ArC(5)H), 7.56 (1H, dd, J 2.9, 1.3, ArC(2)H), 7.78 (1H, d, J 15.9, ArCH=CH). Data in agreement with the literature.133,134

(2E)-3-(Furan-3-yl)prop-2-enoic acid (233)

The title compound was prepared according to General Procedure A from furan-3-carbaldehyde (2.59 mL, 30.0 mmol), malonic acid (3.75 g, 36.0 mmol) and piperidine (0.35 mL, 3.60 mmol) in pyridine (20 mL) to give the carboxylic acid which was recrystallised from EtOAc/hexane to give 233 as a brown solid (2.51 g, 61%); mp 151–152 °C {Lit.135 152.5–154}; δH (500 MHz, d4-MeOD) 6.20 (1H, d, J 15.8, ArCH=CH), 6.75 (1H, d, J 1.9, ArC(4)H), 7.52 – 7.56 (1H, m, ArC(5)H), 7.59 (1H, d, J 15.8, ArCH=CH), 7.80 – 7.85 (1H, m, ArC(2)H). Data in agreement with the literature.135,136

(E)-2,4,6-Trimethylcinnamic acid (236)

Procedure from Aitken et al.99 Mesitaldehyde (1.48 mL, 10.0 mmol) was added dropwise to a suspension of sodium metal (230 mg, 10.0 mmol) in ethyl acetate (20 mL) at 0 °C and the flask stirred for 3 h at 0 °C. Acetic acid was then added dropwise until a persistent yellow colour appeared, followed by water (20 mL). The flask was stirred for 20 min at room temperature then the organic layer separated, washed with saturated NaHCO3 solution (20
6. Experimental

mL × 2), dried over MgSO₄, filtered and concentrated in vacuo to afford the crude ethyl ester which was added to a 2 M solution of NaOH in water (20 mL) and heated at reflux for 3 h. After cooling to room temperature the reaction mixture was acidified using concentrated HCl. The precipitate was isolated by filtration and washed with hexane to give 236 as a pale brown solid (0.99 g, 52%); mp 176–178 °C {Lit.¹³⁷ 178–179 °C}; δH (300 MHz, CDCl₃) 2.29 (3H, s, ArC(4)CH₃), 2.36 (6H, s, 2 × ArC(2)CH₃), 6.10 (1H, d, J 16.3, ArCH=CH), 6.91 (2H, s, 2 × ArC(3)H), 7.98 (1H, d, J 16.3, ArCH=CH). Data in agreement with the literature.¹³⁷,¹³⁸

(2E)-4,4,4-Trifluoro-3-methylbut-2-enoic acid (298)

Procedure from Tarrant and Taylor.¹⁰⁶ Malonic acid (12.5 g, 120 mmol) and piperidine (1.19 mL, 12.0 mmol) were added to pyridine (50 mL) and cooled to 0 °C. 1,1,1-Trifluoromethylketone (8.96 mL, 100 mmol) was added to the flask by syringe addition directly into the pyridine solution to minimise loss through ketone volatility. After 1 h stirring at 0 °C the flask was then warmed to room temperature and stirred for 16 h. The flask was then heated to 90 °C for 24 h, followed by 130 °C for 4 h. The flask was cooled to room temperature and acidified using a 6 M solution of hydrochloric acid. The aqueous layer was washed with ethyl acetate (50 mL × 3) and the combined organic layers dried over MgSO₄, filtered and concentrated in vacuo to afford the β-hydroxy acid which was used without further purification. The hydroxy acid was added to a solution of concentrated sulfuric acid (50 mL) in water (50 mL) at room temperature. The flask was attached to distillation apparatus and heated slowly to 200 °C under atmospheric pressure, with a mixture of water and crude α,β-unsaturated acid collected in the receiver flask. After heating for 16 h at 200 °C the mixture in the receiver flask was washed with CH₂Cl₂ (50 mL × 3), and the combined organic layers dried over MgSO₄, filtered and concentrated in vacuo to afford the crude acid which was purified by vacuum distillation (<1 mbar) at 70 °C to afford acid 298 as a colourless oil (4.18 g, 31%, E:Z 89:11 confirmed by ¹H→¹9F NOE); bp 158–163 °C {Lit.¹⁰⁶ 160–166 °C}; δH (500 MHz, CDCl₃) 1.67 (3H, d, J 1.1, (Z)-CH₃), 2.28 (3H, d, J 1.7, (E)-CH₃), 6.36 (1H, h, J 1.5, (E)-CH), 6.52 – 6.55 (1H, m, (Z)-CH), 12.08 (1H, s, CO₂H); δF (471 MHz, CDCl₃) -82.95 (Z), -71.45 (E). Data in agreement with the literature.¹⁰⁶,¹³⁹
Geraniol (4.38 mL, 25.0 mmol) and activated manganese dioxide (10.88 g, 125 mmol) were added to CH$_2$Cl$_2$ (25 mL) and stirred at room temperature for 18 h, after which more manganese dioxide (3.90 g, 45.0 mmol) was added and the flask stirred for a further 24 h. The reaction mixture was filtered through celite and concentrated in vacuo to afford the aldehyde as a colourless oil (2.83 g, 75%, E:Z = 97:3 by $^1$H NMR) which was used without further purification. To a mixture of i-butanol (100 mL) and 2-methyl-2-butene (2 M in THF, 45 mL, 90.0 mmol) was added the crude aldehyde (2.28 g, 15.0 mmol). A solution of sodium chlorite (2.72 g, 30.0 mmol) and sodium dihydrogen phosphate dihydrate (9.36 g, 60.0 mmol) in water (100 mL) was added to the aldehyde solution and the flask stirred at room temperature for 72 h. The mixture was extracted with ethyl acetate (100 mL $\times$ 3) and the combined organic layers dried over MgSO$_4$, filtered and concentrated in vacuo. The crude acid was purified by column chromatography (10% EtOAc/petrol) to afford acid E-303 as a colourless oil (1.61 g, 64%, E/Z 97:3 by GC); GC analysis: Column: Agilent DB-5 (30 m, 0.25 mm ID, 0.5 μm film), Method: (Injector 250 °C, FID 325 °C, linear velocity 40 cm/s (He), oven ramps (Initial 100 °C (2 min hold) → 220 °C (20 °C/min, 5 min hold)), $t_R$ (E-isomer) 6.69 min, $t_R$ (Z-isomer): 6.89 min); δ$^1$H (300 MHz, CDCl$_3$) 1.61 (3H, d, $J$ 1.4, C(7)(C$_3$(CH$_3$))(CH$_3$)), 1.69 (3H, d, $J$ 1.4, C(7)(CH$_3$)(CH$_3$)), 2.16 – 2.19 (7H, m, C(2)CH$_3$, 2 × CH$_2$), 5.02 – 5.11 (1H, m C(6)H), 5.69 (1H, q, $J$ 1.2, C(2)H). Data in agreement with the literature.$^{140}$

Nerol (4.38 mL, 25.0 mmol) and activated manganese dioxide (10.88 g, 125 mmol) were added to CH$_2$Cl$_2$ (25 mL) and stirred at room temperature for 18 h, after which more manganese dioxide (3.90 g, 45.0 mmol) was added and the flask stirred for a further 24 h. The reaction mixture was filtered through celite and concentrated in vacuo to afford the aldehyde as a colourless oil (3.28 g, 86%, E:Z = 9:91 by $^1$H NMR) which was used without further purification. To a mixture of i-butanol (100 mL) and 2-methyl-2-butene solution (2
m in THF, 45 mL, 90.0 mmol) was added the crude aldehyde (2.28 g, 15.0 mmol). A solution of sodium chlorite (2.72 g, 30.0 mmol) and sodium dihydrogen phosphate dihydrate (9.36 g, 60.0 mmol) dissolved in water (100 mL) was added to the aldehyde solution and the flask stirred at room temperature for 72 h. The mixture was extracted with ethyl acetate (100 mL × 3) and the combined organic layers dried over MgSO$_4$, filtered and concentrated in vacuo. The crude acid was purified by column chromatography (10% EtOAc/petrol) to afford acid Z-303 as a colourless oil (1.58 g, 63%, E/Z 10:90 by GC); GC analysis: Column: Agilent DB-5 (30 m, 0.25 mm ID, 0.5 μm film), Method: (Injector 250 °C, FID 325 °C, linear velocity 40 cm/s (He), oven ramps (Initial 100 °C (2 min hold) → 220 °C (20 °C/min, 5 min hold)), $t_R$ (E-isomer) 6.69 min, $t_R$ (Z-isomer): 6.89 min; δ$_H$ (300 MHz, CDCl$_3$) 1.61 (3H, d, J 1.4, C(7)(C$_3$H$_3$)(CH$_3$)), 1.69 (3H, d, J 1.3, C(7)(CH$_3$)(CH$_3$)), 1.93 (3H, d, J 1.4, C(3)CH$_3$), 2.10 – 2.23 (2H, m, CH$_2$), 2.58 – 2.71 (2H, m, CH$_2$), 5.08 – 5.20 (1H, m, C(6)H), 5.68 (1H, q, J 1.2, 0.8, C(2)H). Data in agreement with the literature.$^{141}$

2-Cyclohexylideneacetic acid (296)

Modified procedure from Peters and Tiseni.$^{142}$ Triethylphosphonoacetate (13.9 mL, 70.0 mmol) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 2.80 g, 70.0 mmol) in dry THF (70 mL) under nitrogen at 0 ºC. The flask was stirred at 0 ºC for 30 min then warmed to room temperature over 30 min. A solution of cyclohexanone (7.0 mL, 70.0 mmol) in dry THF (50 mL) was then added dropwise and the flask stirred at room temperature for 18 h. The reaction was quenched by careful addition of water at 0 ºC then the mixture extracted with Et$_2$O (3 × 100 mL). The combined organic phase was washed with brine, dried over anhydrous MgSO$_4$ and concentrated in vacuo to afford the crude ester which was used without further purification. The crude oil was dissolved in methanol (150 mL) followed by addition of sodium hydroxide (11.8 g, 210.0 mmol) and water (50 mL). The flask was stirred at room temperature for 48 h then quenched by acidification with 6 M HCl. The mixture was concentrated in vacuo then extracted with CH$_2$Cl$_2$ (3 × 100 mL). The combined organic layers were dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo to afford the crude acid. Purification by recrystallisation from ethanol/water afforded acid 296 as a white solid (4.56 g, 47%); mp 89–91 ºC {Lit.$^{143}$ 89–90 ºC}; δ$_H$ (300 MHz,
CDCl$_3$ 1.50 – 1.79 (6H, m, cyclohexylC(3)H$_3$, cyclohexylC(4)H$_3$, cyclohexylC(5)H$_3$), 2.13 – 2.35 (2H, m, cyclohexylC(2/6)H$_2$), 2.72 – 2.94 (2H, m, cyclohexylC(2/6)H$_2$), 5.57 – 5.72 (1H, m, C=CH$_2$), 11.76 (1H, s, O–H). Data in agreement with the literature.$^{143,144}$

(2E)-3-Phenylbut-2-enoic acid (297)

Modified procedure from Peters and Tisen.$^{142}$ Triethylphosphonoacetate (19.8 mL, 100 mmol) was added dropwise to a suspension of sodium hydride (60% in mineral oil, 4.00 g, 100 mmol) in dry THF (100 mL) under nitrogen at 0 °C. The flask was stirred at 0 °C for 30 min then warmed to room temperature over 30 min. A solution of acetophenone (11.7 mL, 100 mmol) in dry THF (50 mL) was then added dropwise and the flask stirred at room temperature for 18 h. The reaction was quenched by careful addition of water at 0 °C then the mixture extracted with Et$_2$O (3 × 100 mL). The combined organic phase was washed with brine, dried over anhydrous MgSO$_4$ and concentrated in vacuo to afford the crude ester which was used without further purification. The crude oil was dissolved in methanol (150 mL) followed by addition of sodium hydroxide (16.8 g, 300.0 mmol) and water (50 mL). The flask was stirred at room temperature for 48 h then quenched by acidification with 6 M HCl. The mixture was concentrated in vacuo then extracted with CH$_2$Cl$_2$ (3 × 100 mL). The combined organic layers were dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo to afford the crude acid. Purification by recrystallisation from ethanol/water afforded acid 297 as a white solid (5.71 g, 35%); mp 93–94 °C {Lit.$^{141}$ 91–92 °C}; $\delta_{H}$ (300 MHz, CDCl$_3$) 2.62 (3H, d, $J$ 1.3, C–CH$_3$), 6.19 (1H, q, $J$ 1.3, C=CH$_2$), 7.37 – 7.43 (3H, m, 2 × PhC(3)H, PhC(4)H), 7.44 – 7.57 (2H, m, 2 × PhC(2)H). Data in agreement with the literature.$^{141}$

(Z)-Ethyl cinnamate (206)

Ethyl phenylpropionate (1.0 mL, 6.00 mmol) was dissolved in a mixture of hexane and 1-hexene (7:2 v/v, 12 mL) under N$_2$ at rt, followed by addition of quinoline (1.1 mL, 9.00 mmol) and palladium on calcium carbonate (Lindlar’s catalyst, 360 mg). The flask was
connected to a hydrogen-filled balloon (1 atm) and stirred at rt. The progress of the reaction was monitored by TLC (CH₂Cl₂). The starting alkyne was consumed after 1 h and the reaction was stopped by displacement of the hydrogen atmosphere with nitrogen. The resulting mixture was filtered through a Celite pad, and the filtrate was washed with 10% acetic acid (4 × 50 mL), water (3 × 50 mL), and saturated NaHCO₃ (4 × 50 mL), then dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography to give the ester 206 as a clear oil (458 mg, 43%); δH (300 MHz, CDCl₃) 1.25 (3H, t, J 7.2, C₃H₃), 4.17 (2H, q, J 7.2, OC₂H₂), 5.95 (1H, d, 12.6, PhCH=CH₂), 6.95 (1H, d, 12.6, PhCH=CH₂), 7.32-7.39 (3H, m, ArH), 7.56-7.60 (2H, m, ArH). Data in agreement with the literature.¹⁴⁵

(Z)-Cinnamic acid (209)

\[
\text{Ph} - \text{CO₂Et} \xrightarrow{\text{LiOH.H₂O}} \xrightarrow{\text{H₂O}} \text{Ph} - \text{CO₂H}
\]

To a solution of cis-ethyl cinnamate (458 mg, 2.60 mmol) in THF (37 mL), was added a solution of LiOH.H₂O (327 mg, 7.80 mmol) in H₂O (12 mL) at rt. The resulting reaction mixture was heated at 60 °C for 16 h then cooled to room temperature and acidified with 8 M HCl. The aqueous phase was extracted with Et₂O (3 × 50 mL) and the combined organic layers were dried over MgSO₄ and concentrated in vacuo to give the acid 209 as a pale yellow solid (327 mg, 85%); mp 64-68 °C {Lit.¹¹ 66-68 °C}; δH (400 MHz, CDCl₃) 5.97 (1H, d, J 12.8, PhCH=CH₂), 7.07 (1H, d, J 12.8, PhCH=CH₂), 7.34-7.39 (3H, m, ArH), 7.58-7.62 (2H, m, ArH). Data in agreement with the literature.⁹⁰

6.3 a,b-Unsaturated Anyhydrides

**General Procedure B: Anhydride Synthesis**

To a solution of carboxylic acid (1.4 equiv) in CH₂Cl₂ or THF as specified (0.8 M) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.HCl (EDCI.HCl) (1.0 equiv) and the solution stirred for 1-2 h at room temperature. The solution was diluted with CH₂Cl₂ (50 mL) and then washed sequentially with water (2 × 50 mL) and saturated aqueous NaHCO₃ solution (50 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to afford the homoanhydride.
(E)-Cinnamic anhydride (149)

The title compound was prepared according to General Procedure B from (E)-cinnamic acid (741 mg, 5.00 mmol) and EDCI.HCl (959 mg, 5.00 mmol) in CH₂Cl₂ (6 mL) to give the homoanhydride 149 as a white solid (448 mg, 64%); mp 118–120 ºC {Lit.¹ 130 ºC}; δ_H (400 MHz, CDCl₃) 6.54 (2H, d, J 16.0, ArCH=CH), 7.40–7.47 (6H, m, ArH), 7.54–7.63 (4H, m, ArH), 7.86 (2H, d, J 16.0, ArCH=CH). Data in agreement with the literature.¹⁴⁶,²

(E)-3-(4-(Trifluoromethyl)phenyl)acrylic anhydride (155)

The title compound was prepared according to General Procedure B from 4-trifluoromethylcinnamic acid (1080 mg, 5.00 mmol) and EDCI.HCl (959 mg, 5.00 mmol) in CH₂Cl₂ (10 mL) to give the homoanhydride 155 as a white solid (425 mg, 41%); mp 127–128 ºC; ν_max (film)/cm⁻¹ 1757, 1705 (C=O), 1631 (C=C), 1321 (CF₃); δ_H (300 MHz, CDCl₃) 6.61 (2H, d, J 16.0, CH=CHCO), 7.69 (8H, s, ArH), 7.88 (2H, d, J 16.0, CH=CHCO); δ_C (75 MHz, DMSO) 119.7 (2×CH=CHCO), 123.9 (q, J_CF 270.8, 2×CF₃), 125.9 (q, J_CF 3.7, 4×ArC(3)), 129.6 (4×ArC(2)), 130.8 (q, J_CF 32.0, 2×ArC(4)), 137.5 (2×ArC(1)), 146.7 (2×CH=CHCO), 162.2 (2×CO); δ_F (282 MHz, CDCl₃) −63.5; m/z (ES⁺) 437 ([M+Na]⁺, 20%), 301 ([M-6F]⁺, 100%); HRMS (ES⁺) C₂₀H₁₄F₆O₃Na⁺ ([M+Na]⁺) requires 437.0585, found 437.0588 (−0.8 ppm).

(E)-3-(4-Fluorophenyl)acrylic anhydride (156)

The title compound was prepared according to General Procedure B from (E)-3-(4-fluorophenyl)acrylic acid (166 mg, 1.00 mmol) and EDCI.HCl (96 mg, 0.50 mmol) in CH₂Cl₂ (4 mL) to give the homoanhydride 156 as a white solid (207 mg, 66%); mp 86-90 ºC; ν_max (film)/cm⁻¹ 1755, 1699 (C=O), 1595, 1508; δ_H (300 MHz, CDCl₃) 6.44 (2H, d, J 16.2, ArCH=CH), 7.07-7.16 (4H, m, ArH), 7.54-7.61 (4H, m, ArH), 7.81 (2H, d, J 16.2, ArCH=CH); δ_C (75 MHz, CDCl₃) 116.3 (d, J_CF 22.1, 4×ArC(3)), 116.4 (d, J_CF 2.2,
2×CH=CHCO), 129.9 (d, 3JCF 3.3, 2×ArC(1)), 130.6 (d, 3JCF 8.7, 4×ArC(2)), 147.3 (2×CH=CHCO), 162.3 (2×CO), 164.4 (d, 3JCF 253.2, 2×ArC(4)); δF (300 MHz, CDCl3) -108.1; m/z (FTMA+) 149 ([M-C9H6FO2]+, 100%), 315 ([M+H]+, 25%); HRMS (FTMS+) C18H13F2O3 ([M+H]+) requires 315.0827, found 315.0831 (+1.2 ppm).

(E)-3-(4-Methoxyphenyl)acrylic 3-(4-methoxyphenyl)propanoic anhydride (157)

The title compound was prepared according to General Procedure B from 4-methoxycinnamic acid (891 mg, 5.00 mmol) and EDCI.HCl (959 mg, 5.00 mmol) in THF (20 mL) to give the homoanhydride 157 as a white solid (442 mg, 52%); mp 116-119 °C {Lit.2 104-105 °C}; δH (400 MHz, CDCl3) 3.86 (6H, s, ArOC6H3), 6.39 (2H, d, J 15.8, ArCH=CH), 6.91-6.96 (4H, m, ArH), 7.50-7.57 (4H, m, ArH), 7.80 (2H, d, J 15.8, ArCH=CH). Data in agreement with the literature.147

(E)-3-(Furan-2-yl)acrylic anhydride (163)

The title compound was prepared according to General Procedure B from furylacrylic acid (690 mg, 5.00 mmol) and EDCI.HCl (959 mg, 5.00 mmol) in THF (10 mL) to give the homoanhydride 163 as a brown solid (485 mg, 75%); mp 68-71 °C; νmax (film)/cm⁻¹ 3142 (C-H), 3123 (C-H), 2965 (C-H), 2936 (C-H), 2909 (C-H), 2856 (C-H), 2818 (C-H), 1772 (C=O), 1695 (C=O), 1624 (furan), 1555 (furan), 1474 (furan), 1226 (C-O); δH (300 MHz, CDCl3) 6.39 (2H, d, J 15.5, CH=CHCO), 6.53 (2H, d, J 3.5, ArH), 6.75 (2H, d, J 3.5, furanylC(3)H), 7.55 (2H, d, J 1.7, furanylC(5)H), 7.58 (2H, d, J 15.5, CH=CHCO); δC (75 MHz, CDCl3) 112.9 (2×furanylC(4)), 114.3 (2×furanylC(3)), 117.1 (2×CH=CHCO), 134.3 (2×CH=CHCO), 146.0 (2×furanylC(5)), 150.6 (2×furanylC(2)), 162.7 (2×C=O); m/z (NSI+) 297 ([M+K]+, 100%), 281 ([M+Na]+, 20%); HRMS (NSI+) C14H10O4Na+ ([M+Na]+) requires 281.0420, found 281.0424 (+1.3 ppm).
(E)-3-(Thiophen-2-yl)acrylic anhydride (164)

The title compound was prepared according to General Procedure B from thienylacrylic acid (770 mg, 5.00 mmol) and EDCI.HCl (959 mg, 5.00 mmol) in THF (10 mL) to give the homoanhydride 164 as a brown solid (522 mg, 72%); mp 86-88 °C; \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2972 (C-H), 1728 (C=O), 1296 (C-S-C); \( \delta_{\text{H}} \) (300 MHz, CDCl\(_3\)) 6.30 (2H, d, \( J = 15.7 \), CH=C\( \text{H} \)CO), 7.10 (2H, dd, \( J = 5.0, 3.7 \), thienylC(4)\( \text{H} \)), 7.31-7.38 (2H, d, \( J = 3.7 \), thienylC(3)\( \text{H} \)), 7.48 (2H, d, \( J = 5.0, 1.0 \), thienylC(5)\( \text{H} \)), 7.94 (2H, dt, \( J = 15.7, 0.8 \), CH=CHCO); \( \delta_{\text{C}} \) (75 MHz, CDCl\(_3\)) 115.3 (2×CH=C\( \text{H} \)CO), 128.6 (2×thienylC(4)), 130.3 (2×thienylC(5)), 132.7 (2×thienylC(3)), 139.1 (2×thienylC(2)), 141.0 (2×CH=CHCO), 162.4 (2×C=O); \( m/z \) (ES\(^+\)) 313 ([M+Na]\(^+\), 100%); HRMS (ES\(^+\)) \( C_{14}H_{10}O_3Na\)\(^+\) ([M+Na]\(^+\)) requires 312.9961, found 312.9969 (+2.6 ppm).

(E)-3-(3-Methylphenyl)acrylic anhydride (158)

The title compound was prepared according to General Procedure B from 3-methylcinnamic acid (810 mg, 5.00 mmol) and EDCI.HCl (576 mg, 3.00 mmol) in CH\(_2\)Cl\(_2\) (10 mL) to give the homoanhydride 158 as a white solid (582 mg, 76%); mp 61-64 °C; \( \nu_{\text{max}} \) (film)/cm\(^{-1} \) 2918 (C-H), 1755 (C=O), 1697 (C=O), 1697 (C=C); \( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 2.39 (6H, s, CH\(_3\)), 6.52 (2H, d, \( J = 15.9 \), CH=CHCO), 7.16-7.42 (8H, m, Ar\( \text{H} \)), 7.83 (2H, d, \( J = 15.9 \), CH=CHCO); \( \delta_{\text{C}} \) (75 MHz, CDCl\(_3\)) 21.5 (2×CH\(_3\)), 116.4 (2×CH=CHCO), 126.0 (2×ArC(6)H), 129.1 (2×ArC(2)H), 129.3 (2×ArC(4)H), 132.3 (2×ArC(5)H), 133.8 (2×ArC(1)), 138.9 (2×ArC(3)), 149.0 (2×CH=CHCO), 162.7 (2×C=O); \( m/z \) (ES\(^+\)) 329 ([M+Na]\(^+\), 100%); HRMS (ES\(^+\)) \( C_{20}H_{16}O_3Na\)\(^+\) ([M+Na]\(^+\)) requires 329.1156, found 329.1154 (+0.7 ppm).
6. Experimental

(E)-3-(3-Chlorophenyl)acrylic anhydride (159)

The title compound was prepared according to General Procedure B from 3-chlorocinnamic acid (732 mg, 4.00 mmol) and EDCI.HCl (461 mg, 2.40 mmol) in CH₂Cl₂ (20 mL) to give the homoanhydride 159 as a white solid (389 mg, 56%); mp 96-99 °C; νmax (film)/cm⁻¹ 3082 (C–H), 1759 (C=O), 1632 (C=C), 1095 (C–Cl); δH (400 MHz, CDCl₃) 6.52 (2H, d, J 15.9, CH=C₃H₂), 7.33-7.49 (6H, m, ArH), 7.57 (2H, t, J 1.7, ArH), 7.78 (2H, d, J 15.9, CH=CHCO); δC (100 MHz, CDCl₃) 118.2 (2×CH=C₃H₂), 126.9 (2×ArC₆H₄), 128.4 (2×ArCH), 130.5 (2×ArCH), 131.3 (2×ArCH), 135.3 (2×ArC), 135.6 (2×ArC), 147.2 (2×CH=CHCO), 162.0 (2×C=O); m/z (ES⁺) 369 ([M+Na]⁺, 10%); HRMS (ES⁺) C₁₈H₁₂Cl₃O₃Na⁺ ([M+Na]⁺) requires 369.0065, found 369.0061 (+0.9 ppm).

(E)-3-(2-Chlorophenyl)acrylic anhydride (S1)

The title compound was prepared according to General Procedure B from 2-chlorocinnamic acid (913 mg, 5.00 mmol) and EDCI.HCl (576 mg, 3.0 mmol) in CH₂Cl₂ (20 mL) to give the homoanhydride S1 as a white solid (417 mg, 48%); mp 139-139 °C; νmax (film)/cm⁻¹ 3082 (C–H), 1759 (C=O), 1632 (C=C), 1078 (C–Cl); δH (400 MHz, CDCl₃) 6.54 (2H, d, J 16.0, CH=C₃H₂), 7.30-7.40 (4H, m, ArH), 7.44-7.47 (2H, m, ArC(5)H), 7.68 (2H, dd, J 7.6, 1.7, ArC(6)H), 8.29 (2H, d, J 16.0, CH=CHCO); δC (100 MHz, CDCl₃) 119.4 (2×CH=C₃H₂), 127.4 (2×ArC₆H₄), 128.1 (2×ArCH), 130.5 (2×ArCH), 132.1 (2×ArC), 132.2 (2×ArCCl), 135.6 (2×ArC), 144.4 (2×CH=CHCO), 161.9 (2×C=O); m/z (ES⁺) 369 ([M+Na]⁺, 50%); HRMS (ES⁺) C₁₈H₁₂Cl₃O₃Na⁺ ([M+Na]⁺) requires 369.0054, found 369.0061 (~1.9 ppm).

(E)-But-2-enoic anhydride (160)

The title compound was prepared according to General Procedure B from crotonic acid (258 mg, 3.00 mmol) and EDCI.HCl (576 mg, 3.00 mmol) in CH₂Cl₂ (6 mL) to give the homoanhydride 160 as a colourless oil (136 mg, 59%); δH (400 MHz, CDCl₃) 1.95 (6H, dd, J
7.0, 1.7, CH$_3$), 5.91 (2H, dq, J 15.5, 1.7, CH$_3$CH=CH$_2$), 7.14 (2H, dq, J 15.5, 7.0, CH$_3$CH=CH$_2$). Data in agreement with the literature.  

(E)-Hex-2-enoic anhydride (161)

The title compound was prepared according to General Procedure B from trans-2-hexenoic acid (342 mg, 3.00 mmol) and EDCI.HCl (576 mg, 3.00 mmol) in CH$_2$Cl$_2$ (6 mL) to give the homoanhydride 161 as a colourless oil (171 mg, 54%); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2962 (C=H), 2934 (C-H), 1780 (C=O), 1645 (C=C); $\delta_{\text{H}}$ (300 MHz, CDCl$_3$) 0.88 (6H, t, J 7.4, CH$_3$), 1.45 (4H, h, J 7.4, C(5)H$_2$), 2.17 (4H, qd, J 7.2, 1.6, C(4)H$_2$), 5.81 (2H, dt, J 15.6, 1.6, CH=CHCO), 7.06 (2H, dt, J 15.6, 7.0, CH=CHCO); $\delta_{\text{C}}$ (75 MHz, CDCl$_3$) 13.6 (2×CH$_3$), 21.1 (2×C(5)H$_2$), 34.5 (2×C(4)H$_2$), 120.6 (2×CH=CHCO), 154.0 (2×CH=CHCO), 162.1 (2×CO); $m/z$ (NSI$^+$) 228 ([M+NH$_4$]$^+$, 100%); HRMS (NSI$^+$) C$_{12}$H$_{22}$NO$_3$ $^+$ ([M+NH$_4$]$^+$) requires 228.1594, found 228.1596 (+0.8 ppm).

(E)-2-Bromocinnamic anhydride (S2)

The title compound was prepared according to General Procedure B from (E)-2-bromocinnamic acid (225 mg, 5.00 mmol) and EDCI.HCl (576 mg, 3.00 mmol) in CH$_2$Cl$_2$ (10 mL) to give the homoanhydride S2 as a white solid (394 mg, 36%); mp 135–138 °C; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2970 (C=H), 1759 (C=O), 1701 (C=O), 1624 (C=C); $\delta_{\text{H}}$ (500 MHz, CDCl$_3$) 6.49 (2H, d, J 15.9, ArCH=CH$_2$), 7.29 (2H, td, J 7.7, 1.7, ArC(3)H), 7.35 – 7.40 (2H, m, ArC(5)H), 7.66 (4H, ddd, J 9.1, 8.0, 1.5, ArC(4)H, ArC(6)H), 8.26 (2H, d, J 15.9, ArCH=CH$_2$); $\delta_{\text{C}}$ (126 MHz, CDCl$_3$) 119.4 (2×ArCH=CH$_2$), 125.9 (2×ArC(1)Br), 127.9 (2×ArC(5)H), 128.1 (2×ArC(3)H), 132.2 (2×ArC(4)H), 133.7 (2×ArC(6)H), 133.7 (2×ArC(2)), 146.8 (2×ArC=CH$_2$), 161.7 (2×CO); $m/z$ (APCI$^+$) 211 ([M–C$_9$H$_5$BrO$_2$]$^+$, 100%), 437 ([M+H]$^+$, 60%), 454 ([M+NH$_4$]$^+$, 80%); HRMS (APCI$^+$) C$_{18}$H$_{13}$Br$^{89}$O$_3$ ([M+H]$^+$) requires 434.9226, found 434.9221 (–1.1 ppm).
(E)-3-Bromocinnamic anhydride (S3)

![Structure of (E)-3-Bromocinnamic anhydride (S3)](image)

The title compound was prepared according to General Procedure B from (E)-3-bromocinnamic acid (7.95 g, 35.0 mmol) and EDCl.HCl (4.03 g, 21.0 mmol) in CH$_2$Cl$_2$ (50 mL) to give the homoanhydride S3 as a white solid (4.75 g, 62%); mp 126–128 °C; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3078 (C-H), 1755 (C=O), 1627 (C=C); $\delta_h$ (500 MHz, CDCl$_3$) 6.51 (2H, d, $J$ 15.9, ArCH=CH), 7.31 (2H, t, $J$ 7.9, ArC(5)H), 7.50 (2H, dt, $J$ 7.8, 1.3 ArC(6)H), 7.57 (2H, ddd, $J$ 8.0, 2.0, 1.0, ArC(4)H), 7.73 (2H, t, $J$ 1.8, ArC(2)H), 7.77 (2H, d, $J$ 15.9, ArCH=CH); $\delta_c$ (75 MHz, CDCl$_3$) 118.2 ($2 \times$ ArCH=C), 123.4 ($2 \times$ ArC(1)Br), 130.7 ($2 \times$ ArC(5)H), 131.3 ($2 \times$ ArC(6)H), 134.2 ($2 \times$ ArC(2)H), 135.8 ($2 \times$ ArC(4)H), 147.1 ($2 \times$ ArCH=CH), 162.0 ($2 \times$ CO); $m/\zeta$ (APCI$^+$) 211 ([M–C$_9$H$_6$BrO$_2$]$,^+$, 100%), 437 ([M+H]$^+$, 65%), 454 ([M+NH$_4$]$^+$, 75%); HRMS (APCI$^+$) C$_{18}$H$_{13}$Br$_7$O$_3$ ([M+H]$^+$) requires 434.9226, found 434.9223 (–0.7 ppm).

(2E)-3-(Furan-3-yl)prop-2-enoic anhydride (S4)

![Structure of (2E)-3-(Furan-3-yl)prop-2-enoic anhydride (S4)](image)

The title compound was prepared according to General Procedure B from (2E)-3-(furan-3-yl)prop-2-enoic acid (1.38 g, 10.0 mmol) and EDCl.HCl (1.15 g, 6.00 mmol) in THF (10 mL) to give the homoanhydride S4 as a brown solid (0.87 g, 67%); mp 109–110 °C; $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3125 (C-H), 1775 (C=O), 1632 (C=C); $\delta_h$ (500 MHz, CDCl$_3$) 6.22 (2H, d, $J$ 15.7, ArCH=CH), 6.63 (2H, d, $J$ 2.0, ArC(4)H), 7.47 (2H, d, $J$ 1.8, ArC(5)H), 7.73 (2H, s, ArC(2)H), 7.74 (2H, d, $J$ 15.7, ArCH=CH); $\delta_c$ (75 MHz, CDCl$_3$) 107.5 ($2 \times$ furylC(4)H), 116.6 ($2 \times$ ArCH=CH), 122.6 ($2 \times$ furylC(3)), 138.7 ($2 \times$ furylC(2)H), 145.0 ($2 \times$ furylC(5)H), 145.9 ($2 \times$ ArCH=CH), 162.6 ($2 \times$ CO); $m/\zeta$ (APCI$^+$) 121 ([M–C$_4$H$_7$O$_3$]$^+$, 100%), 259 ([M+H]$^+$, 35%), 276 ([M+NH$_4$]$^+$, 30%); HRMS (APCI$^+$) C$_{14}$H$_{11}$O$_3$ ([M+H]$^+$) requires 259.0601, found 259.0596 (–1.9 ppm).
6. Experimental

(2E)-3-(Thiophen-3-yl)prop-2-enoic anhydride (S5)

![Chemical structure of (2E)-3-(Thiophen-3-yl)prop-2-enoic anhydride (S5)]

The title compound was prepared according to General Procedure B from (2E)-3-(thiophen-3-yl)prop-2-enoic acid (1.54 g, 10.0 mmol) and EDCI.HCl (1.15 g, 6.00 mmol) in THF (10 mL) to give the homoanhydride S5 as a brown solid (1.16 g, 80%); mp 102–105 °C; νmax (film)/cm−1 3097 (C–H), 1771 (C=O), 1620 (C=C); δH (500 MHz, CDCl3) 6.33 (2H, d, J 15.8, ArCH=C=H), 7.34 (2H, dd, J 5.1, 1.3, ArC(4)H), 7.38 (2H, dd, J 5.2, 2.9, ArC(5)H), 7.61 (2H, dd, J 3.0, 1.3, ArC(2)H), 7.82 (2H, d, J 15.8, ArC=CH); δC (126 MHz, CDCl3) 116.4 (2 × ArCH=C=H), 125.3 (2 × thiopheneC(5)H), 127.6 (2 × thiopheneC(4)H), 130.2 (2 × thiopheneC(2)H), 137.1 (2 × thiopheneC(3)), 142.0 (2 × ArCH=CH), 162.9 (2 × CO); m/z [APCI]+ 137 ([M–C7H5O2S]+, 100%), 291 ([M+H]+, 30%), 308 ([M+NH4]+, 55%); HRMS (APCI+) C14H11O3S2 ([M+H]+) requires 291.0144, found 291.0140 (–1.4 ppm).

(E)-2,4,6-Trimethylcinnamic anhydride (S6)

![Chemical structure of (E)-2,4,6-Trimethylcinnamic anhydride (S6)]

The title compound was prepared according to General Procedure B from (E)-2,4,6-trimethylcinnamic acid (2.85 g, 15.0 mmol) and EDCI.HCl (1.73 g, 9.00 mmol) in CH2Cl2 (20 mL) to give the homoanhydride S6 as a pale brown solid (1.34 g, 49%); mp 131–133 °C; νmax (film)/cm−1 2859 (C–H), 1757 (C=O), 1605 (C=C); δH (300 MHz, CDCl3) 2.30 (6H, s, ArC(4)CH3), 2.38 (12H, s, ArC(2,6)CH3), 6.18 (2H, d, J 16.3, ArCH=CH), 6.88–6.95 (4H, m, ArC(3,5)H), 8.06 (2H, d, J 16.3, ArCH=CH); δC (126 MHz, CDCl3) 21.2 (2 × ArC(4)CH3), 21.4 (4 × ArC(2,6)CH3), 121.5 (2 × ArCH=CH), 129.6 (4 × ArC(3)H), 130.2 (2 × ArC(1)), 137.5 (4 × ArC(2,6)CH3), 139.5 (2 × ArC(4)CH3), 147.3 (2 × ArCH=CH), 162.7 (2 × CO); m/z [APCI]+ 173 ([M–C12H13O2]+, 100%), 363 ([M+H]+, 5%), 380 ([M+NH4]+, 20%); HRMS (APCI+) C24H27O3 ([M+H]+) requires 363.1955, found 363.1951 (–1.0 ppm).

(E)-4,4,4-Trifluoro-3-methylbut-2-enoic anhydride (309)

![Chemical structure of (E)-4,4,4-Trifluoro-3-methylbut-2-enoic anhydride (309)]

The title compound was prepared according to General Procedure B from (E)-4,4,4-trifluoro-3-methylbut-2-enoic acid (2.31 g, 15.0 mmol) and EDCI.HCl (1.73 g, 9.00 mmol) in
CH₂Cl₂ (25 mL) to give the homoanhydride 309 as a pale yellow oil\textsuperscript{xxi} (1.33 g, 60%); \( \nu_{\max} \) \textsuperscript{(film)}/cm\textsuperscript{-1} 2642 (C-H), 1707 (C=O), 1292 (C-F); \( \delta_{\text{H}} \) (500 MHz, CDCl\textsubscript{3}) 2.32 (3H, d, \( J = 1.6, 2 \times CH_{3} \)), 6.33 (1H, dt, \( J = 3.0, 1.6, 2 \times C=CH_{2} \)); \( \delta_{C} \) (126 MHz, CDCl\textsubscript{3}) 13.1 (2 × CH\textsubscript{3}), 119.63 (q, \( 3J_{CF} = 5.8, 2 \times C=C=CH \)), 122.67 (q, \( 1J_{CF} = 274.8, 2 \times CF_{3} \)), 147.78 (q, \( 2J_{CF} = 31.0, 2 \times C\equivCH \)), 159.40 (2 × CO); \( \delta_{F} \) (471 MHz, CDCl\textsubscript{3}) -71.63; \( m/z \) (APCI\textsuperscript{+}) 137 ([M-C\textsubscript{5}H\textsubscript{4}F\textsubscript{3}O\textsubscript{2}]\textsuperscript{+}, 75%); 221 (unknown degradation peak, 100%), 291 ([M+H\textsuperscript{+}]\textsuperscript{+}, 75%); HRMS (APCI\textsuperscript{+}) C\textsubscript{10}H\textsubscript{9}F\textsubscript{6}O\textsubscript{3} ([M+H\textsuperscript{+}]\textsuperscript{+}) requires 291.0450, found 291.0445 (–1.9 ppm).

\textbf{(E)-2-Methylbut-2-enoic anhydride (S7)}

The title compound was prepared according to \textit{General Procedure B} from (E)-2-methylbut-2-enoic acid (500 mg, 5.00 mmol) and EDCI.HCl (576 mg, 3.00 mmol) in CH₂Cl₂ (10 mL) to give the homoanhydride S7 as a pale yellow oil (205 mg, 45%); \( \delta_{H} \) (500 MHz, CDCl\textsubscript{3}) 1.84 (3H, dd, \( J = 7.2, 1.3, C(3)C\textsubscript{H} \)), 1.86 (3H, d, \( J = 1.3, C(2)C\textsubscript{H} \)), 6.97 (1H, dddd, \( J = 8.5, 7.1, 5.7, 1.4, C(3)H \)). Data in agreement with the literature.\textsuperscript{149}

\textbf{2-Cyclohexylideneacetic anhydride (307)}

The title compound was prepared according to \textit{General Procedure B} from 2-cyclohexylideneacetic acid (1.40 g, 10.0 mmol) and EDCI.HCl (1.15 g, 6.00 mmol) in CH₂Cl₂ (20 mL) to give the homoanhydride 307 as a colourless oil (0.59 g, 45%); \( \nu_{\max} \) \textsuperscript{(film)}/cm\textsuperscript{-1} 2926 (C-H), 2855 (C-H), 1776 (C=O), 1676 (C-O), 1630 (C=C); \( \delta_{H} \) (400 MHz, CDCl\textsubscript{3}) 1.48 – 1.73 (12H, m, 6 × CH\textsubscript{3}), 2.20 – 2.28 (4H, m, 4 × CH\textsubscript{2}C=CH\textsubscript{2}), 2.77 – 2.88 (4H, m, 4 × CH\textsubscript{2}C=CH\textsubscript{2}), 5.53 – 5.74 (2H, m, 2 × C=CH\textsubscript{2}); \( \delta_{C} \) (101 MHz, CDCl\textsubscript{3}) 26.2 (2 × CH\textsubscript{2}), 27.3 (2 × CH\textsubscript{2}), 28.4 (2 × CH\textsubscript{3}), 30.4 (2 × CH\textsubscript{2}), 38.3 (2 × CH\textsubscript{2}C=CH\textsubscript{2}), 112.3 (2 × CH\textsubscript{2}C=CH\textsubscript{2}), 162.2 (2 × C=CH\textsubscript{2}), 169.7 (2 × C=O); \( m/z \) (APCI\textsuperscript{+}) 123 ([M–C\textsubscript{6}H\textsubscript{11}O\textsubscript{3}]\textsuperscript{+}, 100%), 263 ([M+H\textsuperscript{+}]\textsuperscript{+}, 40%), 280 ([M+NH\textsubscript{4}]\textsuperscript{+}, 45%); HRMS (APCI\textsuperscript{+}) C\textsubscript{16}H\textsubscript{23}O\textsubscript{3} ([M+H\textsuperscript{+}]\textsuperscript{+}) requires 263.1642, found 263.1637 (–1.8 ppm).

\textsuperscript{xxi} xxii The product was approximately 80% pure and used without further purification.
(2E)-3-Phenylbut-2-enoic anhydride (306)

The title compound was prepared according to General Procedure B from (2E)-3-phenylbut-2-enoic acid (3.24 g, 20.0 mmol) and EDCI.HCl (2.30 g, 12.0 mmol) in CH$_2$Cl$_2$ (50 mL) to give the homoanhydride 306 as a pale yellow oil (1.77 g, 58%); $\nu_{max}$ (film) /cm$^{-1}$ 2922 (C-H), 2852 (C-H), 1771 (C=O), 1709 (C-O), 1609 (C=C); $\delta$H (500 MHz, CDCl$_3$) 2.66 (6H, d, $J$ 1.3, C$_3$H$_3$), 6.19 (2H, d, $J$ 1.3, C=C$_3$H$_3$), 7.38 – 7.44 (6H, m, PhC(2)H, PhC(4)H), 7.49 – 7.53 (4H, m, PhC(3)H), 13.84 (2×C$_3$H$_3$), 115.9 (2×C=C$_3$H), 126.6 (4×ArC(2)H), 128.8 (4×ArC(3)H), 129.9 (2×ArC(4)H), 141.7 (2×ArC(1)), 161.4 (2×CO), 162.3 (2×C=CH); m/z (APCI$^+$) 145 ([M–C$_{10}$H$_7$O$_2$]$^+$, 80%), 307 ([M+H]$^+$, 5%), 324 ([M+NH$_4]^+$, 10%), 318 (unknown product, 100%); HRMS (APCI$^+$) C$_{20}$H$_{19}$O$_3$ ([M+H]$^+$) requires 307.1329, found 307.1326 (–0.9 ppm).

3-Methylbut-2-enoic anhydride (304)

The title compound was prepared according to General Procedure B from 3-methylbut-2-enoic acid (2.00 g, 20.0 mmol) and EDCI.HCl (2.30 g, 12.0 mmol) in CH$_2$Cl$_2$ (50 mL) to give the homoanhydride 304 as a colourless oil (0.71 g, 39%); $\delta$H (500 MHz, CDCl$_3$) 1.93 (3H, d, $J$ 1.5, C$_3$H$_3$), 2.19 (3H, d, $J$ 1.5, C$_3$H$_3$), 5.68 (1H, h, $J$ 1.4, C=CH$_3$). Data in agreement with the literature.

(E)-4-Ethoxy-4-oxobut-2-enoic anhydride (S8)

The title compound was prepared according to General Procedure B from (E)-4-ethoxy-4-oxobut-2-enoic acid (1.44 g, 10.0 mmol) and EDCI.HCl (1.15 g, 6.00 mmol) in CH$_2$Cl$_2$ (20 mL) to give the homoanhydride S8 as a brown oil (795 mg, 59%); $\nu_{max}$ (film) /cm$^{-1}$ 2986 (C-H), 1798 (C=O), 1721 (C=O); $\delta$H (500 MHz, CDCl$_3$) 1.33 (6H, t, $J$ 7.2, CH$_3$), 4.29 (4H, q, $J$ 7.2, CH$_2$CH$_3$), 6.87 (2H, d, $J$ 15.7, CO$_2$EtCH=CH$_2$), 6.98 (2H, d, $J$ 15.8, CO$_2$EtCH=CH$_2$); $\delta$c (75 MHz, CDCl$_3$) 14.2 (2×CH$_3$), 6.20 (2×CH$_3$), 131.4 (2×CO$_2$EtCH=CH$_2$), 137.5 (2×CO$_2$EtCH=CH$_2$), 159.7 (2×C=CHCO), 164 (2×CO$_2$Et); m/z (APCI$^+$) 127 ([M–C$_{10}$H$_7$O$_4$]$^+$, 100%).
6. Experimental

35%), 271 ([M+H]⁺, 5%), 288 ([M+NH₄⁺], 100%); HRMS (APCI⁺) C₁₂H₁₈NO₇ ([M+NH₄⁺]) requires 288.1078, found 288.1074 (−1.3 ppm).

(E)-3,7-Dimethylocta-2,6-dienoic anhydride (E,E)-308

The title compound was prepared according to General Procedure B from (2E)-3,7-dimethylocta-2,6-dienoic acid (840 mg, 5.00 mmol) and EDCI.HCl (576 mg, 3.00 mmol) in CH₂Cl₂ (10 mL) to give the homoanhydride (E,E)-308 as a colourless oil (492 mg, 62%); νmax (film) /cm⁻¹ 2968 (C-H), 2916 (C-H), 2857 (C-H), 2359 (C-H), 1778 (C=O), 1716 (C-O), 1634 (C=C); δH (400 MHz, CDCl₃) 1.61 (6H, d, J 1.4, C(7)CH₃(CH₃)), 1.67 (6H, d, J 1.5, C(7)CH₃(CH₃)), 2.14 – 2.25 (14H, m, C(3)CH₃, C(4)H₂, C(5)H₂), 5.03 – 5.10 (2H, m, C(6)H), 5.67 – 5.72 (2H, m, C(2)H); δC (101 MHz, CDCl₃) 17.8 (2 × CH₃), 19.6 (2 × CH₃), 25.1 (2 × CH₃), 26.0 (2 × CH₃), 41.3 (2 × CH₂), 114.9 (2 × C(2)H), 122.7 (2 × C(6)H), 132.9 (2 × C(7)); m/z (APCI⁺) 151 ([M–C₁₀H₁₅O₂]⁺, 75%), 336 ([M+NH₄⁺], 30%); HRMS (APCI⁺) C₂₀H₃₄NO₃ ([M+NH₄⁺]) requires 336.2533, found 336.2528 (−1.5 ppm).

(Z)-3,7-Dimethylocta-2,6-dienoic anhydride (R,R)-308

The title compound was prepared according to General Procedure B from (2Z)-3,7-dimethylocta-2,6-dienoic acid (840 mg, 5.00 mmol) and EDCI.HCl (576 mg, 3.00 mmol) in CH₂Cl₂ (20 mL) to give the homoanhydride (R,R)-308 as a colourless oil (490 mg, 62%); νmax (film) /cm⁻¹ 2970 (C-H), 2914 (C-H), 2859 (C-H), 2359 (C-H), 2342 (C-H), 1776 (C=O), 1717 (C-O), 1632 (C=C); δH (400 MHz, CDCl₃) 1.62 (6H, d, J 1.5, C(7)CH₃(CH₃)), 1.68 (6H, d, J 1.5, C(7)CH₃(CH₃)), 1.95 (6H, d, J 1.4, C(3)CH₃), 2.13 – 2.23 (4H, m, CH₂), 2.61 – 2.71 (4H, m, CH₂), 5.10 – 5.17 (2H, m, C(6)H), 5.65 – 5.70 (2H, m, C(2)H); δC (101 MHz, CDCl₃) 17.7 (2 × CH₃), 25.9 (2 × CH₃), 26.7 (2 × CH₂), 34.1 (2 × CH₂), 43.7 (2 × CH₂), 115.4 (2 × C(2)H), 123.4 (2 × C(6)H), 132.6 (2 × C(7)), 161.6 (2 × C(1)O), 166.6 (2

The product was approximately 80% pure and used without further purification

The product was approximately 90% pure and used without further purification.
× C(3)); m/z (APCI) 151 ([M–C₈H₁₅O₃]⁺, 100%), 336 ([M+NH₄]⁺, 10%); HRMS (APCI) C₂₀H₃₄NO₃ ([M+NH₄]⁺) requires 336.2533, found 336.2526 (–2.4 ppm).

(Z)-Cinnamic anhydride (210)

The title compound was prepared according to General Procedure B from (Z)-cinnamic acid (318 mg, 2.15 mmol) and EDC.HCl (206 mg, 1.07 mmol) in CH₂Cl₂ (10 mL) to give the homoanhydride 210 as a white gumxxii (169 mg, 56%); νmax (film)/cm⁻¹ 2963 (C-H), 1778 (C=O), 1717 (C=O), 1616 (C=C), 1020 (C-O); δH (400 MHz, CDCl₃) 5.85 (2H, d, J 12.5, ArCH=CH), 7.11 (2H, d, J 12.5, ArCH=CH), 7.32-7.42 (6H, m, ArH), 7.56-7.71 (4H, m, ArH); δC (100 MHz, CDCl₃) 117.8 (2×ArCH=CH), 126.3 (4×ArH), 130.0 (2×ArCH), 130.2 (4×ArH), 134.2 (2×ArC), 147.9 (2×ArCH=CH), 161.4 (2×CO); m/z (ES⁺) 301 ([M+Na]⁺, 100%); HRMS (ES⁺) C₁₈H₁₄O₃Na⁺ ([M+Na]⁺) requires 301.0841, found 301.0840 (–0.3 ppm).

(E)-4-Methylpent-2-enoic anhydride (162)

The title compound was prepared according to General Procedure B from 4-methyl-pentenoic acid (570 mg, 5.00 mmol) and EDC.HCl (959 mg, 5.00 mmol) in CH₂Cl₂ (10 mL) to give the homoanhydride 162 as a colourless oil (194 mg, 37%); δH (400 MHz, CDCl₃) 1.09 (12H, d, J 6.8, CH(CH₃)₂), 2.51 (2H, dpd, J 13.4, 6.8, 1.5, CH(CH₃)₂), 5.83 (2H, dd, J 15.7, 1.5, CH=CHCO), 7.11 (2H, dd, J 15.7, 6.6, CH=CHCO); δC (101 MHz, CDCl₃) 21.13 (CH(CH₃)₂), 31.47 (CH(CH₃)₂), 118.01 (CH=CHCO), 160.21 (CH=CHCO), 162.61 (CHC(O)O). Data in agreement with the literature.¹⁵¹

6.4 Nucleophiles

General Procedure C: Diketone Synthesis

xxii The product was approximately 90% pure and used without further purification.
To a solution of arylketone (1.0 equiv) in THF (10 mL) at −78 °C was added LiHMDS (1.0 M in THF, 1.5 equiv) over 15 min and the resulting mixture stirred at −78 °C for 1 h. Acid chloride (1.2 equiv) was added dropwise as a solution in THF (2 mL) at −78 °C over 5 min 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 H₂O (20 mL), dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification of the residue by chromatography gave the diketone.

**1,3-bis(Furan-2-yl)propane-1,3-dione (179)**

![Chemical structure of 1,3-bis(Furan-2-yl)propane-1,3-dione (179)](image)

The title compound was prepared according to *General Procedure C* from 2-acetylfuran (550 mg, 5.00 mmol), furoyl chloride (590 μL, 6.00 mmol) and LiHMDS (1.0 M in THF, 7.50 mL, 7.50 mmol) and purified by chromatography (20% Et₂O/petrol) to afford diketone 179 as a pale-yellow solid (443 mg, 43% yield); mp 73-74 °C {Lit. 74-75 °C}; δH (400 MHz, CDCl₃) 6.59 (2H, dd, J 3.5, 1.7, Ar(4)H), 6.62 (1H, s, =CH), 7.21 (2H, dd, J 3.5, 0.8, Ar(3)H), 7.62 (2H, dd, J 1.7, 0.8, Ar(5)H). Data in agreement with the literature.¹⁵²

**Compound synthesised by Dr Charlene Fallan.**

**1,3-bis(4-Bromophenyl)propane-1,3-dione (181)**

![Chemical structure of 1,3-bis(4-Bromophenyl)propane-1,3-dione (181)](image)

The title compound was prepared according to *General Procedure C* from 4-bromoacetophenone (995 mg, 5.00 mmol), 4-bromobenzoyl chloride (1.31 g, 6.00 mmol) and LiHMDS (1 M in THF, 7.50 mL, 7.50 mmol) and purified by chromatography (20% Et₂O/petrol) to afford the diketone 181 as a pale-yellow powder (550 mg, 29% yield); mp 185-186 °C {Lit. 185-186 °C}; δH (400 MHz, CDCl₃) 6.79 (1H, s, =CH), 7.64 (4H, d, J 8.7, Ar(3)H), 7.85 (4H, d, J 8.7, Ar(2)H). Data in agreement with the literature.¹⁵³ **Compound synthesised by Dr Charlene Fallan.**
1,3-\textit{bis}(4-Methylphenyl)propane-1,3-dione (180)

The title compound was prepared according to \textit{General Procedure C} from 4-methylacetophenone (671 mg, 5.00 mmol), 4-toluoyl chloride (928 mg, 6.00 mmol) and LiHMDS (1 M in THF, 7.50 mL, 7.50 mmol) and purified by chromatography (20\% Et\textsubscript{2}O/petrol) to afford diketone 180 as a pale-yellow solid (499 mg, 40\% yield); mp 125-126 \degree C {Lit. 127-127.4 \degree C}; \textit{\delta} (400 MHz, CDCl\textsubscript{3}) 2.44 (6H, s, 2 \times \text{ArCH\textsubscript{3}}), 6.83 (1H, s, =CH\textsubscript{H}), 7.30 (4H, d, \text{J} 8.0, \text{Ar(3)}H), 7.90 (4H, dd, \text{J} 8.2, \text{Ar(2)}H). Data in agreement with the literature.\textsuperscript{154} \textbf{Compound synthesised by Dr Charlene Fallan.}

1,3-\textit{bis}(4-Trifluoromethylphenyl)propane-1,3-dione (182)

The title compound was prepared according to \textit{General Procedure C} from 4-trifluoromethylacetophenone (640 mg, 5.00 mmol), 4-trifluoromethylbenzoyl chloride (1.25 g, 6.00 mmol) and LiHMDS (1.0 M in THF, 7.50 mL, 7.50 mmol) and purified by chromatography (20\% Et\textsubscript{2}O/petrol) to afford diketone 182 as a yellow solid (207 mg, 12\% yield); mp 125-126 \degree C; \textit{\delta} (400 MHz, CDCl\textsubscript{3}) 6.89 (1H, s, =CH\textsubscript{H}), 6.83 (1H, s, =CH\textsubscript{H}), 7.78 (4H, d, \text{J} 8.2, \text{Ar(3)}H), 8.11 (4H, d, \text{J} 8.1, \text{Ar(2)}H). Data in agreement with the literature.\textsuperscript{155} \textbf{Compound synthesised by Dr Charlene Fallan.}

\textbf{General Procedure D: Benzazole Synthesis with NaHMDS}

To a degassed solution of chlorobenzazole (1 equiv) and carbonyl nucleophile (3 equiv) in dry toluene (xx mL) was added NaHMDS (3.0 eq, xx M solution in toluene or THF) dropwise at 0 \degree C, and the solution stirred for 5 h at 0 \degree C followed by room temperature for 16 h. Excess NaHMDS was quenched by dropwise addition of saturated aqueous NH\textsubscript{4}Cl (50 mL) at 0 \degree C. The organic layer was separated, then the aqueous layer extracted with EtOAc (2 \times xx mL). The combined organic layers were dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. The residue was as specified to afford the product.
2-Phenacylbenzothiazole (227)

The title compound was prepared according to General Procedure D from 2-chlorobenzothiazole (2.62 mL, 20.0 mmol) and acetophenone (6.99 mL, 60.0 mmol) in dry, degassed toluene (60 mL), with NaHMDS (30 mL, 2 M in THF, 12.0 mmol) and purified by trituration with cold hexane to give the azaarylketone 227 as a yellow-brown solid (4.76 g, 94%); mp 115–117 °C {Lit.9 113–114 °C}; δH (400 MHz, CDCl3) 4.85 (2H, s, keto-CH2COAr), 6.38 (1H, s, enol-CHCOHAr), 7.31 (1H, t, J 7.6, enol-benzothiazole C(6)H), 7.39 (1H, t, J 7.5, enol-benzothiazole C(6)H), 7.42 – 7.52 (6H, m, ArH), 7.51 (1H, t, J 7.7, enol-benzothiazole C(5)H), 7.62 (1H, t, J 7.4, keto-benzothiazole C(5)H), 7.79 (1H, d, J 7.9, enol-benzothiazole C(4)H), 7.82 (1H, d, J 8.2, enol-benzothiazole C(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.156

2-(1,3-Benzothiazol-2-yl)-N,N-dimethylacetamide (256)

The title compound was prepared according to General Procedure D from 2-chlorobenzothiazole (521 μL, 4.00 mmol) and N,N-dimethylacetamide (1.12 mL, 12.0 mmol) in dry, degassed toluene (15 mL), with NaHMDS (6 mL, 2 M in THF, 12.0 mmol) to give the azaaryl amide 256 after aqueous work up as a white solid, no further purification required (875 mg, 99%); mp 98–100 °C {Lit.96 92–93 °C}; δH (300 MHz, CDCl3) 2.88 (3H, s, NCH3CH3), 2.98 (3H, s, NCH3CH3), 4.11 (2H, s, CH3CO), 7.24 (1H, ddd, J 8.4, 7.3, 1.2, benzothiazole C(6)H), 7.34 (1H, ddd, J 8.1, 7.2, 1.2, benzothiazole C(5)H), 7.74 (1H, ddd, J 7.9, 1.3, 0.6, benzothiazole C(4)H), 7.88 (1H, ddd, J 8.2, 1.1, 0.6, benzothiazole C(7)H). Data in agreement with the literature.96
**tert-Butyl 2-(1,3-benzothiazol-2-yl)acetate (257)**

The title compound was prepared according to General Procedure D from 2-chlorobenzothiazole (521 μL, 4.00 mmol) and tert-butylacetate (1.61 mL, 12.0 mmol) in dry, degassed toluene (15 mL), with NaHMDS (20 mL, 0.6 M in toluene, 12.0 mmol) and purified by chromatography (10% hexane/CH₂Cl₂) to give the azarylacetate 257 as an off-white solid (876 mg, 88%); mp 69–72 °C {Lit.¹⁰² (oil)}; δ̇H (300 MHz, CDCl₃) 1.50 (9H, s, C(CH₃)₃), 4.10 (2H, s, CH₂CO), 7.38 (1H, ddd, J 7.8, 7.5, 1.2, benzothiazoleC(6)H), 7.47 (1H, ddd, J 7.8, 7.5, 1.5, benzothiazoleC(5)H), 7.87 (1H, ddd, J 8.0, 1.2, 0.6, benzothiazoleC(4)H), 8.00 (1H, ddd, J 8.0, 1.2, 0.6, benzothiazoleC(7)H). Spectroscopic data in agreement with the literature.¹⁰²

**2-(1,3-Benzoxazol-2-yl)-N,N-dimethylacetamide (258)**

A degassed solution of N,N-dimethylacetamide (5.56 mL, 60.0 mmol) in dry toluene (150 mL) was cooled to −78 °C. To this flask a solution of 2-chlorobenzoazole (4.18 mL, 20.0 mmol) in dry toluene (20 mL) was added via syringe pump over 5 h at −78 °C (slow addition required to minimise double nucleophile addition). The flask was warmed to room temperature for 20 mins then quenched by addition of saturated aqueous NH₄Cl (150 mL). The organic layer was separated, then the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The crude was purified by column chromatography (10% EtOAc/CH₂Cl₂→5% MeOH/CH₂Cl₂) to give the the azarylamide 258 as an off-white solid (1.39 g, 34%); mp 136–137 °C; νₚₑₑₑ (film)/cm⁻¹ 2938 (C-H), 1645 (C=O), 1614 (benzoxazole), 1271 (benzoxazole), 1258 (benzoxazole); δ̇H (500 MHz, CDCl₃) 3.00 (3H, s, CH₃), 3.12 (3H, s, CH₃), 4.06 (2H, s, CH₂), 7.27 – 7.35 (2H, m, benzoxazoleC(5)H, benzoxazoleC(6)H), 7.49 – 7.54 (1H, m, benzoxazoleC(7)H), 7.66 – 7.72 (1H, m, benzoxazoleC(4)H); δ̇C (126 MHz, CDCl₃) 35.0 (CH₂) 35.7 (CH₃), 37.8 (CH₃), 110.6 (benzoxazoleC(7)H), 119.8 (benzoxazoleC(4)H), 124.3 (benzoxazoleC(6)H), 124.9 (benzoxazoleC(5)H), 141.1 (benzoxazoleC(4a)), 151.1 (benzoxazoleC(7a)), 160.8 (benzoxazoleC(2)), 166.1 (C=O); m/z
6. Experimental

(NSI⁺) 205 ([M+H]⁺, 100%), 227 ([M+Na]⁺, 15%); HRMS (NSI⁺) C₁₁H₁₃N₂O₂ ([M+H]⁺) requires 205.0972, found 205.0970 (−0.8 ppm).

**General Procedure E: Benzazole Synthesis via Diesters**

![Diagram of General Procedure E]

To a solution of methylbenzazole (1 equiv) and acyl chloride (2.5 equiv) in HPLC grade acetonitrile stored over molecular sieves (0.6–2.5 M) was added NEt₃ (2.5 equiv) and the solution stirred for 18 h at reflux. On cooling, the double addition ester was isolated by filtration and used immediately without purification. The ester was hydrolysed as specified and the product could be isolated by filtration or aqueous work up.

2-(1,3-Benzothiazol-2-yl)-1-(4-nitrophenyl)ethanone (255)

The title compound was prepared according to **General Procedure E** from 2-methylbenzothiazole (1.27 mL, 10.0 mmol), 4-nitrobenzoyl chloride (4.08 g, 22.0 mmol) and NEt₃ (3.05 mL, 22.0 mmol) in HPLC grade acetonitrile (10 mL) to give the ester as a yellow solid which was used immediately. Heating the ester at reflux in a mixture of DMF (15 mL) and 1-butanol (15 mL) for 16 h gave the *azaarylketone* 255 after filtration as an orange solid (2.32 g, 78%); mp 212–214 °C (dec); ν max (film)/cm⁻¹: 3080 (C-H), 2827 (C-H), 1610 (C=O), 1572 (C=C, aromatic), 1518 (NO₂), 1456 (C=C, heteroaromatic), 1340 (NO₂), 1110 (C-N); δ H (300 MHz, DMSO-d₆) 6.86 (1H, s, enol-C=COH), 7.22 (1H, dt, J 7.9, 4.4, benzothiazole-C(6)H), 7.41 (1H, d, J 3.6, benzothiazole-C(4)H), 7.41–7.56 (1H, m, benzothiazole-C(5)H), 7.84 (1H, d, J 7.8, benzothiazole-C(7)H), 8.11 (2H, d, J 8.7, (C₆H₄NO₂)C(2)H), 8.31 (2H, d, J 8.7, (C₆H₄NO₂)C(3)H); δC (75 MHz, DMSO) 87.7 (enol-CH=COH), 112.0 (benzothiazole-C(4)H), 122.6 (benzothiazole-C(6)H), 122.8 (benzothiazole-C(7)H), 123.8 (2 × (C₆H₄NO₂)C(3)H) 126.3 (benzothiazole-C(7a)), 127.0 (benzothiazole-C(5)H), 127.9 (2 × (C₆H₄NO₂)C(2)H), 138.7 (benzothiazole-C(4a)), 144.8 (C₆H₄NO₂)C(4)), 148.4 (C₆H₄NO₂)C(1)), 163.6 (benzothiazole-C(2)), 179.8 (enol-CH=COH); m/z (NSI⁺) 299 ([M+H]⁺, 100%); HRMS (NSI⁺) C₁₅H₁₁O₃N₁₂S ([M+H]⁺) requires 299.0485, found 299.0484 (−0.3 ppm).
2-Phenacylbenzoxazole (250)

The title compound was prepared according to General Procedure E from 2-methylbenzoxazole (4.76 mL, 40.0 mmol), benzoyl chloride (20.4 mL, 120 mmol) and NEt$_3$ (19.96 mL, 144 mmol) in HPLC grade acetonitrile (200 mL). The acetonitrile was removed in vacuo then the crude dissolved in CH$_2$Cl$_2$ (100 mL). The organic layer was washed with saturated aqueous NaHCO$_3$ solution, dried over MgSO$_4$, filtered, and concentrated in vacuo to reveal the ester as a brown oil that was used without further purification. The crude ester was dissolved in methanol (100 mL), solid KOH (5.6 g, 100.0 mmol) was added portionwise and the flask was stirred at room temperature for 20 h. The methanol was removed in vacuo then the residue dissolved in CH$_2$Cl$_2$ and acidified using 2 M HCl. The aqueous layer was separated and the organic layer washed with saturated aqueous NaHCO$_3$, dried over MgSO$_4$, filtered and concentrated in vacuo. The crude was purified by column chromatography (5% EtOAc/petrol ether) followed by recrystallisation from ethanol to give the azaarylketone 250 as an off-white solid (6.24 g, 67%); mp 90–92 °C {Lit.$^{157}$ 87–89 °C}; $\delta$H (300 MHz, CDCl$_3$) 4.66 (2H, s, keto-C$_2$H$_2$CO), 6.22 (1H, s, enol-CH=COH), 7.27 – 7.39 (4H, m, br, ArH), 7.41 – 7.56 (7H, m, br, ArH), 7.62 (2H, s, br, ArH), 7.72 (1H, s, br, ArH), 7.89 (2H, s, br, ArH), 8.01 – 8.09 (2H, m, br, PhC(2)H)$_2$. Data in agreement with the literature.$^{157}$

2-Phenacylbenzimidazole (254)

The title compound was prepared according to General Procedure E from 2-methylbenzimidazole (6.61 g, 50.0 mmol), benzoyl chloride (19.2 mL, 165 mmol) and NEt$_3$ (22.9 mL, 165 mmol) in HPLC grade acetonitrile (20 mL) to give the ester as a yellow solid which was used immediately. Heating the ester at reflux in isopropylalcohol (50 mL) for 3 h gave the azaarylketone 254 after filtration as a yellow solid as a 1:4 mixture of enamino:keto tautomers (6.54 g, 65%); mp 90–92 °C {Lit.$^{101}$ 178–179 °C}; $\delta$H (300 MHz, DMSO-d$_6$) 4.69 (2H, s, keto-CH$_2$CO), 6.11 (1H, s, enamino-CH$_2$CO), 7.12 – 7.21 (4H, m, benzimidazoleC(5)H and benzimidazoleC(6)H), 7.38 – 7.60 (9H, m, ArH), 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), 12.31 (1H, s, NH). Data in agreement with the literature.\textsuperscript{101}

1-Methyl-2-phenacylbenzimidazole (249)

The title compound was prepared according to General Procedure E from 1,2-dimethylbenzimidazole (1.46 g, 10.0 mmol), benzoyl chloride (2.55 mL, 22.0 mmol) and NEt\textsubscript{3} (3.05 mL, 22.0 mmol) in HPLC grade acetonitrile (10 mL) to give the ester as a yellow solid which was used immediately. Heating the ester at reflux with KOH (0.62 g, 11.0 mmol) and ethanol (10 mL) gave the azaarylketone 249 after filtration as an off-white solid (1.63 g, 65%); mp 138 – 140 °C \{Lit.\textsuperscript{101} 134 – 134.5 °C\}; \(\delta\textsubscript{H} (300 MHz, DMSO-d\textsubscript{6}) 3.72 (3H, s, keto-NC\textsubscript{H}3), 3.77 (3H, s, enamino-NC\textsubscript{H}3), 4.86 (2H, s, keto-CH\textsubscript{2}-CO), 6.30 (1H, s, enamino-\textsubscript{=}C\textsubscript{H}-CO), 7.13 – 7.29 (2H, m, benzimidazoleC(5)H, benzimidazoleC(6)H), 7.41 – 7.53 (4H, m, PhC(3)H, PhC(4)H, benzimidazoleC(7)H), 7.53 – 7.63 (3H, m, PhC(3)H, benzimidazoleC(4)H), 7.61 – 7.75 (1H, m, PhC(4)H), 7.93 – 8.07 (2H, m, PhC(2)H), 8.11 (2H, d, J 7.3, PhC(2)H). Data in agreement with the literature.\textsuperscript{101}

tert-butyl 2-(2-oxo-2-phenylethyl)-1,3-benzodiazole-1-carboxylate (S9)

To a solution of 2-phenacylbenzimidazole (4.73 g, 20.0 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (10 mL) was added NEt\textsubscript{3} (2.91 mL, 21.0 mmol) and DMAP (366 mg, 3.00 mmol) followed by Boc-anhydride (4.58 g, 21.0 mmol). The flask was stirred at room temperature for 18 h then the CH\textsubscript{2}Cl\textsubscript{2} solution was washed with water (15 mL) followed by saturated aqueous NH\textsubscript{4}Cl, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The crude material was purified by column chromatography (CH\textsubscript{2}Cl\textsubscript{2}→5% EtOAc/CH\textsubscript{2}Cl\textsubscript{2} →10% EtOAc/CH\textsubscript{2}Cl\textsubscript{2}) to give the azaarylketone S9 as a pale green solid (3.14 g, 47%); mp 126–128 °C; \(\nu\textsubscript{max} \text{ (film)/cm}^{-1} 2980 \text{ (C-H), 1743 (C=O, Boc), 1694 (C=O, ketone); } \delta\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 1.60 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.78 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 4.99 (2H, s, keto-CH\textsubscript{2}-CO), 7.15 (1H, s, enamino-CHCOH), 7.22 – 7.40 (4H, m, 2 × benzimidazoleC(5)H, 2 × benzimidazoleC(6)H), 7.44 – 7.48 (3H, m, 2
6. Experimental

$\times$ *keto-phenylC(3)H, keto-phenylC(4)H*, $7.51 - 7.56$ (3H, m, $2 \times$ enol-phenylC(3)H, benzimidazoleC(7)H), $7.61 - 7.66$ (1H, m, *enol-phenylC(4)H*), $7.73 - 7.78$ (1H, m, benzimidazoleC(7)H), $7.93 - 7.99$ (4H, m, $2 \times$ *keto-phenylC(2)H, 2 $\times$ benzyldiazoleC(4)H), $8.04 - 8.08$ (2H, m, $2 \times$ *enol-phenylC(2)H); $\delta_c$ (126 MHz, CDCl$_3$) 28.0 (C(CH$_3$)$_3$), 28.3 (C(CH$_3$)$_3$), 42.5 (*keto-CH$_2$CO*), 84.5 (*enol-CHCOH*), 85.8 (C(CH$_3$)$_3$), 85.9 (C(CH$_3$)$_3$), 115.1 (benzimidazoleC(4)H), 115.1 (benzimidazoleC(4)H), 115.8 (benzimidazoleC(7)H), 119.8 (benzimidazoleC(7)H), 123.6 (benzimidazoleC(6)H), 124.2 (benzimidazoleC(5)H), 124.7 (benzimidazoleC(6)H), 124.9 (benzimidazoleC(5)H), 126.2 (2 $\times$ *keto-phenylC(2)H), 128.2 (2 $\times$ *enol-phenylC(2)H), 128.5 (2 $\times$ *keto-phenylC(3)H), 128.9 (2 $\times$ *enol-phenylC(3)H), 130.3 (*keto-phenylC(4)H), 130.5 (benzimidazoleC(7a)), 133.3 (benzimidazoleC(7a)), 133.6 (*enol-phenylC(4)H), 136.4 (*keto-phenylC(1)), 136.7 (*enol-benzimidazoleC(2)), 138.0 (benzimidazoleC(4a)), 142.3 (benzimidazoleC(4a)), 148.9 (CO$_2$C(CH$_3$)$_3$), 149.0 (CO$_2$C(CH$_3$)$_3$), 150.1 (*keto-benzimidazoleC(2)), 154.9 (*enol-phenylC(1)), 171.7 (*enol-CHCOH*), 194.4 (*keto-CH$_2$CO*); $m/z$ (NSI$^+$) 337 ([M+H]$^+$, 100%), 237 ([M+C$_3$H$_2$O$_2$]$^+$, 45%); HRMS (NSI$^+$) C$_{20}$H$_{21}$N$_2$O$_3$ ([M+H]$^+$) requires 337.1547, found 337.1547 (+0.1 ppm).

6.5 **Michael Addition-Lactonisation Products**

**General Procedure F: Lactone formation**

![Michael Addition-Lactonisation Products](image)

To a solution of the corresponding homoanhydride (1.4 equiv) in dry CH$_2$Cl$_2$ (0.72 m) under argon, was added dicarboxyl (1.0 equiv), isothiourea (HBTM 2.1, 0.05 equiv) and polymer-bound 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (PS-BEMP) (1.1 equiv) at 0 °C. The reaction mixture was stirred and gradually warmed to room temperature over 5 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$) to afford the lactone products.
(R)-B-benzoyl-4,6-diphenyl-3,4-dihydro-2H-pyrano-2-one (145)

The title compound was prepared according to modified General Procedure F from (E)-cinnamic anhydride (100 mg, 0.36 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (11.1 mg, 0.036 mmol) and EtN(iPr)2 (78 μL, 0.45 mmol) in CH2Cl2 (0.25 mL) and purified by chromatography (CH2Cl2) to afford the lactone 145 as a white solid (30 mg, 49%); mp 120-125 °C; \([\alpha]_{D}^{22} = -7.6 (c 0.5 \text{ in CHCl}_3)\); \{Lit. \([\alpha]_{D}^{22} = -6.5 (c 1.0 \text{ in CHCl}_3) 95% \text{ ee}\}; chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min\(^{-1}\), 254 nm, 20 °C), \(t_R\) major: 14.7 min, \(t_R\) minor: 32.4 min, 95% ee; δ\(H\) (300 MHz, CDCl3) 3.04 (1H, dd, \(J_15.9, 2.5, \text{ C(3)H}_2\)), 3.19 (1H, dd, \(J_15.9, 7.7, \text{ C(3)H}_2\)), 4.55 (1H, dd, \(J_{7.7, 2.5, (4)H}\)), 7.02-7.29 (11H, m, Ar\(H\)), 7.32-7.38 (2H, m, Ar\(H\)), 7.44-7.51 (2H, m, Ar\(H\)). Data in agreement with the literature.\(^{72}\)

(R)-5-Benzoyl-6-methyl-4-phenyl-3,4-dihydro-2H-pyrano-2-one, (R)-5-Acetyl-4,6-diphenyl-3,4-dihydro-2H-pyrano-2-one (191a, 191b)

The title compound was prepared according to General Procedure F from (E)-cinnamic anhydride (70 mg, 0.25 mmol), 1-phenylbutane-1,3-dione (29 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH2Cl2 (0.25 mL). Chromatographic purification of the residue (CH2Cl2) gave 191a as a white solid (15 mg, 29% in 96:4 rr), 191b as a white solid (2 mg, 4% in 3:96 rr) and a mixture of 191a and 191b (29 mg, 55% in 34:66 rr). Compounds synthesised by Dr Carmen Simal.

191a: mp 80-84 °C; \([\alpha]_{D}^{22} = -19.6 (c 1.0 \text{ in CHCl}_3)\); \{Lit. \([\alpha]_{D}^{22} = -26.7 (c 1.0 \text{ in CHCl}_3) 96% \text{ ee}\}; chiral HPLC analysis, ChiralPak OD-H (15% i-PrOH:hexane, flow rate 1.0 mL min\(^{-1}\), 254 nm, 20 °C), \(t_R\) major: 15.4 min, \(t_R\) minor: 18.9 min, 70% ee; δ\(H\) (300 MHz, CDCl3) 1.91 (3H, d, \(J_{0.9, \text{ CH}_3}\)), 2.95 (1H, dd, \(J_{15.9, 3.6, \text{ CH}_3}\)), 3.08 (1H, dd, \(J_{15.9, 7.5, \text{ CH}_3}\)), 4.32-4.36 (1H, m, \text{ CH}_3), 7.14-7.65 (10H, m, Ar\(H\)).
Representative data for 191b: $[\alpha]_{\text{D}}^{22} = -94.0$ (c 0.15 in CHCl$_3$); chiral HPLC analysis, ChiralPak AS-H (15% i-PrOH:hexane, flow rate 1.0 mL min$^{-1}$, 254 nm, 30 °C), $t_R$ major: 21.4 min, $t_R$ minor: 30.7 min, 61% ee; $\delta$H (500 MHz, CDCl$_3$) 1.80 (3H, s, CH$_3$), 2.94 (1H, dd, $J = 16.0, 2.0$, CH$_2$), 3.06 (1H, dd, $J = 16.0, 7.8$, CH$_2$), 4.48-4.50 (1H, m, CH), 7.21-7.34 (6H, m, ArH), 7.46-7.55 (4H, m, ArH). Data in agreement with the literature.$^9$

$(R)$-Ethyl 2-oxo-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carboxylate (194)

The title compound was prepared according to General Procedure F from (E)-cinnamic anhydride (70 mg, 0.25 mmol), ethyl 3-oxo-3-phenylpropanoate (31 μL, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH$_2$Cl$_2$ (0.25 mL) and purified by chromatography (CH$_2$Cl$_2$) to afford the lactone 194 as a yellow gum (35 mg, 60%); $[\alpha]_{\text{D}}^{22} = -67.0$ (c 1.0 in CHCl$_3$); {Lit.$^9$ $[\alpha]_{\text{D}}^{22} = -70.0$ (c 1.0 in CHCl$_3$, 92% ee); chiral HPLC analysis, ChiralPak AD-H (3% i-PrOH:hexane, flow rate 1.0 mL min$^{-1}$, 254 nm, 20 °C), $t_R$ major: 17.3 min, $t_R$ minor: 26.1 min, 94% ee; $\delta$H (400 MHz, CDCl$_3$) 0.90 (3H, t, $J = 7.2$, CH$_3$), 2.95 (1H, dd, $J = 15.8, 2.4$, C(3)H$_2$), 2.98 (1H, dd, $J = 15.8, 7.6$, C(3)H$_2$), 3.89-4.01 (2H, m, OCH$_2$), 4.43 (1H, dd, $J = 7.6, 2.4$, C(4)H), 7.26-7.54 (10H, m, ArH). Data in agreement with the literature.$^{72}$

$(R)$-Ethyl 2-oxo-6-phenyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-pyran-5-carboxylate (195)

The title compound was prepared according to General Procedure F from (E)-3-(4-(trifluoromethyl)phenyl)acrylic anhydride (104 mg, 0.25 mmol), ethyl 3-oxo-3-phenylpropanoate (31 μL, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH$_2$Cl$_2$ (0.25 mL) and purified by chromatography (CH$_2$Cl$_2$) to afford the lactone 195 as a white gum (43 mg, 61%); $[\alpha]_{\text{D}}^{22} = -56.6$ (c 1.0 in CHCl$_3$); chiral HPLC analysis, ChiralPak AD-H (15% i-PrOH:hexane, flow rate 1.0 mL min$^{-1}$, 254 nm, 30 °C), $t_R$ major: 8.0 min, $t_R$ minor: 11.0 min, 94% ee; $\nu_{\text{max}}$
(R)-Ethyl 4-(4-fluorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (196)

The title compound was prepared according to General Procedure F from (E)-3-(4-fluorophenyl)acrylic anhydride (314 mg, 1.0 mmol), ethyl 3-oxo-3-phenylpropanoate (124 μL, 0.72 mmol), HBTM 2.1 (11.1 mg, 0.036 mmol) and PS-BEMP (2.2 mmol/g loading) (360 mg, 0.80 mmol) in CH₂Cl₂ (1.0 mL) and purified by chromatography (CH₂Cl₂) to afford the lactone 196 as a pale yellow oil (171 mg, 70%); [α]D22 +26.1 (c 1.0 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (10% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C), tr major: 9.4 min, tr minor: 13.1 min, 89% ee; νmax (film)/cm⁻¹ 2926 (C-H), 1784 (C=O), 1705 (C=O), 1508 (C=C), 1224 (C=O); δH (300 MHz, CDCl₃) 0.91 (3H, t, J 7.1, CH₃), 2.94 (1H, dd, J 15.8, 2.4, C(3)H₂), 3.13 (1H, dd, J 15.8, 7.6, C(3)H₂), 3.97 (2H, qd, J 7.1, 2.2, OCH₂), 4.43 (1H, dd, J 7.6, 2.4, C(4)H), 6.99-7.12 (2H, m, FPhC(3,5)H), 7.22-7.28 (2H, m, FPhC(2,6)H), 7.39-7.58 (5H, m, PhH); δC (75 MHz, CDCl₃) 13.6 (CH₃), 36.5 (C(3)H₂), 38.3 (C(4)H), 61.2 (OCH₂), 111.7 (C(5)), 116.2 (d, 2JC,F 21.6, 2×C(4)ArC(3)H), 128.2 (2×ArCH), 128.5 (d, 2JC,F 8.2, 2×C(4)ArC(2)H), 13.0 (ArCH), 133.1 (PhC(1)), 135.8 (d, 2JC,F 3.3, C(4)ArC(1)), 158.8 (C(6)), 162.4 (d, 2JC,F 246.5, CF), 165.9 (CO), 166.4 (CO); δF (282 MHz, CDCl₃) −115.1; m/z (APCI⁺) 341 ([M+H]⁺, 100%); HRMS (APCI⁺) C₂₁H₁₉F₄O₄ ([M+H]⁺) requires 341.1184 found 341.1179 (−1.4 ppm).

Compound synthesised by Dr Carmen Simal.
(R)-Ethyl 4-(3-chlorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (197)

The title compound was prepared according to General Procedure F from (E)-3-chlorophenyl)acrylic anhydride (347 mg, 1.0 mmol), ethyl 3-oxo-3-phenylpropanoate (124 μL, 0.72 mmol), HBTM 2.1 (11.1 mg, 0.036 mmol) and PS-BEMP (2.2 mmol/g loading) (360 mg, 0.80 mmol) in CH₂Cl₂ (1.0 mL) and purified by chromatography (CH₂Cl₂) to afford the lactone 197 as a pale yellow oil (121 mg, 47%); [α]$_D^{22}$ -2.1 (c 0.38 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 0.5 mL min$^{-1}$, 220 nm, 30 °C), $t_R$ major: 25.5 min, $t_R$ minor: 39.1 min, 92% ee; ν$_{max}$ (film)/cm$^{-1}$ 2980 (C-H), 1732 (C=O), 1708 (C=O), 1597 (C=C), 1066 (C-Cl); δ (400 MHz, CDCl$_3$) 0.92 (3H, t, J 7.1, C$_H$), 2.96 (1H, dd, J 15.9, 2.4, C(3)$_H$_2), 3.14 (1H, dd, J 15.9, 7.7, C(3)$_H$_2), 3.98 (2H, qd, J 7.1, 2.0, OCH$_2$), 4.41 (1H, dd, J 7.7, 2.4, C(4)$_H$), 7.17 (1H, dt, J 6.6, 1.9, ArH), 7.25-7.30 (3H, m, ArH), 7.42-7.55 (5H, m, ArH); δ (75 MHz, CDCl$_3$) 13.6 (C$_H$), 36.2 (C(4)$_H$), 38.7 (C(3)$_H$_3), 61.3 (OCH$_2$), 111.1 (C(5)$_H$), 125.0 (ArCH), 127.3 (ArCH), 128.2 (2×ArCH), 128.3 (ArCH), 128.8 (2×ArCH), 130.4 (ArCH), 130.7 (ArCH), 133.0 (PhC(1)), 135.1 (C(4)ArC(3)), 142.1 (C(4)ArC(1)), 159.3 (C(6)$_H$), 165.7 (CO), 166.3 (CO); m/z (APCI$^+$) 357 ([M+H]$^+$, 90%); HRMS (NSI$^+$) C$_{20}$H$_{18}$Cl$_3$O$_4$ ([M+H]$^+$) requires 357.0888, found 357.0888 (−0.0 ppm).

(S)-Ethyl 4-(2-chlorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (198)

The title compound was prepared according to General Procedure F from (E)-3-chlorophenyl)acrylic anhydride (89 mg, 0.25 mmol), ethyl 3-oxo-3-phenylpropanoate (31 μL, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂) to afford
the lactone 198 as a pale yellow oil (29 mg, 46%); [α]$_D^{22}$ = -25.0 (c 1.3 in CHCl$_3$); chiral HPLC analysis, ChiralPak AD-H (15% i-PrOH:hexane, flow rate 1.0 mL min$^{-1}$, 220 nm, 30 °C), t$_R$ major: 6.3 min, t$_S$ minor: 7.4 min, 96% ee; ν$_{max}$ (film)/cm$^{-1}$ 2980 (C-H), 1728 (C=O), 1687 (C=O), 1597 (C=C), 1037 (C-Cl); δ$_H$ (400 MHz, CDCl$_3$) 0.90 (3H, t, J 7.1, CH$_3$), 2.99 (1H, dd, J 15.9, 2.4, C(3)H$_2$), 3.09 (1H, dd, J 16.0, 7.7, C(3)H$_2$), 3.94 (2H, qd, J 7.1, 2.7, OCH$_2$), 4.92 (1H, dd, J 7.7, 2.4, C(4)H), 7.21-7.29 (3H, m ArH), 7.39-7.52 (4H, m, ArH), 7.50-7.61 (2H, m, ArH), δ$_C$ (75 MHz, CDCl$_3$) 13.6 (CH$_3$), 34.7 (C(3)H$_2$), 35.9 (C(4)H), 61.2 (OCH$_3$), 110.6 (C(5)), 127.4 (ArCH), 127.7 (ArCH), 128.2 (2×ArCH), 128.8 (2×ArCH), 129.3 (ArCH), 130.5 (ArCH), 130.5 (ArCH), 132.9 (PhC(1)), 133.5 (C(4)ArC(2)), 136.6 (C(4)ArC(1)), 160.0 (C(6)), 165.7 (CO), 166.0 (CO); m/z (APCI$^+$) 357 ([M+H]$^+$, 65%), 375 ([M+NH$_3$]$^+$, 50%); HRMS (APCI$^+$) C$_{20}$H$_{18}$ClO$_4$ ([M+H]$^+$) requires 357.0888, found 357.0885 (−0.9 ppm).

(5)-Ethyl 4-(furan-2-yl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (200)

![Image of the lactone 200]

The title compound was prepared according to General Procedure F from (E)-3-(furan-2-yl)acrylic anhydride (258 mg, 1.0 mmol), ethyl 3-oxo-3-phenylpropanoate (124 μL, 0.72 mmol), HBTM 2.1 (11.1 mg, 0.036 mmol) and PS-BEMP (2.2 mmol/g loading) (360 mg, 0.80 mmol) in CH$_2$Cl$_2$ (1.0 mL) and purified by chromatography (CH$_2$Cl$_2$) to afford the lactone 200 as a yellow oil (146 mg, 65%); [α]$_D^{22}$ = -6.19 (c 1.0 in CH$_2$Cl$_2$); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 0.5 mL min$^{-1}$, 220 nm, 30 °C), t$_R$ major: 24.8 min, t$_S$ minor: 29.2 min, 92% ee; ν$_{max}$ (film)/cm$^{-1}$ 2982 (C-H), 2928 (C-H), 1728 (C=O), 1684 (C=O), 1014 (C-OC); δ$_H$ (500 MHz, CDCl$_3$) 0.96 (3H, t, J 7.1, CH$_3$CH$_2$H), 2.99 (1H, dd, J 16.0, 7.2, C(3)H$_2$), 3.12 (1H, dd, J 16.0, 1.6, C(3)H$_2$), 3.98-4.05 (2H, m, OCH$_2$), 4.49 (1H, d, J 6.2, C(4)H), 6.18 (1H, d, J 3.0, furylC(3)H), 6.29 (1H, s, furylC(4)H), 7.35 (1H, s, furylC(5)H), 7.37-7.48 (5H, m, PhH); δ$_C$ (75 MHz, CDCl$_3$) 13.6 (CH$_3$), 32.7 (C(4)H), 33.3 (C(3)H$_2$), 61.2 (OCH$_3$), 106.5 (furylC(3)H), 109.5 (C(5)H), 110.5 (furylC(4)H), 128.0 (2×ArCH), 128.7 (2×ArCH), 130.3 (ArCH), 133.1 (PhC(1)), 142.8 (furylC(5)H), 152.4 (furylC(2)H), 159.4 (C(6)H), 165.9 (CO), 166.1 (CO); m/z (APCI$^+$) 345 ([M+MeOH+H]$^+$, 100%), 313 ([M+H]$^+$, 25%); HRMS (APCI$^+$) C$_{18}$H$_{15}$ClO$_3$ ([M+H]$^+$) requires 313.1071, found 313.1068 (−0.8 ppm).
(S)-Ethyl 2-oxo-6-phenyl-4-(thiophen-2-yl)-3,4-dihydro-2H-pyran-5-carboxylate (199)

The title compound was prepared according to General Procedure F from (E)-3-(thiophen-2-yl)acrylic anhydride (110.4 mg, 0.38 mmol), ethyl 3-oxo-3-phenylpropanoate (52 μL, 0.27 mmol), HBTM 2.1 (4.31 mg, 0.014 mmol) and PS-BEMP (2.0 mmol/g loading) (136.0 mg, 0.30 mmol) in CH₂Cl₂ (0.38 mL) and purified by chromatography (CH₂Cl₂) to afford the lactone 199 as a yellow oil (33.3 mg, 38%); [α]₂²⁰D −9.94 (c 0.8 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 0.5 mL min⁻¹, 220 nm, 20 °C), tR major: 25.1 min, tR minor: 29.5 min, 94% ee; ν max (film) /cm⁻¹ 2980 (C-H), 2905 (C-H), 1782 (C=O), 1699 (C=O); δ(H) (400 MHz, CDCl₃) 0.96 (3H, t, J 7.1, CH₃), 2.99 (1H, dd, J 16.0, 7.2, C(3)H), 3.12 (1H, dd, J 16.0, 2.1, C(3)H), 4.02 (2H, qd, J 7.1, 1.2, OCH₂), 4.49 (1H, dd, J 16.0, 1.5, C(4)H), 6.18 (1H, dt, J 3.2, 0.8, thiophenyl C(3)H), 6.29 (1H, dd, J 3.2, 1.9, thiophenyl C(4)H), 7.35 (1H, dd, J 1.9, 0.8, thiophenyl C(5)H), 7.36-7.53 (5H, m, PhH); δ(C) (126 MHz, CDCl₃) 13.6 (CH₃), 34.0 (C(4)), 36.5 (C(3)), 61.2 (OCH₂), 111.9 (C(5)), 124.5 (thienyl C(5)H), 125.0 (thienyl C(3)H), 127.2 (thienyl C(4)H), 128.0 (CHAr), 128.7 (CHAr), 130.2 (CHAr), 133.0 (PhC(1)), 143.0 (thienyl C(2)), 159.1 (C(6)), 165.7 (CO), 166.0 (CO); m/z (NSI⁺) 329 ([M+H⁺], 30%), 351 ([M+Na⁺], 80%); HRMS (NSI⁺) C₁₈H₁₇O₄S ([M+H⁺]) requires 329.0842, found 329.0844 (+0.6 ppm).

(R)-Ethyl 6-methyl-2-oxo-4-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (S10)

The title compound was prepared according to General Procedure F from (E)-cinnamic anhydride (280 mg, 1.00 mmol), ethyl acetoacetate (94 μL, 0.72 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (360 mg, 0.20 mmol) in CH₂Cl₂ (1.0 mL) and purified by chromatography (CH₂Cl₂) to afford the lactone S10 as a white solid (135 mg, 72%); mp 79-80 °C {Lit° 83-84 °C} chiral HPLC analysis, ChiralPak OD-H (15% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 30 °C), tR minor: 6.2 min, tR minor: 10.5 min, 70% ee; [α]₂⁰D −101.5 (c 1.0 in CH₂Cl₂), {Lit° [α]₂⁰D −130.6 (c 1.0 in CH₂Cl₂); 91% ee};
δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 1.20 (3H, t, J 7.1, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.48 (3H, d, J 1.0, C(6)CH<sub>3</sub>), 2.83 (1H, dd, J 15.9, 2.4, C(3)H<sub>2</sub>), 2.96 (1H, dd, J 15.9, 7.5, C(3)H<sub>2</sub>), 4.14 (2H, q, J 7.1, OCH<sub>3</sub>), 4.26-4.28 (1H, m, C(4)H), 7.13-7.16 (2H, m, ArH), 7.22-7.34 (3H, m, ArH). Data in agreement with the literature.

**[(S)-Ethyl 4-methyl-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (201)]**

The title compound was prepared according to General Procedure F from (E)-but-2-enoic anhydride (39 mg, 0.25 mmol), ethyl 3-oxo-3-phenylpropanoate (31 μL, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.25 mL) and purified by chromatography (CH<sub>2</sub>Cl<sub>2</sub>) to afford the lactone 201 as a colourless oil (21 mg, 45%); [α]<sub>D</sub><sup>22</sup> +4.67 (c 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); chiral HPLC analysis, ChiralPak OD-H (2.5% i-PrOH:hexane, flow rate 0.5 mL min<sup>-1</sup>, 220 nm, 30 °C), t<sub>r</sub> minor: 21.1 min, t<sub>r</sub> major: 23.5 min, 65% ee; ν<sub>max</sub> (film)/cm<sup>-1</sup> 2978 (C-H), 2938 (C-H), 1728 (C=O), 1705 (C=O), 1690 (C=O); δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 0.98 (3H, t, J 7.1, CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>), 1.24 (3H, d, J 7.1, C(4)CH<sub>3</sub>), 2.65 (1H, dd, J 15.8, 2.1, C(3)H<sub>2</sub>), 2.83 (1H, dd, J 15.8, 6.7, C(3)H<sub>2</sub>), 3.20 (1H, tt, J 6.9, 3.6, C(4)H), 4.03 (2H, q, J 7.1, OCH<sub>2</sub>), 7.38 (5H, dt, J 14.2, 7.4, PhH); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 13.7 (CH<sub>2</sub>C<sub>6</sub>H<sub>3</sub>), 19.3 (C(4)(CH<sub>3</sub>)), 28.4 (C(4)H), 35.7 (C(3)H<sub>2</sub>), 61.0 (OCH<sub>3</sub>), 114.1 (ArCH), 128.0 (2×ArCH), 128.6 (2×ArCH), 130.0 (ArCH), 133.3 (PhC(1)), 157.5(C(6)), 166.8 (CO), 167.0 (CO); m/z (NSI<sup>+</sup>) 261 ([M+H]<sup>+</sup>); HRMS (NSI<sup>+</sup>) C<sub>15</sub>H<sub>17</sub>O<sub>4</sub> ([M+H]<sup>+</sup>) requires 261.1121, found 261.1125 (+1.4 ppm).

**[(R)-4-Phenyl-3,4,7,8-tetrahydro-2H-chromene-2,5(6H)-dione (111)]**

The title compounds were prepared according to General Procedure E using 1,3-cyclohexanedione (80 mg, 0.72 mmol), anhydride 3 (278 mg, 1.00 mmol), HBTM 2.1 (22 mg, 10 mol %) and EtN(iPr)<sub>2</sub> (138 μL, 0.80 mmol) in THF:DCM (10:1, 2 mL) and purified by chromatography (CH<sub>2</sub>Cl<sub>2</sub>) to afford the title lactone 111 as a yellow solid (139 mg, 80%); mp 112-113 °C; [α]<sub>D</sub><sup>20</sup> -118.2 (c 1.0, CHCl<sub>3</sub>); HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1.0 mL min<sup>-1</sup>, 220 nm, 30 °C), t<sub>r</sub> major: 14.9 min, t<sub>r</sub> minor: 22.5,
82% ee; \( \nu_{\text{max}} \) (film) 2953 (C-H), 1784 (C=O), 1705 (C=O); \( \delta_H \) (400 MHz, CDCl\(_3\)) 2.06-2.18 (2H, m, CH\(_2\)), 2.45-2.48 (2H, m, CH\(_2\)), 2.61-2.75 (2H, m, CH\(_2\)), 2.90-2.99 (2H, m, C(3)H), 4.32 (1H, t, \( J = 5.0 \), C(4)H), 7.14-7.17 (2H, m, 2\( \times \)ArH), 7.20-7.25 (1H, m, ArH), 7.28-7.32 (2H, m, 2\( \times \)ArH); \( \delta_C \) (100 MHz, CDCl\(_3\)) 20.5 (C(7)H\(_2\)), 27.2 (C(8)H\(_2\)), 33.7 (C(4)H), 36.2 (C(3)H\(_2\)), 36.6 (C(6)H\(_2\)), 117.1 (C=CO), 126.4 (2\( \times \)C(4)ArC(2)H), 127.4 (C(4)ArC(4)H), 128.9 (2\( \times \)C(4)ArC(3)H), 140.4 (C(4)ArC(1)), 165.8 (C(10)), 176.3 (C(2)O)), 196.2 (C(5)O); \( m/z \) (NSI\(^+\)) 243 ([M+H]\(^+\), 60%); HRMS (NSI\(^+\)) \( C_{15}H_{15}O_3 \) [M+H]\(^+\) requires 243.1016, found 243.1018 (+0.9 ppm). **Compound synthesised by Dr Charlene Fallan.**

**General Procedure G: Ring-Opened Products**

To a solution of the corresponding homoanhydride (1.4 equiv) in dry CH\(_2\)Cl\(_2\) (0.72 M) under argon, was added isothiourea (HBTM 2.1, 0.05 equiv) and polymer-bound 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (PS-BEMP) (1.1 equiv) at 0 °C followed by addition of the corresponding diketone (1.0 equiv). The reaction mixture was stirred at 0 °C and gradually warmed to room temperature over 5 h. The reaction was quenched with MeOH (2 mL) and stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (CH\(_2\)Cl\(_2\)→2\%EtOAc/CH\(_2\)Cl\(_2\)) to afford the ester 6-22.

(3S)-Methyl 4-benzoyl-5-oxo-3,5-diphenylpentanoate (154)

The title compound was prepared according to **General Procedure G** from (E)-cinnamic anhydride (70 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol), PS-BEMP (2.2 mmol/g loading, 90 mg, 0.20 mmol) and purified by chromatography (CH\(_2\)Cl\(_2\)→2%EtOAc/CH\(_2\)Cl\(_2\)) to afford the ester 154 as a white solid (53 mg, 83%); mp 104-107 °C; \([\alpha]_{D}^{22}\) +9.6 (c 0.25 in CHCl\(_3\)); chiral HPLC analysis,
ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C), tᵣ major: 11.8 min, tᵣ minor: 17.0 min, 96% ee; νₑₛₑ (film)/cm⁻¹ 2367 (C-H), 1742 (C=O), 1690 (C=O), 1653 (C=O), 1489 (CH₃-O); δₓ₁ (400 MHz, CDCl₃) 2.77-2.93 (2H, m, C(2)H₂), 3.50 (3H, s, OCH₃), 4.40 (1H, td, J 9.5, 4.9, C(3)H), 5.84 (1H, d, J 9.5, C(4)H), 7.04-7.19 (3H, m, ArH), 7.21-7.33 (4H, m, ArH), 7.37-7.48 (3H, m, ArH); δₛ (100 MHz, CDCl₃) 38.2 (C(2)), 42.8 (C(3)), 51.7 (OCH₃), 62.4 (C(4)), 127.2 (ArC(4)H), 128.5 (2×ArCH), 128.6 (2×ArCH), 128.7 (2×ArCH), 129.0 (4×ArCH), 133.4 (ArC(4)H), 133.8 (ArCH), 136.7 (ArC), 136.9 (ArC), 140.4 (ArC), 172.1 (C(1)), 194.5 (CO), 194.8 (CO); m/z (NSI⁺) 387 ([M+H]+, 100%), 404 ([M+NH₄]+, 35%); HRMS (NSI⁺) C₂₅H₂₃O₄ ([M+H]+) requires 387.1591, found 387.1596 (+1.3 ppm).

(3R)-Methyl 4-benzoyl-3-(4-trifluoromethylphenyl)-5-oxo-5-phenylpentanoate (165)

The title compound was prepared according to General Procedure G from (E)-4-trifluoromethyl cinnamic anhydride (103 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading, 90 mg, 0.20 mmol) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 165 as a white solid (64 mg, 79%); mp 142-145 °C; [α]₂₂°D −2.5 (c 1.0 in CHCl₃); chiral HPLC analysis, ChiralPak AD-H, (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 20 °C), tᵣ major: 12.7 min, tᵣ minor: 22.1 min, 97% ee; νₑₛₑ (film)/cm⁻¹ 2972 (C-H), 2853 (C-H), 2322 (C-H), 1734 (C=O), 1684 (C=O), 1325 (CF₂); δₓ₁ (400 MHz, CDCl₃) 2.76-2.99 (2H, m, C(2)H₂), 3.51 (3H, s, OCH₃), 4.46 (1H, td, J 9.5, 4.7, C(3)H), 5.84 (1H, d, J 9.5, C(4)H), 7.27-7.51 (9H, m, ArH), 7.52-7.62 (1H, m, ArH), 7.66-7.80 (2H, m, ArH), 7.95-8.03 (2H, m, ArH); δₛ (75 MHz, CDCl₃) 37.9 (C(2)), 42.5 (C(3)), 51.8 (OCH₃), 61.8 (C(4)), 124.1 (q, 1JC₂ 270.2, CF₂), 125.5 (q, 1JC₂ 3.7, C(3)ArC(3)), 128.6 (2×ArCH), 128.8 (2×ArCH), 129.0 (2×ArCH), 129.1 (2×ArCH), 129.4 (q, 1JC₂ 32.3, C(3)ArC(4)), 133.7 (ArC(4)H), 134.1 (ArC(4)H), 136.5 (ArC), 136.6 (ArC), 144.7 (ArC), 171.8 (C(1)), 194.2 (CO), 194.5 (CO); δₓ (282 MHz, CDCl₃) −63.14; m/z (NSI⁺) 472 ([M+NH₄]+, 100%), 455 ([M+H]+, 90%); HRMS (NSI⁺) C₂₆H₂₅F₃O₄ ([M+H]+) requires 455.1465, found 455.1467 (+0.5 ppm).
(3S)-Methyl 4-benzoyl-3-(4-fluorophenyl)-5-oxo-5-phenylpentanoate (166)

The title compound was prepared according to General Procedure G from (E)-3-(4-fluorophenyl)acrylic anhydride (79 mg, 0.25 mmol), 1,3-diphenylpropane-1,3-dione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 166 as a white solid (60 mg, 82%); mp 92-96 °C; [α]D +20.2 (c 1.0 in CHCl₃); chiral HPLC analysis, ChiralPak IA (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 30 °C), tR major: 10.0 min, tR minor: 14.3 min, 95% ee; νmax (film)/cm⁻¹ 2951 (C-H), 1734 (C=O), 1694 (C=O), 1260 (C-F); δH (400 MHz, CDCl₃) 2.78 (1H, dd, J 15.6, 9.6, C(2)H), 2.87 (1H, dd, J 15.6, 9.6, C(2)H), 3.51 (3H, s, OC₃H₃), 4.39 (1H, ddd, J 9.6, 9.6, 4.6, C(3)H), 5.79 (1H, d, J 9.6, C(4)H), 6.81-6.87 (2H, m, ArH), 7.19-7.24 (2H, m, ArH), 7.30-7.34 (2H, m, ArH), 7.41-7.58 (4H, m, ArH), 7.74-7.76 (2H, m, ArH), 7.98-8.00 (2H, m, ArH); δc (100 MHz, CDCl₃) 38.4 (C(2)), 42.1 (C(3)), 51.8 (OCH₃), 62.5 (C(4)), 115.4 (d, JCF 21.4, C(3)Ar(C(3)H)), 128.7 (2×ArCH), 128.8 (2×ArCH), 129.0 (2×ArCH), 129.1 (2×ArCH), 130.2 (d, JCF 8.1, C(3)Ar(C(2)H)), 133.5 (ArC(4)H), 134.0 (ArC(4)H), 136.1 (ArC) 136.6 (ArC), 136.8 (ArC), 161.8 (d, JCF 240.3, CF), 172.0 (C(1)), 194.4 (CO), 194.6 (CO); δF (300 MHz, CDCl₃) −115.9; m/z (NSI⁺) 405 ([M+H]+, 100%), 422 ([M+NH₄]+, 45%); HRMS (NSI⁺) C₂₅H₂₅FO₄ ([M+H]+) requires 405.1497, found 405.1496 (+0.2 ppm).

(3S)-Methyl 4-benzoyl-3-(4-methoxyphenyl)-5-oxo-5-phenylpentanoate (167)

The title compound was prepared according to General Procedure G from (E)-3-(4-methoxyphenyl)acrylic anhydride (85 mg, 0.25 mmol), 1,3-diphenylpropane-1,3-dione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 167 as a pale yellow solid (33 mg, 44%).
mp 110-114 °C; $[\alpha]_D^{22} +18.1$ (c 1.0 in CHCl$_3$); chiral HPLC analysis, ChiralPak AD-H (15% i-PrOH:hexane, flow rate 1.0 mL min$^{-1}$, 254 nm, 20 °C), $t_R$ major: 26.7 min, $t_R$ minor: 44.7 min, 94% ee;

The reaction was repeated using a modified General Procedure D with increased catalyst loading from (E)-3-(4-methoxyphenyl)acrylic anhydride (85 mg, 0.25 mmol), 1,3-diphenylpropane-1,3-dione (40 mg, 0.18 mmol), HBTM 2.1 (5.6 mg, 0.018 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH$_2$Cl$_2$ (0.25 mL) and purified by chromatography (CH$_2$Cl$_2$→2%EtOAc/CH$_2$Cl$_2$) to afford the ester 167 as a pale yellow solid (42 mg, 56%); mp 110-114 °C; $[\alpha]_D^{22} +8.2$ (c 1.0 in CHCl$_3$); chiral HPLC analysis, ChiralPak AD-H (15% i-PrOH:hexane, flow rate 1.0 mL min$^{-1}$, 254 nm, 20 °C), $t_R$ major: 26.7 min, $t_R$ minor: 44.7 min, 88% ee;

$\nu$ max (film)/cm$^{-1}$ 1732 (C=O), 1690 (C=O), 1252 (C-O), 1159 (C=O); $\delta_H$ (300 MHz, CDCl) 2.78 (1H, dd, $J$ 15.6, 9.6, C(2)H), 2.86 (1H, dd, $J$ 15.6, 5.1, C(2)H), 3.50 (3H, s, CO$_2$C$_3$H$_3$), 3.70 (3H, s, ArOC$_3$H$_3$), 4.36 (1H, ddd, $J$ 9.6, 9.6, 4.8, C(3)H), 5.80 (1H, d, $J$ 9.6, C(4)H), 6.66-6.71 (2H, m, ArH), 7.13-7.18 (2H, m, ArH), 7.28-7.57 (6H, m, ArH), 7.74-7.78 (2H, m, ArH), 7.98-8.00 (2H, m, ArH); $\delta_C$ (75 MHz, CDCl$_3$) 38.5 (C(2)), 42.1 (C(3)), 51.7 (CO$_2$C$_3$H$_3$), 55.2 (OCH$_3$), 62.7 (C(4)), 113.9 (2×C(4)ArC(3)H), 128.7 (2×C(4)ArC(2)H), 128.7 (2×ArCH), 129.0 (4×ArCH), 129.5 (2×ArCH), 132.3 (ArC), 133.3 (ArCH), 133.8 (ArCH), 136.8 (ArC), 136.9 (ArC), 158.5 (ArC), 172.2 (C(1)), 194.6 (CO), 194.9 (CO); $m/z$ (NSI$^+$) 417 ([M+H]$^+$, 85%), 434 ([M+NH$_4^+$]$^+$,100%); HRMS (NSI$^+$) C$_{26}$H$_{25}$O$_5$ ([M+H]$^+$) requires 417.1697, found 417.1699 (+0.6 ppm).

(3S)-Methyl 4-benzoyl-3-(furan-2-yl)-5-oxo-5-phenylpentanoate (171)

![Chemical Structure](https://example.com/structure.png)

The title compound was prepared according to General Procedure G from (E)-furylacrylic anhydride (65 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH$_2$Cl$_2$ (0.25 mL) and purified by chromatography (CH$_2$Cl$_2$→2%EtOAc/CH$_2$Cl$_2$) to afford the ester 171 as a dark yellow solid (46 mg, 69%); mp 74-77 °C; $[\alpha]_D^{22} +30.6$ (c 0.5 in CHCl$_3$); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL
6. Experimental

min⁻¹, 254 nm, 20 °C), tₘ major: 15.0 min, tₘ minor: 17.1 min, 96% ee; νₓₓ (film)/cm⁻¹ 1738 (C=O), 1697 (C=O), 1655(C=O), 1593 (furan), 1578 (furan), 1508 (furan), 1445 (C-O); δₓ (400 MHz, CDCl₃) 2.78-2.94 (2H, m, C(2)H₂), 3.60 (3H, s, OCH₃), 4.46 (1H, td, J 8.9, 4.5, C(3)H), 5.97-6.09 (3H, m, furanyl(H)), 7.13-7.19 (1H, m, C(4)H₃), 7.33-7.43 (4H, m, ArH), 7.45-7.56 (2H, m, ArH), 7.87 (4H, ddd, J 17.5, 8.4, 1.1, ArH); δₓ (100 MHz, CDCl₃) 35.9 (C(2)H₂), 36.3 (C(3)H), 51.9 (OCH₃), 58.7 (C(4)H), 107.8 (furanylC(4)H), 110.5 (furanylC(3)H), 128.7 (2×ArCH), 128.7 (2×ArCH), 128.8 (2×ArCH), 129.0 (2×ArCH), 133.5 (ArC(4)H), 133.8 (ArC(4)H), 136.2 (ArC(1)), 136.6 (ArC(1)), 141.6 (furanylC(5)H), 153.2 (furanylC(2)), 172.1 (C(1)), 194.4 (CO), 194.7 (CO); m/z (NSI⁺) 377 ([M+H]+, 100%), 394 ([M+NH₄]+, 45%); HRMS (NSI⁺) C₂₃H₂₁O₅ ([M+H]+) requires 377.1384, found 377.1387 (+0.9 ppm).

(3S)-Methyl 4-benzoyl-5-oxo-5-phenyl-3-(thiophen-2-yl)pentanoate (172)

The title compound was prepared according to General Procedure G from (E)-thienyl acrylic anhydride (73 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 172 as a dark yellow solid (51 mg, 86%); mp 91-94 °C; [α]₂²D +29.5 (c 0.4 in CHCl₃); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 20 °C), tₘ major: 16.1 min, tₘ minor: 22.9 min, 94% ee; νₓₓ (film)/cm⁻¹ 1736 (C=O), 1686 (C=O), 1655 (C=O), 1593 (C-C), 1578 (C-C), 1445 (C-O), 1263 (C-S); δₓ (400 MHz, CDCl₃) 2.80-2.99 (2H, m, C(2)H₂), 3.58 (3H, s, OCH₃), 4.70 (1H, td, J 8.9, 4.5, C(3)H), 5.99 (1H, d, J 9.0, C(4)H), 6.74 (1H, dd, J 5.1, 3.5, thienylC(4)H), 6.80-6.85 (1H, m, thienylC(3)H), 7.03 (1H, dd, J 5.1, 0.9, thienylC(5)H), 7.30-7.58 (6H, m, ArH), 7.80-7.86 (2H, m, ArH), 7.94-8.00 (2H, m, ArH); δₓ (100 MHz, CDCl₃) 38.2 (C(3)H), 39.0 (C(2)H), 51.9 (OCH₃), 62.0 (C(4)H), 124.4 (thienylC(5)H), 126.5 (thienylC(3)H), 126.8 (thienylC(4)H), 128.8 (4×ArCH), 129.0 (2×ArCH), 133.5 (ArC(4)H), 133.9 (ArC(4)H), 136.6 (ArC), 136.7 (ArC), 143.5 (thienylC(2)), 172.1 (C(1)), 194.4 (CO), 194.5 (CO); m/z (NSI⁺) 393 ([M+H]+, 55%); HRMS (NSI⁺) C₂₃H₂₀O₅S ([M+H]+) requires 393.1155, found 393.1157 (+0.5 ppm).
(3S)-Methyl 4-benzoyl-3-(3-chlorophenyl)-5-oxo-5-phenylpentanoate (169)

The title compound was prepared according to General Procedure G from (E)-3-(3-chlorophenyl)acrylic anhydride (87 mg, 0.25 mmol), 1,3-diphenylpropane-1,3-dione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH2Cl2 (0.25 mL) and purified by chromatography (CH2Cl2 → 2% EtOAc/CH2Cl2) gave the ester 169 as a pale yellow solid (51 mg, 67%); mp 124-126 °C; [α]D^22 +18.1 (c 1.0 in CHCl3); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C), tR major: 10.3 min, tR minor: 13.2 min, 96% ee; νmax (film)/cm⁻¹ 2361 (C=O), 1738 (C=O), 1684 (C=O), 1261 (C-O); δH (400 MHz, CDCl3) 2.74-2.95 (2H, m, C(2)H2), 3.52 (3H, s, OCH3), 4.36 (1H, td, J 9.5, 4.6, C(3)H), 5.82 (1H, d, J 9.5, C(4)H), 7.01-7.17 (3H, m, ArH), 7.24 (1H, d, J 1.8, ArH), 7.29-7.38 (2H, m, ArH), 7.38-7.51 (3H, m, ArH), 7.55 (1H, tt, J 6.9, 1.2, ArH), 7.77 (2H, dd, J 8.4, 1.2, ArH), 7.98 (2H, dd, J 8.4, 1.2, ArH); δC (100 MHz, CDCl3) 38.0 (C(2)), 42.4 (C(3)), 51.8 (OCH3), 127.0 (C(3)ArC(6)H), 127.5 (C(3)ArC(2)H), 128.6 (ArC(1)H), 128.7 (2×ArCH), 128.8 (2×ArCH), 128.9 (2×ArCH), 129.1 (2×ArCH), 129.8 (C(3)ArC(5)H), 133.6 (PhC(4)H), 134.0 (PhC(4)H), 134.3 (C(3)ArC(3)Cl), 136.5 (PhC(1)), 136.7 (PhC(1)), 142.6 (C(3)ArC(1)), 171.8 (C(1)), 194.2 (CO), 194.5 (CO); m/z (NSI⁺) 421 ([M+H]+, 100%); HRMS (NSI⁺) C25H22ClKO4S requires 421.1202, found 421.1201 (+0.2 ppm).

(3S)-Methyl 4-benzoyl-3-(2-chlorophenyl)-5-oxo-5-phenylpentanoate (170)

The title compound was prepared according to General Procedure G from (E)-3-(2-chlorophenyl)acrylic anhydride (87 mg, 0.25 mmol), 1,3-diphenylpropane-1,3-dione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH2Cl2 (0.25 mL) and purified by chromatography (CH2Cl2 → 2%
EtOAc/CH₂Cl₂) gave the ester 170 as a yellow solid (53 mg, 69%); [α]_D\(^{22}\) −46.8 (c 1.3 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (10% i-PrOH:hexane, flow rate 1.0 mL min\(^{-1}\), 254 nm, 30 °C), t\(_R\) major: 10.8 min, t\(_R\) minor: 14.1 min, 93% ee; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2924 (C-H), 2361 (C-H), 1734 (C=O), 1686 (C=O), 1651 (C=O), 1258 (C-O); δ\(_{\text{H}}\) (400 MHz, CDCl₃) 2.90-3.09 (2H, m, C(2)H₂), 3.50 (3H, s, OCCH₃), 4.79 (1H, q, J 7.8, C(3)H), 6.08 (1H, d, J 7.8, C(4)H), 7.04 (2H, pd, J 7.3, 1.8, ArH), 7.22-7.31 (2H, m, ArH), 7.36 (4H, dt, J 13.4, 7.7, PhH), 7.43-7.58 (2H, m, PhH), 7.79-7.93 (4H, m, PhH); δ\(_{\text{C}}\) (100 MHz, CDCl₃) 35.8 (C(2)), 39.1 (C(3)), 51.7 (OCH₃), 59.1 (C(4)), 126.9 (C(3)ArC(5)H), 128.4 (ArCH), 128.7 (2×ArCH), 128.8 (2×ArCH), 128.9 (2×ArCH), 130.2 (ArCH), 133.4 (PhC(4)H), 133.8 (PhC(4)H), 134.0 (CCL), 136.4 (PhC(1)), 136.9 (PhC(1)), 137.8 (C(3)ArC(1)), 172.1 (C(1)), 194.4 (CO), 195.1 (CO); m/z (NSI\(^{+}\)) 421 ([M+H\(^{+}\)], 100%); HRMS (NSI\(^{+}\)) C₂₅H₂₁Cl₃O₄ ([M+H\(^{+}\)]\(^{+}\)) requires 421.1203, found 421.1201 (+0.4 ppm).

(3S)-Methyl 4-benzoyl-3-methyl-5-oxo-5-phenylpentanoate (173)

The title compound was prepared according to a General Procedure G from (E)-crotonic anhydride (39 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 173 as a colourless oil (39 mg, 67%); [α]_D\(^{22}\) +31.8 (c 1.25 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 0.5 mL min\(^{-1}\), 220 nm, 30 °C), t\(_R\) major: 35.0 min, t\(_R\) minor: 38.7 min, 70% ee; compound data as below.

The reaction was repeated using a modified General Procedure D at a lower temperature from (E)-crotonic anhydride (39 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL), the reaction was carried out at −78 °C and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 15 as a colourless oil (24 mg, 41%); [α]_D\(^{22}\) +32.7 (c 0.9 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 0.5 mL min\(^{-1}\), 220 nm, 30 °C), t\(_R\) major: 35.0 min, t\(_R\) minor: 38.7 min, 85% ee; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2974 (C-H), 2953 (C-H), 2924 (C-H), 1724 (C=O), 1686.
6. Experimental

(C=O), 1670 (C=O), 1593 (O-CH₃); δ_H (300 MHz, CDCl₃) 1.09 (3H, d, J 7.0, CH(CH₃)), 2.38-2.68 (2H, m, C(2)H₂), 3.00-3.20 (1H, m, C(3)H), 3.65 (3H, s, OCH₃), 5.66 (1H, d, J 8.0, C(4)H), 7.37-7.62 (6H, m, ArH), 7.95-8.06 (4H, m, ArH); δ_C (100 MHz, CDCl₃) 17.8 (CH(CH₃)), 31.5 (C(3)), 38.6 (C(2)), 51.7 (OCH₃), 60.0 (C(4)), 128.8 (2×ArH), 128.8 (2×ArCH), 129.0 (2×ArCH), 133.6 (ArC), 137.0 (ArC), 173.2 (C(1)), 195.6 (CO), 195.8 (CO); m/z (NSI⁺) 325 ([M+H]+, 100%), 342 ([M+NH₄]+, 35%); HRMS (NSI⁺) C₂₀H₁₅O₄ ([M+H]+) requires 325.1434, found 325.1440 (+1.7 ppm).

(3S)-Methyl 3-(1,3-dioxo-1,3-diphenylpropan-2-yl)hexanoate (174)

The title compound was prepared according to General Procedure G from (E)-hexenoic anhydride (53 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 174 as a colourless oil (36 mg, 57%); [α]D²² +0.2 (c 1.0 in CHCl₃); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 0.5 mL min⁻¹, 220 nm, 30 °C), tₘₘₕ major: 29.5 min, tₘᵢₙor: 32.8 min, 80% ee; compound data as below.

The reaction was repeated using a modified General Procedure D at a lower temperature from (E)-hexenoic anhydride (53 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) at -78 °C and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 174 as a colourless oil (22 mg, 35%); [α]D²² +45.8 (c 0.5 in CHCl₃); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 0.5 mL min⁻¹, 220 nm, 30 °C), tₘₘₕ major: 29.5 min, tₘᵢₙor: 32.8 min, 93% ee; ν_max (film)/cm⁻¹ 2957 (C-H), 2932 (C-H), 2872 (C-H), 1730 (C=O), 1694 (C=O), 1668 (C=O), 1595 (O-CH₃); δ_H (400 MHz, CDCl₃) 0.81 (3H, t, J 7.1, C(6)H₃), 1.16-1.31 (1H, m, C(4)H₂), 1.33-1.45 (2H, m, C(5)H₂), 1.49-1.63 (1H, m, C(4)H₂), 2.47-2.72 (2H, m, C(2)H₂), 2.84-3.00 (1H, m, C(3)H), 3.62 (3H, s, OCH₃), 5.87 (1H, d, J 7.2, CH(COPh)₂), 7.35-7.63 (6H, m, ArH), 8.00 (4H, dt, J 8.6, 1.4, ArH); δ_C (100 MHz, CDCl₃) 14.1 (C(6)), 20.8 (C(5)), 33.5 (C(4)), 35.2 (C(2)), 36.3 (C(3))CH), 51.6 (OCH₃), 58.4 (CH(COPh)₂), 128.8 (2×ArCH), 128.8 (2×ArCH), 129.0 (2×ArCH), 133.6 (ArCH), 133.6 (ArCH), 136.8
(ArC), 137.0 (ArC), 173.7 (C(1)), 195.9 (CO), 196.2 (CO); m/z (NSI⁺) 353 ([M+H]⁺, 100%); HRMS (NSI⁺) C₂₂H₂₅O₄ ([M+H]⁺) requires 353.1747, found 353.1753 (+1.6 ppm).

(3S)-Methyl 4-acetyl-5-oxo-3-phenylhexanoate (176)

![Chemical structure](image1)

The title compound was prepared according to General Procedure G from (E)-cinnamic anhydride (70 mg, 0.25 mmol), pentane-2,4-dione (19 μL, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 176 as a white solid (30 mg, 64%); mp 68-72 °C; [α]D²² +57.3 (c 1.0 in CHCl₃); chiral HPLC analysis, ChiralPak OJ-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 30 °C), tR major: 20.9 min, tR minor: 34.2 min, 37% ee; νmax (film)/cm⁻¹ 1722, 1686, 1356, 1146; δH (400 MHz, CDCl₃) 1.85 (3H, d, J 0.4, C₃H₃), 2.27 (3H, d, J 0.4, CH₃), 2.58 (2H, dd, J 7.2, 6.6, C(2)H₂), 3.52 (3H, s, OCH₃), 3.97 (1H, ddd, J 11.6, 7.2, 6.6, C(3)H), 4.26 (1H, d, J 11.6, C(4)H), 7.18-7.24 (3H, m, ArH), 7.26-7.31 (2H, m, ArH); δC (100 MHz, CDCl₃) 29.7 (CH₃), 30.0 (CH₃), 39.3 (C(2)), 41.7 (C(3)), 51.8 (OCH₃), 74.2 (C(4)), 127.6 (C(3)ArC(4)H), 128.1 (2×ArCH), 129.0 (2×ArCH), 139.9 (C(3)ArC(1)), 171.6 (C(1)), 202.8 (CO), 203.0 (CO); m/z (NSI⁺) 263 ([M+H]⁺, 100%); HRMS (NSI⁺) C₁₅H₁₉O₄ ([M+H]⁺) requires 263.1278, found 263.1270 (−3.0 ppm). Compound synthesised by Dr Carmen Simal.

(3S)-Methyl 5-(4-methylphenyl)-4-[(4-methylphenyl)carbonyl]-5-oxo-3-[4-(trifluoromethyl)phenyl]pentanoate (186)

![Chemical structure](image2)

The title compound was prepared according to General Procedure G from (E)-3-(4-(Trifluoromethyl)phenyl)acrylic anhydride (104 mg, 0.25 mmol), 1,3-bis(4-Methylphenyl)propane-1,3-dione (45 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 186 as an off-white
solid (47 mg, 54%); mp 120-123 °C; [α]_D^{22} -23.2 (c 1.1 in CHCl₃); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 220 nm, 30 °C), tᵣ major: 14.1 min, tᵣ minor: 20.1 min, 97% ee; ν_max (film)/cm⁻¹ 2954 (C-H), 1730 (C=O), 1686 (C=O), 1605 (C=C), 1110 (C-F); δ_H (500 MHz, CDCl₃) 2.32 (3H, s, PhCH₃), 2.38 (3H, s, PhCH₃), 2.74-2.96 (2H, m, C(2)H₂), 3.50 (3H, s, OCH₃), 4.45 (1H, td, J 9.6, 4.4, C(3)H), 5.77 (1H, d, J 9.6, C(4)H), 7.11 (2H, d, J 8.0, tolylC(2)H), 7.22 (2H, d, J 8.0, tolylC(2)H), 7.40 (4H, q, J 8.3, C(3)ArH), 7.67 (2H, d, J 8.1, tolylC(3)H), 7.90 (2H, d, J 8.1, tolylC(3)H); δ_C (125 MHz, CDCl₃) 21.7 (ArC'H₃), 21.8 (ArCH₃), 37.9 (C(2)H), 159 (C(3)H), 51.8 (OCH₃), 61.8 (C(4)H), 124.1 (q, J_CF 272.0, CF₃), 125.4 (q, J_CF 3.6, 2×C(3)ArC(3)), 128.8 (2×ArCH), 129.0 (2×ArCH), 129.1 (2×ArCH), 129.5 (2×ArCH), 129.8 (2×ArCH), 134.0 (C(5)ArC(1)), 134.2 (C(5)ArC(1)), 147.7 (C(3)ArC(1)), 145.0 (C(5)ArC(4)), 145.1 (C(5)ArC(4)), 171.8 (OCH₃), 193.7 (CO), 194.1 (CO); δ_ν (282 MHz, CDCl₃) -63.10; m/z (NSI⁺) 483 ([M+H⁺], 100%), 500 ([M+NH₄⁺], 30%); HRMS (NSI⁺) C₂⁸H₂₆F₃O₄ ([M+H⁺]) requires 483.1778, found 483.1775 (+0.8 ppm).

(3S)-Methyl-5-(furan-2-yl)-4-[(furan-2-yl)carbonyl]-5-oxo-3-[4-(trifluoromethyl)phenyl]pentanoate (188)

The title compound was prepared according to General Procedure G from (E)-3-(4-(Trifluoromethyl)phenyl)acrylic anhydride (104 mg, 0.25 mmol), 1,3-bis(furan-2-yl)propane-1,3-dione (37 mg, 0.18 mmol), HBTM 2.1 (2.8 mg, 0.009 mmol) and PS-BEMP (2.2 mmol/g loading) (90 mg, 0.20 mmol) in CH₂Cl₂ (0.25 mL) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) gave 188 as a yellow solid (71 mg, 91%); mp 151-154 °C; [α]_D^{22} -10.8 (c 1.0 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 30 °C), tᵣ major: 12.7 min, tᵣ minor: 21.4 min, 94% ee; ν_max (film)/cm⁻¹ 2974 (C-H), 2926 (C-H), 1734 (C=O), 1458 (furan), 1113 (C-F); δ_H (500 MHz, CDCl₃) 2.81 (2H, qd, J 15.9, 7.2, C(2)H₂), 3.49 (3H, s, OCH₃), 4.40 (1H, td, J 10.0, 4.5, C(3)H), 5.50 (1H, d, J 10.3, C(4)H), 6.43 (1H, dd, J 3.5, 1.5, furanyl(4)H), 6.55 (1H, dd, J 3.5, 1.5, furanyl(4)H), 7.12 (1H, d, J 3.5, furanyl(3)H), 7.34-7.46 (5H, m, 4×ArH and furanyl(3)H), 7.50 (1H, s, furanyl(5)H), 7.59 (1H, s, furanyl(4)H); δ_C (125 MHz, CDCl₃)
6. Experimental

38.1 (C(2)H), 41.6 (OCH₃), 51.8 (C(3)H), 61.6 (C(4)H), 113.0 (furanylC(4)H), 113.1 (furanylC(4)H), 119.1 (furanylC(3)H), 119.6 (furanylC(3)H), 124.1 (q, ^3J_{CF} 272.0, CF₃). 125.4 (d, ^2J_{CF} 3.6, 2×C(3)ArC(3)H), 128.8 (2×C(3)ArC(2)H), 129.4 (q, ^3J_{CF} 32.4, ArC(4)CF₃), 144.3 (ArC(1)), 147.2 (furanylC(5)H), 147.7 (furanylC(3)H), 124.1 (q, ^1J_{CF} 272.0, CF₃). 125.4 (d, ^3J_{CF} 3.6, 2×C(3)ArC(3)H), 128.8 (2×C(3)ArC(2)H), 129.4 (q, ^3J_{CF} 32.4, ArC(4)CF₃), 144.3 (ArC(1)), 147.2 (furanylC(5)H), 147.7 (furanylC(3)H), 124.1 (q, ^1J_{CF} 272.0, CF₃). 125.4 (d, ^3J_{CF} 3.6, 2×C(3)ArC(3)H), 128.8 (2×C(3)ArC(2)H), 129.4 (q, ^3J_{CF} 32.4, ArC(4)CF₃), 144.3 (ArC(1)), 147.2 (furanylC(5)H), 147.7 (furanylC(3)H), 124.1 (q, ^1J_{CF} 272.0, CF₃). 125.4 (d, ^3J_{CF} 3.6, 2×C(3)ArC(3)H), 128.8 (2×C(3)ArC(2)H), 129.4 (q, ^3J_{CF} 32.4, ArC(4)CF₃), 144.3 (ArC(1)), 147.2 (furanylC(5)H), 147.7 (furanylC(3)H), 124.1 (q, ^1J_{CF} 272.0, CF₃). 125.4 (d, ^3J_{CF} 3.6, 2×C(3)ArC(3)H), 128.8 (2×C(3)ArC(2)H), 129.4 (q, ^3J_{CF} 32.4, ArC(4)CF₃), 144.3 (ArC(1)), 147.2 (furanylC(5)H), 147.7 (furanylC(3)H), 124.1 (q, ^1J_{CF} 272.0, CF₃).

δF (282 MHz, CDCl₃) −63.12; m/z (NSI⁺) 435 ([M+H]+, 100%), 452 ([M+NH₄]+, 70%); HRMS (NSI⁺) C₂₂H₁₈F₃O₆ ([M+H]+) requires 435.1050, found 435.1052 (+0.5 ppm).

(3S)-Methyl 4-benzoyl-3-(3-methylphenyl)-5-oxo-5-phenylpentanoate (168)

The title compound was prepared according to General Procedure G from (E)-3-(3-methylphenyl)acrylic anhydride (76 mg, 0.25 mmol), 1,3-diphenyl-1,3-propanedione (40 mg, 0.18 mmol), and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 168 as an off-white solid (56 mg, 75%); mp 110-112 °C; [α]D₂² +19.8 (c 0.8 in CHCl₃); chiral HPLC analysis, Chiralcel AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 30 °C) tR major: 9.9 min, tR minor: 13.3 min, 91% ee; νmax (film)/cm⁻¹ 1728 (C=O, ester), 1688 (C=O), 1668 (C=O) 1257 (CH₃-O); δH (400 MHz, CDCl₃) 2.20 (3H, s, ArCH₃), 2.81 (1H, dd, J 15.7, 9.3, C(2)H), 2.89 (1H, dd, J 15.7, 5.0, C(2)H), 3.51 (3H, s, CO₂CH₃), 4.36 (1H, td, J 9.3, 5.0, C(3)H), 5.83 (1H, d, J 9.4, C(4)H), 6.94-6.82 (1H, m, C(3)Ar(2)H), 7.03 (3H, dd, J 4.9, 3.8, ArC(4,5,6)H), 7.37-7.29 (2H, m, ArH), 7.49-7.37 (3H, m, ArH), 7.55 (1H, tt, J 7.4, 2.8, ArH), 7.84-7.71 (2H, m, ArH), 8.04-7.93 (2H, m, ArH); δC (100 MHz, CDCl₃) 21.3 (C(3)ArCH(3)), 38.0 (C(2)), 42.5 (C(3)), 51.5 (CO₂CH₃), 62.1 (C(4)), 125.3 (C(3)-ArC(6)), 127.8 (C(3)-ArC(2)), 128.3 (C(3)-ArC), 128.4 (C(5)-ArC), 128.5 (C(5)-ArCH), 128.8 (C(5)-ArC), 129.2 (C(3)-ArC), 133.1 (C(5)-ArC(4)), 133.6 (C(5)-ArC(4)), 136.6 (C(5)-ArC(1)), 136.8 (C(5)-ArC(1)), 137.9 (C(3)-ArC(3)), 140.1 (C(3)-ArC(1)), 172.04 (C(1)), 194.4 (C(5)), 194.8 (C(5)); m/z (ESI⁺) 401 ([M+H]+, 100%); HRMS (ESI⁺) C₂₂H₂₅O₆ ([M+H]+), found 401.1750, requires 401.1747 (+0.7 ppm).
(3S)-Methyl-5-(4-bromophenyl)-4-[(4-bromophenyl)carbonyl]-5-oxo-3-phenylpentanoate (183)

The title compound was prepared according to General Procedure G from (E)-cinnamic anhydride (70 mg, 0.25 mmol) and 1,3-bis(4-bromophenyl)propane-1,3-dione (78 mg, 0.18 mmol) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 183 as a white solid (50 mg, 52%); mp 172-173 °C; [α]$_{D}^{22}$ +9.2 (c 0.9 in CHCl₃); chiral HPLC analysis; Chiralcel AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 30 °C) tᵣ major: 13.8 min, tᵣ minor: 18.3 min, 66% ee; ν$_{max}$ (film) 1734 (C=O, ester), 1701 (C=O), 1664 (C=O), 1264 (CH₃O); δH (400 MHz, CDCl₃) 2.80 (1H, dd, J 15.7, 9.0, C(2)H), 2.87 (1H, dd, J 15.7, 4.8, C(2)H), 3.52 (3H, s, CO₂C₃H₃), 4.37 (1H, td, J 9.3, 4.8, C(3)HPh), 5.74 (1H, d, J 9.7, C(4)H), 7.28-6.82 (5H, m, 5 × Ar(3)H), 7.46 (2H, d, J 8.6, Ar(4,2)H), 7.58 (4H, dd, J 9.4, 8.6, Ar(4,2)H), 7.84 (2H, d, J 8.6 Hz, ArH); δC (100 MHz, CDCl₃) 38.0 (C(2)), 42.6 (C(3)), 51.7 (CO₂CH₃), 62.5 (C(4)), 127.3, 128.3, 128.6, 128.8 (C(5)-ArC), 129.3 (C(5)-ArC), 130.0 (C(5)-ArCH), 130.3 (C(5)-ArCH), 131.9 (C(5)-ArCH), 132.2 (C(5)-ArCH), 135.1 (C(5)-ArC), 135.2 (C(5)-ArC), 139.8 (C(3)-ArC(1)), 171.9 (C(1)), 193.3 (C(5)), 193.5 (C(5)); HRMS (ESI+) C₂₅H₂₁Br₇O₄ [M+H]⁺, found 542.9800, requires 542.9801 (−0.5 ppm). Compound synthesised by Dr Charlene Fallan.

(3S,5)-Methyl-5-oxo-3-phenyl-5-[4-(trifluoromethyl)phenyl]-4-[(4-(trifluoromethyl)phenyl)carbonyl]pentanoate (184)

The title compound was prepared according to General Procedure G from 1,3-bis(4-trifluoromethylphenyl)propane-1,3-dione (76 mg, 0.18 mmol) and (E)-cinnamic anhydride (70 mg, 0.25 mmol) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 184 as a white solid (62 mg, 67%); mp 121-122 °C; [α]$_{D}^{22}$ +63.2 (c 1.55 in CHCl₃); chiral HPLC analysis; Chiralcel AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 254 nm, 30 °C) tᵣ major: 10.0 min, tᵣ minor: 13.5 min, 81% ee; ν$_{max}$ (film) 1734 (C=O,
6. Experimental

ester), 1705 (C=O), 1668 (C=O); δH (400 MHz, CDCl₃) 2.80 (1H, dd, J 15.7, 9.0, C(2)H), 2.87 (1H, dd, J 15.7, 4.8, C(2)H), 3.52 (3H, s, CO₂CH₃), 4.37 (1H, td, J 9.3, 4.8, C(3)H), 5.74 (1H, d, J 9.7, C(4)H), 7.28-6.82 (5H, m, 5 × Ar(3)H), 7.46 (2H, d, J 8.6, Ar(4,2)H), 7.58 (4H, dd, J 9.4, 8.6, Ar(4,2)H), 7.84 (2H, d, J 8.6 Hz, ArH); δc (100 MHz, CDCl₃) 37.9 (C(2)), 42.6 (C(3)), 51.7 (CO₂CH₃), 62.8 (C(4)), 123.3 (q, JCF 273.0 Hz, 2 × C(5)-ArCF₃), 125.7 (q, JCF 3.3 Hz, C(5)-Ar(3)CH), 126.0 (q, JCF 3.4 Hz, C(5)-Ar(3)CH), 127.5 (C(3)-Ar(4)C), 128.3 (C(3)-Ar(2)C), 128.6 (C(3)Ar(3)C), 128.7 (C(5)Ar(2)C), 129.1 (C(5)Ar(2)C), 134.9 (q, JCF 32.9 Hz, C(5)-ArC(4)), 135.2 (q, JCF 32.8 Hz, C(5)-ArC(4)), 139.1 (C(5)-ArC(1)), 139.5 (C(5)-ArC(1)), 171.9 (C(1)), 193.6 (C(5)), 193.7 (C(5)); δb (376 MHz, CDCl₃) -63.8 (CF₃); m/ζ pending. Compound synthesised by Dr Charlene Fallan.

(3S)-Methyl-5-(4-methylphenyl)-4-[(4-methylphenyl)carbonyl]-5-oxo-3-phenylpentanoate (185)

\[ \text{\includegraphics[width=0.5\textwidth]{structure.png}} \]

The title compound was prepared according to General Procedure G from 1,3-bis(4-methylphenyl)propane-1,3-dione (55 mg, 0.18 mmol) and (E)-cinnamic anhydride (70 mg, 0.25 mmol) and purified by chromatography (CH₂Cl₂→2%EtOAc/CH₂Cl₂) to afford the ester 185 as an off-white solid (30 mg, 40%); mp 142-143 °C; [α]D²², -3.6 (c 0.65 in CHCl₃); chiral HPLC analysis; Chiralcel AD-H (20% i-PrOH/hexane, flow rate 1.0 mL min⁻¹, 254 nm, 30 °C) tr major: 16.9 min, tr minor: 23.6 min, 90% ee; νmax (film) 2970 (C−H), 1736 (C=O, ester), 1693 (C=O), 1654 (C=O); δH (400 MHz, CDCl₃) 2.32 (3H, s, ArCH₃), 2.38 (3H, s, ArCH₃), 2.83 (1H, dd, J 15.7, 9.6, C(2)H), 2.88 (1H, dd, J 15.7, 4.7, C(2)H), 3.49 (3H, s, CO₂CH₃), 4.40 (1H, dd, J 15.7, 4.7, C(3)H), 5.77 (1H, d, J 9.6, C(4)H), 7.35-7.03 (9H, m, 5 × Ar(3)H, and 4 × C(5)-Ar(3)H), 7.68 (2H, d, J 8.3, C(5)-Ar(2)H), 7.90 (2H, d, J 8.3, C(5)-Ar(2)H); δc (100 MHz, CDCl₃) 21.6 (ArCH₃), 21.6 (ArCH₃), 38.2 (C(2)), 42.6 (C(3)), 51.5 (CO₂CH₃), 62.1 (C(4)), 127.0 (C(3)-ArC(4)), 128.3 (C(3)-ArC(2,3)), 128.7 (C(5)-ArC(3)), 129.0 (C(5)-ArC(2)), 129.0 (C(5)-ArC(3)), 129.2 (C(5)-ArC(2)), 129.5 (C(5)-ArC(2)), 134.1 (C(5)-ArC(1)), 134.3 (C(5)-ArC(1)), 140.5 (C(3)-ArC(1)), 144.1 (C(5)-ArC(4)), 144.7 (C(5)-ArC(4)), 172.0 (C(1)), 193.8 (C(5)), 194.3 (C(5)); m/ζ (ESI+) 302 ([M+H]+, 100%); HRMS (ESI+) C₂₇H₂₇O₄ ([M+H]+), found 415.1906, requires 415.1904 (+0.5 ppm). Compound synthesised by Dr Charlene Fallan.
(3S)-Methyl-5-(furan-2-yl)-4-[(furan-2-yl)carbonyl]-5-oxo-3-phenylpentanoate (187)

The title compound was prepared according to *General Procedure G* from 1,3-bis(Furan-2-yl)propane-1,3-dione (37 mg, 0.18 mmol) and (E)-cinnamic anhydride (70 mg, 0.25 mmol) and purified by chromatography (CH$_2$Cl$_2$→2%EtOAc/CH$_2$Cl$_2$) to afford the ester 187 as a pale yellow solid (61 mg, 93%); mp 131-133 °C; [α]$_D^{22}$+21.1 (c 1.65 in CHCl$_3$); chiral HPLC analysis; Chiralcel AD-H (20% i-PrOH:hexane, flow rate 1.0 mL.min$^{-1}$, 254 nm, 30 °C) $t_R$ major: 14.1 min, $t_R$ minor: 21.1 min, 90% ee; $v_{max}$ (film) 1732 (C=O, ester), 1674 (C=O), 1645 (C=O); $\delta$H (400 MHz, CDCl$_3$) 2.86-2.82 (2H, m, C(2)H), 3.49 (3H, s, CO$_2$C$_6$H$_5$), 4.38 (1H, td, $J$ 9.8, 4.7, C(3)H), 5.50 (1H, dd, $J$ 10.4, 0.9, C(4)H), 6.42 (1H, ddd, $J$ 3.7, 1.7, 0.9 Hz, furanyl(4)H), 6.54 (1H, ddd, 3.7, 1.7, 1.0, furanyl(4)H), 7.20-7.07 (4H, m, C(3)Ar(2,3)H), 7.27-7.25 (2H, m, C(3)Ar(4)H and furanyl(3)H), 7.72 (1H, m, furanyl(4)H), 7.60-7.59 (1H, m, furanyl(5)H); $\delta$C (100 MHz, CDCl$_3$) 38.4 (C(2)), 41.8 (C(3)), 51.5 (CO$_2$C$_6$H$_5$), 62.0 (C(4)), 112.7 (C(5)-furanyl(4)C), 112.8 (C(5)-furanyl(4)C), 118.7 (C(5)-furanyl(3)C), 119.3 (C(5)-furanyl(3)C), 127.1 (C(3)-Ar(4)H), 128.2 (C(3)-Ar(2)CH), 128.3 (C(3)-Ar(3)CH), 139.8 (C(3)-Ar(1)H), 146.8 (C(5)-furanyl(5)), 147.4 (C(5)-furanylC(5)), 151.9 (C(5)-furanylC(2)), 152.1 (C(5)-furanylC(2)), 171.6 (C(1)), 181.9 (C(5)), 182.0 (C(5)); $m/z$ (ESI+) 367 ([M+H]+, 100%); HRMS (ESI+) C$_{21}$H$_{19}$O$_6$ ([M+H]+), found 367.1175, requires 367.1176 (−0.3 ppm). **Compound synthesised by Dr Charlene Fallan.**

*General Procedure H: Lactams and Lactones From Benzazoles*

![Diagram](image_url)

To a solution of the corresponding homoanhydride (1.4 equiv) in bench grade THF (0.72 M), was added benzazole (1.0 equiv), isothiourea (HBTM 2.1, 0.05 equiv) and EtN(iPr)$_2$ (1.1 equiv) at 0 °C. The reaction mixture was stirred and gradually warmed to room temperature over 5 h. The solution was diluted with EtOAc and washed sequentially with...
0.1 M HCl and saturated NaHCO$_3$ solution, dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the product(s).

(11R)-10-Benzyol-11-phenyl-8-thia-1-azatricyclo[7.4.0.0$^{2,7}$]trideca-2,4,6,9-tetraen-13-one (228a) and (4R)-5-(1,3-benzothiazol-2-yl)-4,6-diphenyl-3,4-dihydro-2H-pyran-2-one (228b)

The title compounds were prepared according to General Procedure H from (E)-cinnamic anhydride (700 mg, 2.50 mmol) and 2-phenacyl benzothiazole (455 mg, 1.80 mmol), EtN(iPr)$_2$ (0.35 mL, 2.00 mmol) and HBTM 2.1 (5.5 mg, 1 mol %) in THF (5 mL) and purified by chromatography on silica gel (10:2 CH$_2$Cl$_2$/hexane) to afford 228a as a yellow solid (595 mg, 86%) and 228b as a yellow solid (63 mg, 9%). The major isomer was suspended in Et$_2$O then recrystallised from EtOAc: crystals were obtained (68 mg, 10% overall yield, 4% ee) plus liquors which were concentrated in vacuo to give a yellow solid.

228a (major): (472 mg, 68% yield); mp 168-171 °C; [α]$_{D}^{20}$ -148.5 (c 1.0 in CHCl$_3$); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min$^{-1}$, 211 nm, 30 °C), $t_{R}$ minor: 13.2 min, $t_{R}$ major: 22.5 min, 97% ee; $v_{max}$ (film)/cm$^{-1}$ 3024 (C-H), 2984 (C-H), 2913 (C-H), 1722 (C=O), 1597 (C=C), 1574 (C=C), 1477 (C-N), 1360 (C-S), 1269 (C-O); $\delta$$_H$ (500 MHz, CDCl$_3$) 3.05 (1H, dd, $J$ 15.9, 2.2, C(12)H$_2$), 3.29 (1H, dd, $J$ 15.9, 6.9, C(12)H$_2$), 4.38 (1H, dd, $J$ 6.9, 2.2, C(11)H$_2$), 7.11 (2H, d, $J$ 7.2, 2×C(11)PhC(2)H), 7.21-7.44 (10H, m, ArH), 7.62 (1H, s, C(6)H), 8.47 (1H, d, $J$ 7.8, C(3)H); $\delta$$_C$ (126 MHz, CDCl$_3$) 38.6 (C(11)H), 41.4 (C(12)H$_2$), 107.7 (C(10)), 117.5 (C(3)H$_2$), 122.0 (C(6)H), 125.9 (C(5)H)$_2$, 126.8 (2×C(11)PhC(2)H), 127.0 (2×C(10)COPhC(3)H), 127.6 (C(4)H)$_2$, 127.8 (C(7)), 128.1 (2×C(10)COPhC(2)H), 129.3 (2×C(11)PhC(3)H), 130.3 (C(10)COPhC(4)H), 136.0 (C(2)), 139.4 (C(10)COPhC(1)), 140.8 (C(11)PhC(1)), 156.2 (C(9)), 167.9 (C(13)O), 191.2 (C(10)CO); $m/z$ (NSI$^+$) 384 ([M+H$^+$], 60%); HRMS (NSI$^+$) C$_{24}$H$_{18}$O$_2$NS ([M+H$^+$]) requires 384.1053, found 384.1052 (−0.2 ppm).
6. Experimental

228b (minor): (63 mg, 9%); mp 192–194 °C; [α]_D^{20} = –18.4 (c 1.0 in CHCl₃); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), t_R major: 7.7 min, t_R minor: 10.8 min, 86% ee; ν_{max} (film) cm⁻¹: 2974 (C-H), 2372 (C-H), 1775 (C=O), 1647 (C=N), 1491 (C=C), 1435 (C=C), 1339 (C=S), 1271 (C-O); δ_H (300 MHz, CDCl₃) 3.08 (1H, dd, J = 15.8, 1.6, C(3)H₂), 3.32 (1H, dd, J = 15.8, 7.6, C(3)H₂), 5.03 (1H, dd, J = 7.6, 1.6, C(4)H), 7.23–7.36 (6H, m, ArH), 7.38–7.52 (3H, m, ArH), 7.55–7.63 (4H, m, ArH), 7.93 (1H, d, J = 7.8, HetArH); δ_C (75 MHz, CDCl₃) 36.9 (C(3)H₂), 115.1 (C(5)HetArC), 121.3 (C(5)HetArCH), 127.0 (2×C(4)PhC(2)H), 127.8 (C(4)PhC(4)H), 129.3 (2×C(4)PhC(3)H), 130.1 (2×C(6)PhC(2)H), 130.8 (C(6)PhC(4)H), 131.9 (C(6)PhC(1)), 135.7 (C(5)HetArC), 139.6 (C(4)PhC(1)), 152.4 (C(5)HetArC), 154.4 (C(6)), 164.2 (C(5)HetArC=N), 166.6 (C(2)O); m/z (NSI⁺) 384 ([M+H]⁺, 60%); HRMS (NSI⁺) [M+H]⁺ requires 384.1053, found 384.1052 (–0.2 ppm).

(11R)-10-Benzoyl-11-(3-methylphenyl)-8-thia-1-azatricyclo[7.4.0.0²⁷]trideca-2(7),3,5,9-tetraen-13-one (S11a) and (R)-5-(benzo[d]thiazol-2-yl)-6-phenyl-4-n-tolyl-3,4-dihydro-2H-pyran-2-one (S11b)

The title compounds were prepared according to General Procedure H from (E)-3-(3-Methylphenyl)acrylic anhydride (771 mg, 2.52 mmol) and 2-phenacyl benzothiazole (607 mg, 2.40 mmol), EtN(iPr)₂ (0.46 mL, 2.64 mmol) and HBTM 2.1 (7 mg, 1 mol %) in THF (4 mL) and purified by chromatography (20% hexane/CH₂Cl₂) to afford the title compounds S11a and S11b as yellow solids.

S11a (major): (732 mg, 77%); mp 159-161 °C; [α]_D^{20} = –101.0 (c 1.0, CHCl₃); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), t_R minor: 10.8 min, t_R major: 16.4 min, 86% ee; ν_{max} (film) cm⁻¹: 1714(C=O), 1604 (C=O), 1481; δ_H (400 MHz, CDCl₃) 2.28 (3H, s, ArCH₃), 3.05 (1H, dd, J = 15.9, 2.4, C(12)H), 3.27 (1H, dd, J = 15.9, 6.9, C(12)H), 4.31 (1H, dd, J = 6.9, 2.4, C(11)H), 6.89 (2H, d, J = 9.3, ArH), 7.06 (1H, d, J = 7.5, ArH), 7.17 (1H, t, J = 7.5, ArH), 7.28 (2H, s, ArH), 7.29 (2H, s, ArH), 7.32-7.42 (3H, m,
6. Experimental

ArH), 7.61-7.64 (1H, m, ArH), 8.45-8.49 (1H, m, ArH); δc (100 MHz, CDCl3) 21.5 (C(11)ArCH3), 38.4 (C(11)H), 41.3 (C(12)H), 107.7 (C10), 117.5 (C(6)ArCH), 121.9 (C(5)ArCH), 123.7 (C(11)ArC(6)H), 125.8 (C(4)H), 126.9 (C(11)ArC(4)H), 127.0 (2×C(10)ArC(2)H), 127.4 (C(3)H), 127.8 (C(7)), 128.0 (2×C(10)ArC(3)H), 128.3 (C(11)ArC(5)H), 129.1 (C(11)ArC(2)H), 130.2 (C(10)ArC(4)H), 136.0 (C(11)Ar(3)C), 138.9 (C(10)ArC(1)), 139.3 (C(2)ArC), 140.7 (C(11)ArC(1)), 156.1 (C(9)), 156.9 (C(13)=O), 191.2 (C(10)=O).

S11b (minor): (39 mg, 4%); mp 146-147 °C; [α]D20 −9.7 (c 0.75, CHCl3); HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min−1, 211 nm, 30 °C), tR minor: 6.9 min, tR major: 9.7 min, 85% ee; ν max (film) 2982 (C-H), 1772 (C=O), 1504; δH (400 MHz, CDCl3) 2.31 (3H, s, C(4)ArC3H3), 3.07 (1H, dd, J 15.7, 0.7, C(3)H2), 3.31 (1H, dd, J 15.7, 7.6, C(3)H2), 4.97 (1H, dd, J 7.7, 1.7, C(4)H), 7.04 (1H, d, J 7.8, C(4)ArC(4)H), 7.11-7.13 (1H, m, C(4)ArC(6)H), 7.16-7.22 (1H, m, C(4)ArC(2)H), 7.25-7.32 (2H, m, 2×C(5)HetArCH3), 7.37-7.46 (3H, m, C(6)ArC(3,4)H), 7.48-7.53 (1H, m, C(4)ArC(5)H), 7.56-7.60 (2H, m, 2×C(6)ArC(2)H), 7.62 (1H, d, J 8.0, C(5)HetArCH), 7.93 (1H, d, J 8.2, C(5)HetArCH); δc (100 MHz, CDCl3) 21.5 (ArC3H3), 36.9 (C(3)H2), 41.2 (C(4)H), 115.0 (C(6)), 121.2 (C(5)HetArCH), 123.0 (C(5)HetArCH), 123.8 (C(5)HetArCH), 125.3 (C(4)ArC(6)H), 125.9 (C(5)HetArCH), 127.7 (C(4)ArC(4)H), 128.5 (C(6)ArC(4)H), 128.8 (2×C(6)ArC(2)H), 129.0 (C(4)ArC(5)H), 129.9 (2×C(6)ArC(3)H), 130.7 (C(4)ArC(2)H), 131.9 (C(6)ArC(1)), 135.7 (C(5)HetArC), 138.8 (C(4)ArC(3)), 139.4 (C(4)ArC(1)), 152.4 (C(5)), 154.1 (C(5)HetArC), 164.1 (C(5)HetArC=N), 166.6 (C(2)).

The title compounds were prepared according to General Procedure H from (E)-3-(Furan-2-yl)acrylic anhydride (430 mg, 1.67 mmol) and 2-phenacyl benzothiazole (421 mg, 1.67 mmol), EtN(iPr)2 (319 μL, 1.8 mmol) and HBTM 2.1 (5 mg, 1 mol %) in THF (3 mL) and

(11S)-10-Benzoyl-11-(furan-2-yl)-8-thia-1-azatricyclo[7.4.0.02,7]trideca-2,4,6,9-tetraen-13-one (242a) and (4S)-5-(1,3-benzothiazol-2-yl)-4-(furan-2-yl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (242b)
purified by chromatography (20% hexanes/CH₂Cl₂) to afford the title compounds 38a as a yellow solid and 38b as a yellow solid.

**38a (major):** (446 mg, 72%); mp 127-128 °C; [α]_D^20 −30.3 (c 1.0, CHCl₃); HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), τₘ minor: 15.0 min, τₘ major: 20.3 min, 80% ee; ν_max (film)/cm⁻¹ 3142 (C-H), 3136 (C-H), 1732 (C=O), 1626 (C=C), 1605 (C=C), 1474 (C-N), 1362 (C-S), 1275 (C-O); δ H (400 MHz, CDCl₃) 3.16 (1H, dd, J 16.1, 6.0, C-H₂), 3.24 (1H, dd, J 16.1, 2.6, C-H₂), 4.43 (1H, ddd, J 6.1, 2.6, 1.0, C(11)H), 5.95 (1H, m, furanylC(x)H), 6.24 (1H, dd, J 3.3, 1.9, furanylC(4)H), 7.29-7.51 (8H, m, ArH), 7.54-7.61 (1H, m, ArH), 8.46-8.53 (1H, m, ArH); δ C (100 MHz, CDCl₃) 32.9 (C(11)H), 37.9 (C12H₂), 105.6 (C(10)), 106.8 (furanylC(3)H), 110.3 (furanylC(4)H), 117.6 (ArCH₂), 121.9 (ArCH₂), 125.8 (ArCH₂), 126.9 (2×ArCH₂), 127.0 (ArCH₂), 127.5 (C(7)), 128.2 (2×ArCH₂), 130.4 (ArCH₃), 136.0 (C(10)ArC(1)), 139.3 (C(2)), 142.7 (furanylC(5)H), 153.5 (furanylC(1)), 156.6 (C(9)), 167.7 (C(13)=O), 190.8 (C(10)C=O).

**38b (minor):** (60 mg, 10%) mp 122-125 °C; [α]_D^22 −6.2 (c 1.0 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), τₘ minor: 7.6 min, τₘ major: 15.0 min, 80% ee; ν_max (film)/cm⁻¹ 3117 (C-H), 3063 (C-H), 2924 (C-H), 1782 (C=O), 1597 (C=C), 1344 (C-S), 1277 (C-O); δ H (300 MHz, CDCl₃) 3.20 (1H, dd, J 15.9, 6.7, C(3)H₂), 3.26 (1H, dd, J 15.9, 1.9, C(3)H₂), 5.14 (1H, dd, J 6.8, 2.0, C(4)H₂), 6.18 (1H, d, J 3.3, furanyl(3)H), 6.24 (1H, dd, J 3.3, 1.8, furanyl(4)H), 7.31 (1H, t, J 7.6, ArH), 7.34 (1H, d, J 1.8, furanyl(5)H), 7.44 (3H, td, J 7.3, 1.5, ArH), 7.49-7.57 (3H, m, ArH), 7.61-7.68 (1H, m, ArH), 7.98 (1H, d, J 8.2, ArH); δ C (75 MHz, CDCl₃) 33.9 (C(3)), 35.1 (C(4)), 106.9 (furanylC(3)H), 110.4 (furanylC(4)H), 113.3 (C(5)), 121.3 (C(5)HetArC(7)H), 123.1 (C(5)HetArC(4)H), 125.6 (C(5)HetArC(6)H), 126.2 (C(5)HetArC(5)H), 129.0 (2×C(6)PhC(3)H), 130.1 (2×C(6)PhC(2)H), 131.0 (C(6)PhC(4)H), 131.8 (C(6)PhC(1)), 135.7 (C(5)HetArC(7a)), 142.8 (furanylC(5)H), 152.2 (furanylC(2)), 152.4 (C(5)HetArC(3a)), 154.8 (C(6)), 164.0 (C(5)HetArC=N), 166.4 (C(2)O).
The title compounds were prepared according to General Procedure H from \((E)\)-Hex-2-enoic anhydride (314 mg, 1.00 mmol) and 2-phenacyl benzothiazole (182 mg, 0.72 mmol), EtN(Pr)_2 (138 μL, 0.79 mmol) and HBTM 2.1 (2 mg, 1 mol %) in THF (2 mL) and purified by chromatography on silica gel (10:2 CH_2Cl_2/hexane) to afford S12a as a yellow solid and S12b as a yellow solid.

**S12a (major):** (502 mg, 79%); mp 143-145 °C; \([\alpha]_D^{20} +148.1 (c 1.0 \text{ in CHCl}_3)\); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min\(^{-1}\), 211 nm, 30 °C), \(t_R\) minor: 10.3 min, \(t_R\) major: 16.0 min, 88% ee; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2957 (C-H), 2930 (C-H), 2870 (C-H), 1717 (C=O), 1599 (C=C), 1574 (C=C), 1474 (C-N), 1368 (C-S), 1275 (C-O); \(\delta_H\) (400 MHz, CDCl_3) 0.55 (3H, t, \(J_7.3\), C_3H_3), 1.04 (2H, dq, \(J_{15.3}, 7.9, 7.0\), C_2H_2CH_3), 1.30 (2H, q, \(J_{7.9}\), C_2H_2CH_3), 2.77 (1H, dd, \(J_{16.2}, 2.1\), C(12)H), 2.96 (1H, dd, \(J_{16.2}, 6.3\), C(12)H), 3.13 (1H, qd, \(J_{7.0}, 2.1\), C(11)H), 7.17-7.23 (1H, m, C(5)H), 7.23-7.29 (1H, m, C(4)H), 7.33-7.38 (3H, m, C(10)COPhC(3)H), C(10)COPhC(4)H), 7.39-7.47 (2H, m, C(10)COPhC(2)H), 7.44 (1H, dd, \(J_{7.5}, 1.1\), C(6)H), 8.39-8.47 (1H, m, C(3)H); \(\delta_C\) (126 MHz, CDCl_3) 13.6 (CH_3), 19.6 (CH_2CH_2CH_3), 32.3 (C(11)H), 35.8(CH_2CH_2CH_3), 37.7, (C(12)H), 109.8 (C(10)), 117.6 (C(3)H), 121.9 (C(6)H), 125.8 (C(5)H), 127.0 (C(4)H), 127.2 (2×C(10)COPhC(3)H), 127.7 (C(7)), 128.4 (2×C(10)COPhC(2)H), 130.1 (C(10)COPhC(4)H), 136.2 (C(2)), 140.1 (C(10)COPhC(1)), 154.4 (C(9)), 169.1 (C(13)O), 191.8 (C(10)CO); \(m/z\) (NSI\(^+\)) 372 ([M+Na\(^+\), 100%], 350 ([M+H\(^+\), 30%]; HRMS (NSI\(^+\)) \(C_{21}H_{20}O_2NS\) (M+H\(^+\)) requires 350.1209, found 350.1204 (−1.5 ppm).

**S12b (minor):** (47 mg, 7%); mp 192-194 °C; \([\alpha]_D^{20} -1.3 (c 1.0 \text{ in CHCl}_3)\); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min\(^{-1}\), 211 nm, 30 °C), \(t_R\) minor: 4.9 min, \(t_R\) major: 7.0 min, 92% ee; \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2953 (C-H), 2926 (C-H), 2870 (C-H), 1770 (C=O), 1651 (C=N), 1491 (C=C), 1354 (C-S), 1273 (C-O); \(\delta_H\) (500 MHz,
6. Experimental

CDCl₃ 0.90 (3H, t, J 7.2, CH₃), 1.32 (1H, dq, J 18.8, 6.1, CH₂CH₂CH₃), 1.40-1.58 (2H, m, CH₂CH₂CH₃), 1.61-1.71 (1H, m, CH₂CH₂CH₃), 2.85-3.00 (2H, m, C(3)H₂), 3.70-3.77 (1H, m, C(4)H), 7.32 (1H, t, J 7.5, C(5)HetArCH), 7.34-7.36 (2H, m, ArH), 7.37-7.49 (4H, m, ArH), 7.66 (1H, d, J 8.0, C(5)HetArCH), 7.98 (1H, d, J 8.2, (C(5)HetArCH); δc (126 MHz, CDCl₃) 14.1 (CH₃), 19.9 (CH₂C₂H₂CH₃), 33.5 (CH₂CH₂CH₃), 35.2 (C(4)H), 35.5 (C(3)H₂), 117.2 (C(5)), 121.4 (C(5)HetArC(7)H), 123.0 (C(5)HetArC(4)H), 125.5 (C(5)HetArC(6)H), 126.2 (C(5)HetArC(5)H), 128.9 (2×C(6)PhC(3)H), 130.1 (2×C(6)PhC(2)H), 130.6 (C(6)PhC(4)H), 132.1 (C(6)PhC(1)), 134.7 (C(5)HetArC), 152.5 (C(5)HetArC), 153.5 (C(6)), 164.7 (C(5)HetArC=N), 167.8 (C(2)O); m/z (NSI⁺) 372 ([M+Na]⁺, 100%), 350 ([M+H]⁺, 55%); HRMS (NSI⁺) C₂₁H₂₀O₂N₂ ([M+H]⁺) requires 350.1209, found 350.1210 (+0.2 ppm).

(11R)-10-Benzoyl-11-(4-methoxyphenyl)-8-thia-1-azatricyclo[7.4.0.0²⁷]trideca-2,4,6,9-tetraen-13-one (239a) and (4R)-5-(1,3-benzothiazol-2-yl)-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (239b)

The title compounds were prepared according to General Procedure H from (E)-3-(4-Methoxyphenyl)acrylic 3-(4-methoxyphenyl)propanoic anhydride (314 mg, 1.00 mmol) and 2-phenacyl benzthiazole (182 mg, 0.72 mmol), EtN(iPr)₂ (138 μL, 0.79 mmol) and HBTM 2.1 (2 mg, 1 mol %) in THF (2 mL) and purified by chromatography on silica gel (10:2 CH₂Cl₂/hexane) to afford 40a as a yellow solid and 40b as a yellow solid.

239a (major): (436 mg, 59%); mp 190-191 °C; [α]D²⁰ +135.6 (c 1.0 in CHCl₃); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tₘₐᵢₙᵋ 14.8 min, tₘₐᵢₙᵋ 31.1 min, 85% ee; νmax (film)/cm⁻¹ 2972 (C-H), 2843 (C-H), 1721 (C=O), 1603 (C=C), 1510 (C=C), 1474 (C-N), 1358 (C-S), 1298 (C-O); δH (300 MHz, CDCl₃) 0.00 (1H, dd, J 15.8, 2.3, C(12)H₂), 3.24 (1H, dd, J 15.8, 6.6 C(12)H₂), 3.77 (3H, s, OCH₃), 4.29 (1H, dd, J 6.6, 2.2, C(11)H), 6.78-6.84 (2H, m, C(11)ArC(3)H), 6.97-7.05 (2H, m, C(11)ArC(2)H), 7.37-7.51 (4H, m, ArH), 7.44-7.53 (3H, m, ArH), 7.56-7.65 (1H, m, C(6)H), 8.43-8.49 (1H, m, C(3)H); δc (75 MHz, CDCl₃) 38.0 (C(11)H), 41.8 (C(12)H₂), 55.4...
(OCH₃), 108.2 (C(10)), 114.8 (2×C(11)ArC(3)H), 117.7 (C(3)H), 122.1 (C(6)H), 126.0 (C(5)H), 127.2 (2×ArCH and C(4)H), 127.9 (C(7)), 128.0 (2×ArCH), 128.2 (2×ArCH), 130.4 (C(10)COPhC(4)H), 132.7 (C(11)ArC(1)), 136.2 (C(2)), 139.5 (C(10)COPhC(1)), 156.1 (C(9)), 159.0 (C(11)ArC(4)), 168.2 (C(13)O), 191.4 (C(10)COPhC(7)); m/z (NSI⁺) 436 ([M+Na⁺], 100%), 414 ([M+H⁺], 60%); HRMS (NSI⁺) C₃₂H₂₀O₃NS ([M+H⁺]) requires 414.1158, found 414.1160 (+0.4 ppm).

239b (minor): (41 mg, 6%); mp 148-151 °C; [α]D²⁰ +19.2 (c 1.0 in CHCl₃); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tᵣ minor: 9.7 min, tᵣ major: 14.6 min, 89% ee; vₘₚ (film)/cm⁻¹ 2944 (C-H), 1778 (C=O), 1645 (C=N), 1510 (C=C), 1346 (C-S), 1240 (C-O); δH (500 MHz, CDCl₃) 3.06 (1H, dd, J 15.7, 1.4, C(3)H₂), 3.30 (1H, dd, J 15.7, 7.5, C(3)H₂), 3.75 (3H, s, OC₃H₃), 4.97 (1H, d, J 6.5, C(4)H), 6.84 (2H, d, J 8.7, C(4)ArC(3)H), 7.28 (3H, dd, J 16.1, 8.3, C(4)ArC(2)H, C(5)HetArC(5)H), 7.38-7.46 (3H, m, C(5)HetArC(6)H, C(6)PhC(3)H), 7.50 (1H, m, C(6)PhC(4)H), 7.55-7.59 (2H, m, C(6)PhC(2)H), 7.62 (1H, d, J 8.0, C(5)HetArC(4)H), 7.95 (1H, d, J 8.2, C(5)HetArC(7)H); δC (126 MHz, CDCl₃) 37.2 (C(3)H₂), 40.6 (C(4)H), 55.3 (OCH₃), 114.6 (2×C(4)ArC(3)H), 115.4 (C(5)), 121.3 (C(5)HetArC(7)), 123.1 (C(5)HetArC(5)), 125.5 (C(5)HetArC(6)), 126.2 (C(5)HetArC(4)), 128.2 (2×ArCH), 128.9 (2×ArCH), 130.1 (2×ArCH), 130.8 (C(6)PhC(4)H), 131.6 (C(4)ArC(1)), 131.9 (C(6)PhC(1)), 138.2 (C(5)HetArC), 152.2 (C(5)HetArC), 154.2 (C(6)), 159.1 (C(4)ArC(4)), 164.4 (C(5)HetArC=N)), 166.8 (C(2)O); m/z (NSI⁺) 436 ([M+Na⁺], 100%), 414 ([M+H⁺], 90%); HRMS (NSI⁺) C₃₂H₂₀O₃NS ([M+H⁺]) requires 414.1158, found 414.1156 (~0.6 ppm).

(R)-4-benzoyl-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-one (238a) and (R)-5-(benzo[d]thiazol-2-yl)-6-phenyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-pyran-2-one (239b)

The title compounds were prepared according to General Procedure H from (E)-p-trifluoromethylcinnamic anhydride (275 mg, 0.66 mmol) and 2-phenacylbenzothiazole (120
mg, 0.47 mmol), EtN(δPr)₂ (90 μL, 0.52 mmol) and HBTM 2.1 (7.3 mg, 0.024 mmol) in THF (1.5 mL) and purified by chromatography on silica gel (CH₂Cl₂) to give 239a/239b as a yellow solid (83:17 mixture of regioisomers, 252 mg, 78%). Analytical samples were separated by careful chromatography.

**239a (major):** mp 168–170 °C; [α]ᵢ⁻¹ D -100.0 (c 1.0 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tᵢₘ major: 56.3 min, tᵢₘ minor: 31.1 min, 79% ee; νₘₙₖ (film)/cm⁻¹ 2359 (C-H), 1719 (C=O), 1618 (C=O), 1489 (C=C); δ₁H (500 MHz, CDCl₃) 3.02 (1H, dd, J 7.1, 2.4, C(3)H), 7.17 – 7.33 (2H, m, 2 × C(3)ArC(3)H, C(5')H, C(6')H), 7.25 – 7.33 (2H, m, 2 × C(3)ArC(2)H), 7.33 – 7.44 (3H, m, 2 × C(4)COPhC(3)H), 7.52 – 7.58 (2H, m, 2 × C(4)COPhC(2)H), 7.59 – 7.65 (1H, m, C(7')H), 8.46 (1H, dd, J 7.9, 1.5, C(4')H); δ₁C (126 MHz, CDCl₃) 38.6 (C(3)H), 41.2 (C(2)H), 106.9 (C(4)), 117.7 (C(4)H), 122.2 (C(7')H), 124.0 (q, 3JCF 272.2, CF₃), 126.3, (C(6')H), 126.5 (q, 3JCF 3.7, 2 × C(3)ArC(3)H), 126.9 (2 × C(4)COPhC(2)H), 127.3 (C(5')H), 127.5 (2 × C(4)COPhC(3)H), 127.7 (C(7a')), 128.5 (2 × C(3)ArC(2)H), 130.0 (q, 3JCF 32.7, C(3)ArC(4)-CF₃), 130.6 (C(4)COPhC(4)H), 136.0 (C(4'a')), 139.5 (C(4)COPhC(1)), 145.3 (C(3)ArC(1)), 156.8 (C(5)), 167.4 (C(1)O), 191.2 (C(4)COPh); δᵢ (470 MHz, CDCl₃) –62.6; m/z (APCI⁺) 452 ([M+H]⁺, 100%); HRMS (APCI⁺) C₂₅H₁₇NO₃S ([M+H]⁺) requires 452.0927, found 452.0923 (–0.8 ppm).

**239b (minor):** mp 208–211 °C; [α]ᵢ⁻¹ D +14.4 (c 0.125 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tᵢₘ major: 15.2 min, tᵢₘ minor: 11.5 min, 90% ee; νₘₙₖ (film)/cm⁻¹ 2955 (C-H), 2926 (C-H), 1782 (C=O); δ₁H (500 MHz, CDCl₃) 3.01 (1H, dd, J 15.8, 1.7, C(3)H), 3.35 (1H, dd, J 15.6, 1.9, C(3)H), 5.14 (1H, dd, J 7.7, 1.7, C(4)H), 7.27 – 7.33 (1H, m, benzothiazoleC(6)H), 7.36 – 7.43 (1H, m, benzothiazoleC(5)H), 7.43 – 7.50 (4H, m, ArH), 7.49 – 7.65 (6H, m, ArH), 7.91 (1H, d, J 8.3, benzothiazoleC(7)H), δ₁C (126 MHz, CDCl₃) 36.6 (C(3)H₂), 40.8 (C(4)H), 114.8 (C(5)), 121.4 (benzothiazoleC(4)H), 123.2 (benzothiazoleC(7)H), 125.7 (benzothiazoleC(6)H), 126.3 (benzothiazoleC(5)H), 126.3 (q, 3JCF 4.0, 2 × C(4)ArC(3)H), 127.6 (2 × C(6)PhC(2)H), 129.2 (2 × C(4)ArC(2)H), 130.2 (2 × C(6)PhC(3)H), 131.2 (C(6)PhC(4)H), 131.7 (C(6)PhC(1)), 135.7 (benzothiazoleC(7a)), 143.9 (C(4)ArC(1)), 154.2 (benzothiazoleC(4a)), 155.0 (C(6)), 163.6 (benzothiazoleC(2)), 166.2 (C(2)O) [C(4)ArC(4)-CF₃ and CF₃ not seen in ¹³C NMR due to low sample quantity, visibility could not be...
improved); $\delta_\nu$ (470 MHz, CDCl$_3$) –62.7; $m/z$ (APCI$^+$) 452 ([M+H]$^+$, 100%); HRMS (APCI$^+$) C$_{25}$H$_{17}$NO$_2$S ([M+H]$^+$) requires 452.0927, found 452.0920 (–1.5 ppm).

(S)-4-benzoyl-3-(2-bromophenyl)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-one (240a) and (S)-5-(benzo[d]thiazol-2-yl)-4-(2-bromophenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (240b)

The title compounds were prepared according to General Procedure H from (E)-2-bromocinnamic anhydride (436 mg, 1.0 mmol) and 2-phenacyl benzothiazole (182 mg, 0.72 mmol), EtN(iPr)$_2$ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (20% EtOAc/petrol) to give 240a/240b as a yellow oil (92:8 mixture of regioisomers, 204 mg, 62%); $[\alpha]_D^{20}$ –137.6 (c 0.5, CH$_2$Cl$_2$); $\nu_{max}$ (film)/cm$^{-1}$ 3061 (C-H), 3011 (C-H), 2905 (C-H), 1780 (C=O, lactone), 1720 (C=O, ketone), 1606 (C=O, lactam), 1572 (C=N), 1481 (C=C); $m/z$ (APCI$^+$) 462 ([M+H]$^+$, 100%); HRMS (APCI$^+$) C$_{24}$H$_{17}$Br$_7$9NO$_2$S ([M+H]$^+$) requires 462.0158, found 462.0156 (–0.4 ppm).

240a (major): chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ major: 18.7 min, $t_R$ minor: 13.0 min, 81% ee; $\delta_\nu$ (500 MHz, CDCl$_3$) 3.12 (1H, dd, J 16.1, 2.3, C(2)H), 3.23 (1H, dd, J 16.1, 7.3, C(2)H), 4.73 (1H, dd, J 7.3, 2.3, C(3)H), 7.13 – 7.26 (5H, m, ArH), 7.27 – 7.33 (2H, m, ArH), 7.34 – 7.43 (3H, m, ArH), 7.61 – 7.66 (2H, m, 2 × C(4)COArC(2)H), 8.40 – 8.56 (1H, m, C(4')H); $\delta$C (126 MHz, CDCl$_3$) 38.4 (C(3)H), 39.1 (C(2)H$_2$), 107.2 (C(4)), 117.5 (C(4')H), 122.1 (C(7')H), 123.7 (C(3)ArC(1)Br), 126.0 (C(6')H), 126.6 (2 × C(4)COArC(2)H), 127.2 (C(5')H), 127.8 (C(7a)'), 128.1 (C(3)ArCH), 128.2 (2 × C(4)COArC(3)H), 128.5 (C(3)ArCH), 129.4 (C(3)ArCH), 130.3 (C(4)COArC(4)H), 134.0 (C(3)ArC(6)H), 136.0 (C(4a)'), 139.0 (C(4)COArC(1)), 139.0 (C(3)ArC(2)), 157.0 (C(5)), 167.6 (C(1)O), 191.0 (C(4)COPh).

240b (minor): chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ major: 8.2 min, $t_R$ minor: 7.6 min, 33% ee; $\delta_\nu$ (500 MHz, CDCl$_3$, characteristic peaks) 3.18 (1H, dd, J 16.1, 1.8, C(3)H), 3.30 (1H, dd, J 15.9, 7.8,
C(3)H), 5.47 (1H, dd, J 7.8, 1.7, C(4)H), 7.93 (1H, d, J 8.4, benzothiazoleC(7)H); δC (126 MHz, CDCl3) 35.3 (C(3)H), 41.1 (C(4)H), 114.0 (C(5)), 121.2 (ArCH), 123.3 (ArCH), 125.5 (ArCH), 126.1 (ArCH), 127.4 (ArCH), 128.9 (2 × C(6)ArC(3)H), 129.5 (ArCH), 129.9 (2 × C(6)ArC(3)H), 131.7 (C(6)ArC(1)), 133.9 (ArC(1)), 135.6 (benzothiazoleC(7a)), 137.7 (C4)ArC(2), 152.3 (benzothiazoleC(4a)), 155.3 (C(6)), 163.6 (benzothiazoleC(2)), 166.1 (C(2)O).

(R)-4-benzoyl-3-(3-bromophenyl)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-one (241a) and (R)-5-(benzo[d]thiazol-2-yl)-4-(3-bromophenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (241b)

![Chemical structure](image)

The title compounds were prepared according to General Procedure H from (E)-3-bromocinnamic anhydride (436 mg, 1.00 mmol) and 2-phenacyl benzothiazole (182 mg, 0.72 mmol), EtN(iPr)2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (20% EtOAc/petrol) to give 241a/241b as a yellow solid (86:14 mixture of regioisomers, 287 mg, 86%); mp 163–167 °C; [α]D20 –197.8 (c 0.5, CH2Cl2); νmax (film)/cm⁻¹ 3050 (C-H), 1774 (C=O, lactone), 1717 (C=O, ketone), 1601 (C=O, lactam), 1571 (C=N), 1474 (C=C); m/z (APCI⁺) 462 ([M+H]+, 100%); HRMS (APCI⁺) C24H17Br79NO2S ([M+H]+) requires 462.0158, found 462.0156 (–0.4 ppm).

241a (major): chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR major: 21.4 min, tR minor: 15.8 min, 84% ee; δH (500 MHz, CDCl3) 3.04 (1H, dd, J 16.0, 2.4, C(2)H), 3.25 – 3.33 (1H, m, C(2)HH), 4.34 (1H, dd, J 7.1, 2.4, C(3)H), 7.02 – 7.07 (1H, m, C(3)ArC(6)H)), 7.16 (2H, t, J 7.8, ArH), 7.24 – 7.45 (9H, m, ArH), 7.62 (1H, dd, J 7.4, 1.7, C(7)H), 8.48 (1H, dd, J 8.1, 1.4, C(4)H); δC (126 MHz, CDCl3) 38.3 (C(3)H), 41.1 (C(2)H), 106.8 (C(4)), 117.6 (C(4)H), 122.0 (C(7)H), 123.3 (C(3)ArC(1)Br), 125.3 (C(6)H), 126.1 (C(3)ArC(6)H), 126.8 (2 × C(4)COArC(2)H), 127.2 (C(3)ArC(2)H), 127.6 (C(7a)), 128.2 (2 × C(4)COArC(2)H), 130.1 (ArCH), 130.4
6. Experimental

(245a) and (245b)

The title compounds were prepared according to General Procedure H from (E)-crotonic anhydride (154 mg, 1.00 mmol) and 2-phenacyl benzothiazole (182 mg, 0.72 mmol), EtN(Pr)2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10:2 CH2Cl2/hexane→CH2Cl2) to give 245a as a yellow solid (126 mg, 55%) and 245b as a yellow oil (21 mg, 9%).

245a (major): mp 156–157 °C; [α]20D +93.2° (c 0.5 in CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR major: 14.6 min, tR minor: 11.6 min, 86% ee; δH (400 MHz, CDCl3, characteristic peaks) 1.08 (3H, d, J 7.0, C3H), 2.69 (1H, dd, J 16.0, 2.2, C2H), 3.04 (1H, dd, J 16.0, 6.3, C2H), 3.28 (1H, pd, J 6.9, 2.2, C3H), 7.22 – 7.31 (1H, m, ArH), 7.28 – 7.38 (1H, m, ArH), 7.39 – 7.46 (3H, m, ArH), 7.46 – 7.53 (3H, m, ArH), 8.48 – 8.54 (1H, m, C4'H); δC (101 MHz, CDCl3) 19.6 (CH3), 27.8 (C5'H), 40.0 (C2'H2), 110.5 (C4), 117.5 (C4'H), 121.9 (C7'H), 125.8 (C6'H), 126.8 (2 × C4'COPhC3'H), 126.9 (C5'H), 127.7 (C7a'), 128.4 (2 × C4'COPhC2'H), 130.0 (ArH), 130.9 (ArH), 130.9 (ArH), 136.0 (C4'a'), 139.3 (C4'COArC1), 143.4 (C3'ArC3'), 156.5 (C5'), 167.5 (C1'O), 191.2 (C4'COAr).

245b (minor): chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR major: 11.7 min, tR minor: 8.4 min, 84% ee; δH (500 MHz, CDCl3, characteristic peaks) 3.08 (1H, dd, J 15.8, 1.7, C3H), 3.34 (1H, dd, J 15.8, 7.6, C3'H), 5.06 (1H, dd, J 7.7, 1.7, C4'H), 7.94 (1H, d, J 8.2, benzothiazoleC7'H); δC (126 MHz, CDCl3, characteristic peaks) 36.7 (C3H2), 40.6 (C4H), 114.5 (C5), 121.2 (benzothiazoleC7'H), 123.0 (benzothiazoleC4'H), 123.2 (C4'ArC1Br), 125.4 (ArH), 125.5 (ArH), 126.1 (ArH), 129.0 (2 × C6'ArC3'H), 130.0 (2 × C6'ArC2'H), 130.8 (ArH), 131.0 (ArH), 131.6 (C6'ArC1), 135.6 (benzothiazoleC7a'), 142.0 (C4'ArC3), 152.2 (benzothiazoleC4a'), 154.9 (C6), 163.6 (benzothiazoleC2), 166.1 (C2'O).
6. Experimental

(C)CO\textsubscript{Ph}C\textsubscript{(4)H}, 136.1 (C\textsubscript{(4a)′}), 140.0 (C)CO\textsubscript{Ph}(C\textsubscript{1})), 154.2 (C\textsubscript{(5)}), 168.9 (C\textsubscript{(1)}O), 191.4 (C)CO\textsubscript{Ph}; \textit{m}/\textit{z} (NSI\textsuperscript{+}) 322 ([M+H\textsuperscript{+}], 100%); HRMS (NSI\textsuperscript{+}) C\textsubscript{19}H\textsubscript{16}NO\textsubscript{2}S ([M+H\textsuperscript{+}]) requires 322.0896, found 322.0901 (+1.5 ppm).

\textbf{245b (minor): }[\alpha]_{D}^{20} +21.0 (c 0.2 in CH\textsubscript{2}Cl\textsubscript{2}); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1 mL min\textsuperscript{-1}, 211 nm, 30 °C), t\textsubscript{R} major: 18.9 min, t\textsubscript{R} minor: 9.5 min, 92% ee; \nu\textsubscript{max} (film)/cm\textsuperscript{-1} 3057 (C-H), 2963 (C-H), 1775 (C=O); \delta\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 1.30 (3H, d, J 7.1, C\textsubscript{3}H\textsubscript{3}), 2.79 (1H, dd, J 15.7, 2.0, C(3)\textsubscript{2}H\textsubscript{2}), 3.02 (1H, dd, J 15.7, 6.7, C(3)\textsubscript{2}H\textsubscript{2}), 3.82 (1H, pd, J 7.1, 2.0, C(4)\textsubscript{2}H\textsubscript{2}), 7.28–7.35 (1H, m, benzothiazoleC(6)\textsubscript{H}), 7.37–7.52 (6H, m, Ar\textsubscript{H}), 7.63–7.68 (1H, m, benzothiazoleC(4)\textsubscript{H}), 7.95–8.01 (1H, m, benzothiazoleC(7)\textsubscript{H}); \delta\textsubscript{C} (126 MHz, CDCl\textsubscript{3}) 19.0 (C\textsubscript{3}H\textsubscript{3}), 30.8 (C\textsubscript{(4)H}), 117.9 (C\textsubscript{(5)}), 121.3 (benzothiazoleC(4)\textsubscript{H}), 123.0 (benzothiazoleC(7)\textsubscript{H}), 125.5 (benzothiazoleC(4)\textsubscript{H}), 126.2 (benzothiazoleC(5)\textsubscript{H}), 129.0 (2 × C(6)PhC\textsubscript{(3)H}), 130.1 (2 × C(6)PhC\textsubscript{(2)H}), 130.7 (C(6)PhC\textsubscript{(4)H}), 132.1 (C(6)PhC\textsubscript{(1)}), 135.7 (benzothiazoleC(7a)), 152.6 (benzothiazoleC(4a)), 153.3 (C\textsubscript{(6)}), 164.2 (benzothiazoleC(2)), 167.6 (C\textsubscript{(2)O}); \textit{m}/\textit{z} (NSI\textsuperscript{+}) 322 ([M+H\textsuperscript{+}], 100%); HRMS (NSI\textsuperscript{+}) C\textsubscript{19}H\textsubscript{16}NO\textsubscript{2}S ([M+H\textsuperscript{+}]) requires 322.0896, found 322.0901 (+1.5 ppm).

(R)-4-benzoyl-3-(furan-3-yl)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-one (243a) and (R)-5-(benzo[d]thiazol-2-yl)-4-(furan-3-yl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (243b)

![Chemical Structure]

The title compounds were prepared according to General Procedure H from (2E)-3-(furan-3-yl)prop-2-enoic anhydride (258 mg, 1.00 mmol) and 2-phenacyl benzothiazole (182 mg, 0.72 mmol), EtN(iPr)\textsubscript{2} (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10:2 CH\textsubscript{2}Cl\textsubscript{2}/hexane) to give 243a as a yellow solid (132 mg, 40%) and 243b as a yellow oil (15 mg, 5%).

\textbf{243a (major): }mp 92–94 °C; [\alpha]_{D}^{20} +11.2 (c 0.5, CH\textsubscript{2}Cl\textsubscript{2}); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min\textsuperscript{-1}, 211 nm, 30 °C), t\textsubscript{R} major: 31.0 min, t\textsubscript{R}
6. Experimental

Minor: 17.0 min, 90% ee; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3063 (C-H), 1721 (C=O), 1607 (C=O), 1574 (C=N), 1474 (C=C); \( \delta \) (300 MHz, CDCl\(_3\)) 3.04 (1H, dd, \( J \) 15.9, 2.4, C(2)H), 3.20 (1H, dd, \( J \) 6.2, 2.4, 1.1, C(3)H), 6.21 (1H, dd, \( J \) 1.9, 1.0, furylC(4)H), 7.16 (1H, q, \( J \) 1.2, furylC(2)H), 7.27 – 7.47 (6H, m, ArH), 7.49 – 7.59 (3H, m, ArH), 8.39 – 8.59 (1H, m, C(4')3)H; \( \delta \) (75 MHz, CDCl\(_3\)) 30.3 (C(3)H), 40.0 (C(2)H\(_2\)), 107.9 (C(4)), 109.3 (furylC(4)H), 117.6 (C(4')H), 122.0 (C(7)H), 125.6 (furylC(2)H), 125.9 (C(6')H), 127.1 (C(7')H), 127.1 (2 × C(4)COPhC(2)H), 127.7 (C(7a')), 128.3 (2 × C(4)COPhC(3)H), 130.5 (C(4)COPhC(4)H), 136.1 (C(4a')), 139.4 (C(4)COPhC(1)), 139.7 (furylC(2)H), 144.2 (furylC(5)H), 156.0 (C(5)), 168.1 (C(1)O), 190.6 (C(4)CO); \( m/z \) (APCI\(^+\)) 374 ([M+H\(^+\)], 100%); HRMS (APCI\(^+\)) C\(_{22}\)H\(_{16}\)O\(_3\)N\(_2\) ([M+H\(^+\)]) requires 374.0845, found 374.0841 (–0.1 ppm).

243b (minor): \( [\alpha]_{D}^{20} \) +65.5 (\( c \) 0.2, CH\(_2\)Cl\(_2\)); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min\(^{-1}\), 211 nm, 30 °C), \( t_R \) major: 13.9 min, \( t_R \) minor: 7.9 min, 94% ee; \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3117 (C-H), 3065 (C-H), 2920 (C-H), 1782 (C=O), 1647 (C=N), 1597 (C=C), 1343 (C=N); \( \delta \) (300 MHz, CDCl\(_3\)) 3.11 (1H, dd, \( J \) 15.8, 2.2, C(3)H), 3.21 (1H, dd, \( J \) 15.8, 6.5, C(3)H), 4.87 – 5.09 (1H, m, C(4)H), 6.32 (1H, dd, \( J \) 1.9, 1.0, furylC(4)H), 7.28 – 7.37 (3H, m, ArH), 7.39 – 7.47 (3H, m, ArH), 7.47 – 7.55 (3H, m, ArH), 7.64 (1H, dt, \( J \) 7.9, 0.9, benzothiazoleC(4)H), 7.97 (1H, dt, \( J \) 8.1, 0.9, benzothiazoleC(7)H); \( \delta \) (126 MHz, CDCl\(_3\)) 32.3 (C(4)H), 35.5 (C(3)H), 109.5 (furylC(4)H), 115.8 (C(5)), 121.4 (benzothiazoleC(7)H), 123.2 (benzothiazoleC(4)H), 124.2 (furylC(3)), 125.6 (benzothiazoleC(6)H), 126.2 (benzothiazoleC(5)H), 129.1 (2 × C(6)PhC(2)H), 130.1 (2 × C(6)PhC(3)H), 131.0 (C(6)PhC(4)H), 131.8 (C(6)PhC(1)), 135.8 (benzothiazoleC(4a)), 139.5 (furylC(2)H), 143.9 (furylC(5)H), 152.5 (benzothiazoleC(7a)), 154.18 (C(6)), 164.0 (benzothiazoleC(2)), 167.0 (C(2)O); \( m/z \) (APCI\(^+\)) 374 ([M+H\(^+\)], 100%); HRMS (APCI\(^+\)) C\(_{22}\)H\(_{16}\)O\(_3\)N\(_2\) ([M+H\(^+\)]) requires 374.0845, found 374.0845 (–0.1 ppm).
(R)-4-benzoyl-3-(thiophen-3-yl)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-one (244a) and (R)-5-(benzo[d]thiazol-2-yl)-6-phenyl-4-(thiophen-3-yl)-3,4-dihydro-2H-pyran-2-one (244b)

The title compounds were prepared according to General Procedure H from (2E)-3-(thiophen-3-yl)prop-2-enoic anhydride (290 mg, 1.0 mmol) and 2-phenacyl benzothiazole (182 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (6:4→10:2 CH₂Cl₂/hexane) to give 244a as a yellow solid (123 mg, 46%) and 244b as a yellow solid (16 mg, 6%)

244a (major): mp 154–157 °C; [α]_D^20 -82.4 (c 1.0, CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), t_R major: 31.3 min, t_R minor: 18.2 min, 82% ee; ν_max (film)/cm⁻¹ 3090 (C–H), 2924 (C–H), 1726 (C=O), 1582 (C=C), 1474 (C=C); δ_H (500 MHz, CDCl₃) 3.08 (1H, dd, J 16.1, 2.4, C(2)H), 3.22 (1H, dd, J 16.0, 6.4, C(2)H), 4.44 (1H, dd, J 6.6, 2.4, C(3)H), 6.84 (1H, d, J 5.0, thiophene-C(4)H), 6.92 (1H, d, J 3.4, thiophene-C(2)H), δ_C (126 MHz, CDCl₃) 34.5 (C(2)H), 38.3 (C(2)HH), 109.8 (C(4)H), 117.7 (C(4')H); δ_C (CDCl₃) 120.9 (C(7a')H), 121.7 (thiophene-C(2)H), 122.0 (C(7)H), 125.6 (C(6')H), 126.4 (thiophene-C(5)H), 127.1 (C(5')H), 127.2 (2 × C(4)COPh-C(2)H), 127.5 (thiophene-C(4)H), 127.8 (C(7a')H), 128.3 (2 × C(4)COPh-C(3)H), 131.0 (C(4)COPh-C(4)H), 136.1 (C(4')H), 139.4 (C(4)COPh-C(1)H), 141.8 (thiophene-C(3)H), 168.4 (C(5)H), 168.1 (C(1)OH), 191.0 (C(4)COPh); m/z (APCI⁺) 390 ([M+H]+'', 100%); HRMS (APCI⁺) C_{22}H_{16}O_{2}NS₂ ([M+H]') requires 390.0617, found 390.0617 (+0.0 ppm).

244b (minor): mp 149–152 °C; [α]_D^20 -52.5 (c 0.4, CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), t_R major: 13.7 min, t_R minor: 8.8 min, 85% ee; ν_max (film)/cm⁻¹ 3102 (C-H), 2920 (C-H), 1780 (C=O), 1647 (C=N), 1595 (C=C), 1431 (C=C); δ_H (500 MHz, CDCl₃) 3.18 (1H, dd, J 15.8, 2.0, C(3)HH), 3.25 (1H, dd, J 15.8, 6.9, C(3)HH), 5.13 (1H, dd, J 6.7, 2.5 (C(4)H), 7.01 (1H, dd,
J 5.0, 1.4, thiopheneC(4)H), 7.16 – 7.18 (1H, m, thiopheneC(2)H), 7.25 – 7.28 (1H, m, ArH), 7.28 – 7.34 (1H, m, ArH), 7.39 – 7.45 (3H, m, ArH), 7.48 – 7.54 (3H, m, ArH), 7.62 – 7.65 (1H, m, benzothiazoleC(7)H), 7.96 (1H, dt, J 8.2, 0.9, benzothiazoleC(4)H); δc (126 MHz, CDCl3) 36.0 (C(3)H3), 36.6 (C(4)H), 116.0 (C(5)), 121.4 (benzothiazoleC(4)H), 121.7 (thiopheneC(2)H), 123.2 (benzothiazoleC(7)H), 125.6 (benzothiazoleC(6)H), 126.2 (benzothiazoleC(5)H), 126.6 (thiopheneC(5)H), 127.0 (thiopheneC(4)H), 129.0 (2 × C(6)PhC(2)H), 130.1 (2 × C(6)PhC(3)H), 130.9 (C(6)PhC(4)H), 131.9 (C(6)PhC(1)), 135.9 (benzothiazoleC(4a)), 140.2 (thiopheneC(3)), 152.5 (benzothiazoleC(7a)), 154.0 (C(6)), 164.2 (benzothiazoleC(2)), 167.0 (C(2)O); m/z (APCI+) 390 ([M+H]+, 100%); HRMS (APCI+) C20H10O2NS2 ([M+H]+) requires 390.0617, found 390.0616 (−0.2 ppm).

**Ethyl (S)-4-benzoyl-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-3-carboxylate (246a) and ethyl (S)-5-(benzo[d]thiazol-2-yl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-carboxylate (246b)**

The title compounds were prepared according to General Procedure H from (E)-4-ethoxy-4-oxobut-2-enoic anhydride (297 mg, 1.00 mmol) and 2-phenacyl benzothiazole (182 mg, 0.72 mmol), EtN(OPr)2 (140 μL, 0.80 mmol) and HBTM 2.1 (1.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10:2 CH2Cl2/hexane→CH2Cl2) to give 246a as a yellow oil (136 mg, 50%) and 246b as a yellow oil (13 mg, 5%).

246a (major): [α]D

20 -20.1 (c 1.0, CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH-hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR major: 27.6 min, tR minor: 23.9 min, 52% ee; νmax (film)/cm⁻¹ 2982 (C=H), 2249 (C=H), 1724 (C=O), 1609 (C=O); δH (300 MHz, CDCl3) 1.13 (3H, t, J 7.1, CH3CH3), 3.05 (1H, dd, J 16.4, 6.5, C(2)H), 3.19 (1H, dd, J 16.4, 2.6, C(2)H), 4.00 – 4.10 (3H, m, CH2CH3, C(3)H), 7.29 – 7.35 (1H, m, C(6′)H), 7.35 – 7.42 (1H, m, C(6′)H), 7.42 – 7.60 (6H, m, ArH), 8.34 – 8.72 (1H, m, C(4′)H); δc (75 MHz, CDCl3) 14.0 (CH2CH3), 115.0 (C(2)H), 39.1 (C(3)H), 61.8 (CH2CH3), 102.8 (C(4)), 117.8 (C(4′)H), 121.9 (C(7′)H), 126.0 (C(6′)H), 127.0 (2 × C(4)COPhC(2)H), 127.2 (C(5′)H), 127.4 (C(7a)), 128.5 (2 × C(4)COPhC(3)H), 130.2 (C(4)COPhC(4)H), 136.1 (C(4a′)), 139.8 (C(4)COPhC(1)), 157.3 (C(5)), 167.3 (C(1)O), 171.6 (COOEt), 191.1
(C(4)COPh); m/z (NSI⁺) 380 ([M+H]⁺, 70%), plus unknown degradation peaks; HRMS (NSI⁺) C₂₃H₁₅O₅NS ([M+H]⁺) requires 380.0951, found 380.0951 (-0.0 ppm).

**246b (minor):** [α]D²⁰ = -2.0 (c 0.25, CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tₘ major: 22.7 min, tₘ minor: 11.1 min, 56% ee; νmax (film)/cm⁻¹ 2982 (C-H), 2361 (C-H), 1782 (C=O), 1728 (C=O), 1651 (C=O); δH (400 MHz, CDCl₃) 1.15 (3H, t, J 7.1, CH₂CH₃), 3.05 (1H, dd, J 16.3, 7.4, C(3)HH), 3.27 (1H, dd, J 16.3, 2.1, C(3)HH), 4.06 – 4.22 (2H, m, CH₂CH₃), 4.68 (1H, dd, J 7.4, 2.1, benzothiazoleC(6)H), 7.32 (1H, dd, J 8.2, 7.2, 1.2, benzothiazoleC(5)H), 7.37 – 7.54 (6H, m, ArH), 7.65 (1H, ddd, J 8.0, 1.3, 0.7, benzothiazoleC(7)H), 7.97 (1H, ddd, J 8.2, 1.2, 0.6, benzothiazoleC(4)H); δC (126 MHz, CDCl₃) 14.1 (CH₃CH₃), 31.3 (C(3)H₃), 41.5 (C(4)H), 62.0 (CH₂CH₃), 110.9 (C(5)), 121.4 (benzothiazoleC(4)H), 123.2 (benzothiazoleC(7)H), 125.6 (benzothiazoleC(6)H), 126.2 (benzothiazoleC(5)H), 129.0 (2 × C(6)PhC(2)H), 130.1 (2 × C(6)PhC(3)H), 131.1 (C(6)PhC(4)H), 131.7 (C(6)PhC(1)), 135.8 (benzothiazoleC(7a), 152.5 (benzothiazoleC(4a), 155.4 (C(6)), 163.9 (benzothiazoleC(2)), 165.6 (C(2)O), 170.7 (COOEt); m/z (NSI⁺) 380 ([M+H]⁺, 15%), plus unknown degradation peaks; HRMS (NSI⁺) C₂₃H₁₅O₅NS ([M+H]⁺) requires 380.0951, found 380.0950 (-0.3 ppm).


![Chemical Structure](image)

The title compound was prepared according to *General Procedure H* from (E)-cinnamic anhydride (70 mg, 0.25 mmol), and 2-(1,3-benzothiazol-2-yl)-N,N-dimethylacetamide (40 mg, 0.18 mmol), EtN(iPr)₂ (35 μL, 0.20 mmol) and HBTM 2.1 (2.8 mg, 0.05 mmol) in THF (0.5 mL) and purified by chromatography on silica gel (10% EtOAc/CH₂Cl₂) to give 260 as an off-white foamy solid (44 mg, 70%); mp 71–74 °C; [α]D²⁰ = -96.4 (c 0.5 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), tₘ major: 17.1 min, tₘ minor: 27.3 min, 96% ee; νmax (film)/cm⁻¹ 3061 (C-H), 2924 (C-H), 1703 (C=O), 1614 (C=C), 1584 (C=C), 1489 (C=N), 1385 (C-S), 1306 (C-O); δH (300 MHz, CDCl₃) 2.85 (6H, s, N(CH₃)₂), 2.98 (1H, dd, J 16.2, 5.9, C(2)HH), 3.19 (1H,
6. Experimental

(dd, J 16.2, 7.1, C(2)H), 4.21 (1H, t, J 6.5, C(3)H), 7.14 – 7.18 (1H, m, ArH), 7.20 – 7.26 (4H, m, ArH), 7.28 – 7.32 (3H, m, ArH), 8.36 (1H, dd, J 8.1, 1.0, C(4')H); δc (126 MHz, CDCl3) 37.0 (2 × N(CH3)2), 40.2 (C(2)H2), 40.9 (C(3)H), 106.4 (C(4)), 117.6 (C(4')H), 121.4 (C(7)H), 125.5 (C(6')H), 126.1 (C(7a')H), 126.4 (C(5')H), 126.9 (2 × C(3)PhC(2)H), 127.6 (C(3)PhC(4)H), 129.2 (2 × C(3)PhC(3)H), 137.3 (C(4a')H), 140.9 (C(3)PhC(1)), 142.3 (C(5)), 167.8 (C(1)O), 169.4 (CONMe2); m/z [M+Na]+ 373 (100%), 389 (M+K)+ 70%; HRMS (NSI+) C20H18O2N2NaS [M+Na]+ requires 373.0981, found 373.0974 (-1.9 ppm).

(R)-N,N-dimethyl-1-oxo-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxamide (269)

The title compound was prepared according to General Procedure H from (E)-p-trifluoromethylcinnamic anhydride (414 mg, 1.00 mmol), and 2-(1,3-benzothiazol-2-yl)-N,N-dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)2 (140 μL, 0.80 mmol) and HBTM (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10% EtOAc/CH2Cl2) to give 269 as a yellow foamy solid (179 mg, 60%); mp 192–193 °C; [α]20D = -104.1 (c 1 in CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), tR major: 14.3 min, tR minor: 21.2 min, 95% ee; νmax (film)/cm⁻¹ 2974 (C-H), 2938 (C-H), 1705 (C=O), 1626 (C=C); δH (500 MHz, CDCl3) 2.89 (6H, s, N(CH3)2), 2.96 (1H, dd, J 16.2, 6.2, C(2)H), 3.19 (1H, dd, J 16.3, 7.1, C(2)H), 4.27 (1H, t, J 6.7, C(3)H), 7.12 – 7.19 (1H, m, ArH), 7.18 – 7.25 (1H, m, ArH), 7.26 – 7.31 (1H, m, ArH), 7.37 (2H, d, J 8.1, 2 × C(3)ArC(2)H), 7.53 – 7.60 (2H, m, 2 × C(3)ArC(3)H), 8.31 – 8.36 (1H, m, C(4')H); δc (126 MHz, CDCl3) 36.9 (2 × N(CH3)2), 40.0 (C(3)H), 40.5 (C(2)H2), 105.0 (C(4)), 117.5 (C(4')H), 121.3 (C(7)H), 124.0 (q, J 272.1, CF3), 125.5 (C(6')H), 125.6 (C(7a')H), 126.1 (q, J 3.8, 2 × C(3)ArC(3)H), 126.4 (C(5)H), 127.3 (2 × C(3)ArC(2)H), 129.7 (q, J 32.5 C(3)ArC(4)CF3), 137.0 (C(4a')H), 142.9 (C(3)ArC(1)), 145.1 (C(5)), 167.0 (C(1)O), 169.0 (CONMe2); δF (470 MHz, CDCl3) -62.53; m/z (APCI⁺) 419 ([M+H]+, 100%); HRMS (NSI+) C21H18F3N2O2S ([M+H]+) requires 419.1036, found 419.1040 (+1.1 ppm).
(R)-3-(4-methoxyphenyl)-N,N-dimethyl-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxamide (270)

The title compound was prepared according to General Procedure H from (E)-4-methoxycinnamic anhydride (338 mg, 1.00 mmol), and 2-(1,3-benzothiazol-2-yl)-N,N-dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10% EtOAc/CH₂Cl₂) to give 270 as a yellow solid (145 mg, 53%); mp 157–159 °C; [α]D -120.3 (c 1 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), tr major: 19.9 min, tr minor: 27.8 min, 93% ee; νmax (film)/cm⁻¹ 2929 (C–H), 1711 (C=O), 1688 (C=O), 1609 (C=C); δH (500 MHz, CDCl₃) 2.87 (6H, s, N(CH₃)₂), 2.95 (1H, dd, J 16.1, 5.9, C(2)H), 3.15 (1H, dd, J 16.1, 7.0, C(2)H), 3.77 (3H, s, OCH₃), 4.15 (1H, t, J 6.4, C(3)H), 6.80 – 6.86 (2H, m, C(3)ArC(3)H), 7.12 – 7.19 (3H, m, ArH), 7.22 (1H, ddd, J 8.3, 7.5, 1.4, ArH), 7.26 – 7.31 (1H, m, ArH), 8.35 (1H, dd, J 8.2, 1.2, C(4')H); δC (126 MHz, CDCl₃) 36.9 (2 × N(CH₃)₂), 39.3 (C(3)H), 41.0 (C(2)H), 55.3 (OCH₃), 106.6 (C(4)), 114.4 (2 × C(3)ArC(3)H), 117.5 (C(4')H), 121.2 (C(7')H), 125.3 (C(6')H), 126.0 (C(7a')H), 126.2 (C(5')H), 127.9 (2 × C(3)ArC(2)H), 132.7 (C(3)ArC(4)), 137.2 (C(4a')H), 142.1 (C(3)ArC(1)), 158.82 (C(5)), 167.8 (CO), 169.3 (CO); m/z (NSI⁺) 381 ([M+H⁺], 100%), 761 ([2M+H⁺], 35%); HRMS (NSI⁺) C₂₁H₂₉N₂O₃S ([M+H⁺]) requires 381.1267, found 381.1267 (−0.1 ppm).

(S)-3-(2-bromophenyl)-N,N-dimethyl-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxamide (271)

The title compound was prepared according to General Procedure H from (E)-2-bromocinnamic anhydride (436 mg, 1.00 mmol) and 2-(1,3-benzothiazol-2-yl)-N,N-
6. Experimental

dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10% EtOAc/CH₂Cl₂) to give **271** as a yellow solid (243 mg, 79%); mp 149–152 °C; [α]ᵦ²⁰ = –20.0 (c 1.0, CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tᵦ major: 22.8 min, tᵦ minor: 16.2 min, 96% ee; vₘₐₓ (film)/cm⁻¹ 2924 (C–H), 1710 (C=O), 1604 (C=O), 1585 (C=N), 1454 (C=C); δₜ (500 MHz, CDCl₃) 2.87 (6H, s, N(CH₃)₂), 2.95 (1H, dd, J 16.2, 5.6, C(2)H), 3.14 (1H, dd, J 16.2, 6.9, C(2)H), 4.64 (1H, dd, J 6.9, 5.6, C(3)H), 7.08–7.15 (1H, m, ArH), 7.16–7.29 (4H, m, ArH), 7.35 (1H, dd, J 7.5, 1.5, C(3)ArC(2)H), 7.59 (1H, dd, J 8.0, 1.3, C(7')H), 8.31–8.36 (1H, m, C(4')H), δₜ (126 MHz, CDCl₃) 37.2 (2 × N(CH₃)₂), 39.2 (C(3)H), 39.5 (C(2)H), 104.8 (C(4)), 117.5 (C(4')H), 121.3 (C(7')H), 123.7 (C(3)ArC(1)Br), 125.5 (C(6')H), 126.2 (ArCH), 126.8 (C(7a'')), 128.1 (ArCH), 128.3 (ArCH), 129.2 (ArCH), 133.7 (C(3)ArC(6)), 136.8 (C(4a'')), 139.2 (C(3)ArC(2)), 147.3 (C(5)), 167.3 (C(1)O), 169.0 (CONMe₂); m/z (APCI⁺) 431 ([M+H⁺], 100%); HRMS (APCI⁺) C₂₀H₁₈Br₂NO₂N₂S ([M+H⁺] requires 429.0267, found 429.0267 (+0.0 ppm).


The title compound was prepared according to General Procedure H from (E)-3-bromocinnamic anhydride (436 mg, 1.00 mmol) and 2-(1,3-benzothiazol-2-yl)-N,N-dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (CH₂Cl₂ → 10% EtOAc/CH₂Cl₂) to give **272** as a yellow solid (283 mg, 92%); mp 69–72 °C; [α]ᵦ²⁰ = –103.3 (c 1.0, CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tᵦ major: 15.4 min, tᵦ minor: 38.8 min, 96% ee; vₘₐₓ (film)/cm⁻¹ 2922 (C–H), 1701 (C=O), 1613 (C=O), 1587 (C=N), 1452 (C=C); δₜ (500 MHz, CDCl₃) 2.89 (6H, s, N(CH₃)₂), 2.94 (1H, dd, J 16.3, 6.1, C(2)H), 3.16 (1H, dd, J 16.3, 7.2, C(2)H), 4.18 (1H, dd, J 7.2, 6.0, C(3)H), 7.14–7.19 (3H, m,
ArH), 7.20 – 7.25 (1H, m, ArH), 7.28 – 7.30 (1H, m, ArH), 7.35 – 7.40 (2H, m, ArH), 8.35 (1H, dd, J 8.3, 0.8, C(4')H); δC (75 MHz, CDCl3) 37.0 (2 × N(CH3)2), 40.0 (C(3)H), 40.6 (C(2)H2), 105.4 (C(5)), 117.7 (C(4')H), 121.4 (C(7')H), 123.1 (C(3)ArC(1)Br), 125.5, (ArCH), 125.6 (ArCH), 125.8 (C(7a')), 126.5 (C(5')H), 130.1 (ArCH), 130.8 (ArCH), 130.8 (ArCH), 137.2 (C(4a'), 142.7 (C(3)ArC(3)), 143.4 (C(5)), 167.3 (C(1)O), 169.1 (CONMe2); m/z (APCI+) 429 ([M+H]+, 100%); HRMS (APCI+) C20H18Br79N2O2S ([M+H]+) requires 429.0267, found 429.0267 (+0.0 ppm).

(S)-N,N,3-trimethyl-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxamide (276)

The title compound was prepared according to General Procedure H from (E)-crotonic anhydride (154 mg, 1.0 mmol), and 2-(1,3-benzothiazol-2-yl)-N,N-dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10% EtOAc/CH2Cl2→10% EtOAc/CH2Cl2) to give 276 as a yellow oil (146 mg, 71%); [α]20D +9.7 (c 1.5 in CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min−1, 211 nm, 30 °C), tR major: 9.6 min, tR minor: 13.6 min, 94% ee; νmax (film)/cm−1 2963 (C-H), 2926 (C-H), 1699 (br, 2 × C=O), 1622 (C=C); δH (500 MHz, CDCl3) 1.19 (3H, d, J 6.9, C(3)CH3), 2.59 (1H, dd, J 16.1, 6.9, C(2)H), 2.90 (1H, dd, J 16.1, 6.3, C(2)H), 3.01 (1H, h, J 7.0, C(3)H), 3.07 (6H, s, N(CH3)2), 7.12 (1H, td, J 7.6, 1.2, C(5')H), 7.18 – 7.21 (1H, m, C(6')H), 7.21 – 7.24 (1H, m, C(7')H), 8.31 – 8.39 (1H, m, C(4')H); δC (126 MHz, CDCl3) 18.7 (C(3)CH3), 29.6 (C(3)H), 36.7 (2 × N(CH3)2), 40.4 (C(2)H2), 108.5 (C(4)), 117.4 (C(4')H), 121.2 (C(7')H), 125.2 (C(6')H), 125.4 (C(7a')), 126.2 (C(5')H), 137.3 (C(4a')), 138.3 (C(5)), 168.3 (C(1)O), 169.5 (CONMe2); m/z (NSI+) 289 ([M+H]+, 20%), 311 ([M+Na]+, 40%), 327 ([M+K]+, 90%) plus degradation peaks; HRMS (NSI+) C15H16N2O2S ([M+H]+) requires 289.1005, found 289.1005 (−0.1 ppm).
(S)-3-(furan-2-yl)-N,N-dimethyl-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxamide (273)

The title compound was prepared according to General Procedure H from (E)-3-(furan-2-yl)acrylic anhydride (258 mg, 1.00 mmol), and 2-(1,3-benzothiazol-2-yl)-N,N-dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (CH2Cl2 → 10% EtOAc/CH2Cl2) to give 273 as a brown oil (193 mg, 79%); [α]D20 -109.3 (c 0.5 in CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), tR major: 14.4 min, tR minor: 20.3 min, 95% ee; νmax (film)/cm⁻¹ 2974 (C-H), 2928 (C-H), 1583 (furan), 1489 (furan); δH (500 MHz, CDCl3) 2.97 (6H, s, N(C(3)H3)2), 3.10 (1H, dd, J 16.2, 3.9, C(2)H), 3.18 (1H, dd, J 16.4, 7.0, C(2)H), 4.26 (1H, dd, J 7.1, 3.9 C(3)H), 6.15 (1H, d, J 3.2 (C(3)furylC(3)H), 6.28 (1H, dd, J 3.3, 1.9, C(3)furylC(4)H), 7.14 – 7.19 (1H, m, C(5')H), 7.21 – 7.27 (1H, m, C(6')H), 7.27 – 7.31 (1H, m C(3)furylC(5)H), 7.32 (1H, dd, J 1.9, 0.9, C(7')H), 8.38 (1H, dd, J 8.2, 1.1, C(4')H); δC (126 MHz, CDCl3) 33.7 (C(3)H), 37.0 (2 × N(CH3)2), 37.4 (C(2)H2), 103.6 (C(4)), 106.2 (C(3)furylC(3)H), 110.6 (C(3)furylC(4)H), 117.7 (C(4')H), 121.3 (C(7')H), 125.4 (C(6')H), 125.6 (C(7a')), 126.4 (C(5')H), 137.4 (C(4a')), 141.6 (C(3)furylC(2)), 142.4 (C(3)furylC(5)H), 153.4 (C(5)), 167.6 (C(1)O), 169.2 (CONMe2); m/z (NSI⁺) 341 ([M+H]+, 15%), 363 ([M+Na]+, 100%), 379 ([M+K]+, 10%); HRMS (NSI⁺) C18H17N3O3S ([M+H]+) requires 341.0954, found 341.0949 (–1.6 ppm).

(R)-3-(furan-3-yl)-N,N-dimethyl-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxamide (274)

The title compound was prepared according to General Procedure H from (2E)-3-(furan-3-yl)prop-2-enoic anhydride (258 mg, 1.00 mmol) and 2-(1,3-benzothiazol-2-yl)-N,N-
dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10% EtOAc/CH₂Cl₂) to give 274 as a yellow oil (130 mg, 53%); [α]_D^{20} = −53.7 (c 1.0 in CH₂Cl₂); chiral HPLC analysis, ChiralPak OJ-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), t_R major: 24.5 min, t_R minor: 19.4 min, 96% ee; v_max (film)/cm⁻¹ 2926 (C-H), 1701 (C=O), 1583 (C=N), 1462 (C=C); δ (300 MHz, CDCl₃) 2.85 (1H, dd, J 4.9, 16.1, C(2)H), 2.89 (6H, s, N(C₃H₅)₂), 3.02 (1H, dd, J 16.1, 6.6, C(2)H), 3.95 – 4.06 (1H, m, C(3)H), 6.22 (1H, dd, J 1.9, 1.0, furylC(4)H), 7.06 (1H, td, J 7.5, 1.4, C(5')H), 7.09 – 7.16 (1H, m, C(6')H), 7.16 – 7.21 (1H, m, C(7')H), 7.24 (1H, dt, J 1.7, 0.9, furylC(2)H), 7.27 (1H, t, J 1.7, furylC(5)H), 8.20 – 8.29 (1H, m, C(4')H); δ (75 MHz, CDCl₃) 31.0 (C(3)H), 37.1 (2 × N(C₃H₅)₂), 39.5 (C(2)H) 105.7 (C(4)), 109.3 (furylC(4)H), 117.5 (C(4')H), 121.2 (C(7')H), 124.7 (furylC(3)), 125.3 (C(6')H), 125.8 (C(7a')), 126.2 (C(5')H), 137.1 (C(4a)), 139.3 (furylC(2)H), 142.0 (C(5)), 143.9 (furylC(5)H), 167.8 (C(1)O), 169.2 (CONMe₂); m/z (APCI⁺) 341 ([M+H⁺]+, 100%); HRMS (APCI⁺) C₁₈H₁₇O₃N₂S ([M+H⁺] requires 341.0954, found 341.0953 (–0.4 ppm).

(R)-N,N-dimethyl-1-oxo-3-(thiophen-3-yl)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxamide (275)

The title compound was prepared according to General Procedure H from (2E)-3-(thiophen-3-yl)prop-2-enolic anhydride (290 mg, 1.00 mmol) and 2-(1,3-benzothiazol-2-yl)-N,N-dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (CH₂Cl₂→10% EtOAc/CH₂Cl₂) to give 275 as a yellow oil (148 mg, 58%); [α]_D^{20} = −85.6 (c 1.0, CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), t_R major: 25.6 min, t_R minor: 22.8 min, 96% ee; v_max (film)/cm⁻¹ 3069 (C-H), 2926 (C-H), 1701 (C=O), 1613 (C=O), 1483 (C=N), 1452 (C=C); δ (300 MHz, CDCl₃) 2.91 (6H, s, N(C₃H₅)₂), 3.01 (1H, dd, J 16.2, 4.7, C(2)H), 3.16 (1H, dd, J 16.2, 6.8, C(2)H), 4.27 (1H, dd, J 6.7, 4.9, C(3)H), 6.95 (1H, dd, J 5.0, 1.4, thiopheneC(4)H), 7.05 – 7.11 (1H, m, thiopheneC(2)H), 7.12 – 7.18 (1H, m, ArH), 7.19 – 7.25 (1H, m, ArH), 7.25 –
6. Experimental

7.32 (2H, m, ArH), 8.31 – 8.38 (1H, m, C(4')H); δc (126 MHz, CDCl3) 35.4 (C(3)H), 37.1 (2 × N(CH3)2), 39.9, (C(2)H), 106.2 (C(4)), 117.6 (C(4')H), 121.3 (thiopheneC(2)H), 121.3 (C(5')H), 125.4 (C(6')H), 126.0 (C(7')), 126.4 (thiopheneC(5)H), 127.1 (thiopheneC(4)H), 137.3 (C(4a')), 141.2 (C(5)), 142.0 (thiopheneC(3)), 167.9 (C(1)O), 169.4 (C(1)ONMe2); m/z (APCI+ +) 357 ([M+H]+, 100%); HRMS (APCI+) C18H17O2N2S2 ([M+H]+) requires 357.0726, found 357.0725 (-0.3 ppm).

**Ethyl (S)-4-(dimethylcarbamoyl)-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-3-carboxylate (277)**

![structure](image)

The title compound was prepared according to General Procedure H from (E)-4-ethoxy-4-oxobut-2-enoic anhydride (270 mg, 1.00 mmol), and 2-(1,3-benzothiazol-2-yl)-N,N-dimethylacetamide (158 mg, 0.72 mmol), EtN(iPr)2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10% EtOAc/CH2Cl2) to give 277 as a yellow oil (191 mg, 77%); [α]20 D = -81.6 (c 1.0 in CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), tr major: 17.5 min, tr minor: 31.2 min, 92% ee; νmax (film)/cm⁻¹ 2928 (C-H), 1724 (C=O), 1709 (C=O), 1620 (C=O); δH (500 MHz, CDCl3) 1.24 (3H, t, J 7.2, CH2CH3), 3.02 (1H, dd, J 16.5, 7.3, C(2)H), 3.08 (6H, s, N(CH3)2), 3.10 (1H, dd, J 11.3, 5.2, C(2)H), 3.91 (1H, dd, J 7.3, 5.1, C(3)H), 4.06 – 4.22 (2H, m, CH2CH3), 7.14 (1H, td, J 7.6, 1.2, C(5')H), 7.19 – 7.27 (2H, m, ArH), 8.34 (1H, dd, J 8.3, 1.1, C(4')H); δc (126 MHz, CDCl3) 14.1 (C(3)H), 34.6 (C(2)H), 37.0 (2 × N(CH3)2), 40.1 (CH2CH3), 61.7, CH2CH3), 100.5 (C(5)), 117.6 (C(4')H), 121.1 (C(7')H), 124.8 (C(7a')), 125.3 (C(6')H), 126.4 (C(5')H), 137.2 (C(4a')), 141.4 (C(5)), 166.7 (C(1)O), 169.2 (CONMe2), 171.4 (CO2Et); m/z (NSI+) 347 ([M+H]+, 100%), plus unknown degradation peaks; HRMS (NSI+) C18H19O2N2S ([M+H]+) requires 347.1060, found 347.1062 (+0.6 ppm).
(R)-5-(benzo[d]oxazol-2-yl)-4,6-diphenyl-3,4-dihydro-2H-pyran-2-one (263)

The title compound was prepared according to General Procedure H from (E)-cinnamic anhydride (70 mg, 0.25 mmol), and 2-phenacylbenzoxazole (43 mg, 0.18 mmol), EtN(iPr)2 (35 μL, 0.20 mmol) and HBTM 2.1 (2.8 mg, 0.05 mmol) in THF (0.5 mL) and purified by chromatography on silica gel (CH2Cl2) to give 263 as an off-white foamy solid (61 mg, 95%); mp 125–128 °C; [α]20D +28.8 (c 1.0 in CH2Cl2); chiral HPLC analysis, ChiralPak OJ-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), tR major: 13.6 min, tR minor: 17.3 min, 98% ee; νmax (film)/cm⁻¹ 3061 (C-H), 1778 (C=O), 1690 (C=O), 1645 (C=N), 1530 (C=C); δH (500 MHz, CDCl3) 3.12 (1H, dd, J 15.7, 1.4, C(3)H), 3.31 (1H, dd, J 15.7, 7.6, C(3)H), 4.94 (1H, d, J 6.6, C(4)H), 7.17 – 7.20 (1H, m, ArH), 7.21 – 7.27 (3H, m, ArH), 7.28 – 7.36 (4H, m, ArH), 7.37 – 7.42 (2H, m, ArH), 7.45 – 7.49 (1H, m, ArH), 7.51 – 7.55 (2H, m, ArH), 7.62 – 7.66 (1H, m, benzoxazoleC(4)H); δC (126 MHz, CDCl3) 36.6 (C(3)H2), 40.2 (C(4)H), 107.5 (C(5)), 110.4 (benzoxazoleC(7')H), 119.9 (benzoxazoleC(4')H), 124.5 (benzoxazoleC(6')H), 125.3 (benzoxazoleC(5')H), 126.9 (2 × ArCH), 127.8 (C(4)PhC(4)H), 128.2 (2 × ArCH), 129.0 (2 × ArCH), 129.3 (2 × ArCH), 130.4 (C(6)PhC(4)H), 132.6 (C(6)PhC(1)), 139.4 (benzoxazoleC(4a')), 141.5 (C(4)PhC(1)), 150.2 (benzoxazoleC(7'a')), 156.0 (C(6)), 160.9 (benzoxazoleC(2')), 166.2 (C(2)O); m/z (NSI⁺) 390 ([M+Na⁺], 100%), 368 ([M+H⁺], 40%); HRMS (NSI⁺) C24H17O3NNa ([M+Na⁺]) requires 390.1101, found 390.1094 (−1.7 ppm).

(R)-5-(benzo[d]oxazol-2-yl)-6-phenyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-pyran-2-one (278)

The title compound was prepared according to General Procedure H from (E)-p-trifluoromethylcinnamic anhydride (414 mg, 1.00 mmol), and 2-phenacylbenzoxazole (171
mg, 0.72 mmol), EtN(iPr)_2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10:2 CH_2Cl_2/hexane) to give 278 as a light green solid (112 mg, 36%); mp 193–196 °C; [α]_D^{20} +30.4 (c 0.5 in CH_2Cl_2); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, t_R major: 14.3 min, t_R minor: 15.7 min, 99% ee; ν_{max} (film)/cm⁻¹ 3061 (C-H), 2974 (C-H), 1770 (C=O), 1655 (C=C), 168 (C=C); δ_H (500 MHz, CDCl_3) 3.10 (1H, dd, J 15.8, 1.8, C(3)H), 3.34 (1H, dd, J 15.8, 7.6, C(3)H), 4.98 (1H, dd, J 7.8, 2.0, C(4)H), 7.20–7.24 (1H, m, benzoxazoleC(7)H), 7.24–7.33 (2H, m, ArH), 7.44 (2H, t, J 7.7 ArH), 7.52 (3H, tdd, J 7.8, 1.8, ArH), 7.54–7.59 (2H, m, ArH), 7.61 (2H, d, d, J 8.2, 2 × C(6)ArC(2)H), 7.66 (1H, dd, J 7.3, 1.6, benzoxazoleC(4)H); δ_C (126 MHz, CDCl_3) 36.3 (C(3)H), 40.1 (C(4)H), 106.9 (C(5)), 110.6 (benzoxazoleC(7)H), 124.0 (q, J 272.2, CF_3), 124.7 (benzoxazoleC(6)H), 125.6 (benzoxazoleC(5)H), 126.4 (q, J 3.8, 2 × C(4)ArC(3)H), 127.5 (2 × C(4)ArC(2)H), 128.4 (2 × C(6)ArC(3)H), 129.1 (2 × C(6)ArC(2)H), 130.28 (q, J 32.6, C(4)ArC(4)), 130.8 (C(6)ArC(4)H), 132.4 (C(6)ArC(1)), 141.5 (benzoxazoleC(4a)), 143.7 (C(4)ArC(1)), 150.3 (benzoxazoleC(7a)), 156.6 (C(6)), 160.6 (benzoxazoleC(2)), 165.8 (C(2)O); δ_F (470 MHz, CDCl_3) –62.68; m/z (APCI⁺) 435 ([M+H]⁺, 85%), plus decomposition peaks: 198 (100%), 252 (100%), 331 (90%), 359 (90%); HRMS (APCI⁺) C_{25}H_{17}F_3NO_3 ([M+H]⁺) requires 436.1155, found 436.1154 (–0.2 ppm).

(R)-5-(benzo[d]oxazol-2-yl)-4-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (279)

The title compound was prepared according to General Procedure H from (E)-p-methoxycinnamic anhydride (338 mg, 1.00 mmol), and 2-phenacylbenzoxazole (171 mg, 0.72 mmol), EtN(iPr)_2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (CH_2Cl_2→10% EtOAC/CH_2Cl_2) to give 279 as a yellow foamy solid (211 mg, 74%); mp 98–99 °C; [α]_D^{20} +47.0 (c 0.5 in CH_2Cl_2); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), t_R major: 31.6 min, t_R minor: 26.7 min, 90% ee; ν_{max} (film)/cm⁻¹ 2974
(C-H), 2901 (C-H), 1772 (C=O), 1636 (C=C), 1601 (C=C); δH (500 MHz, CDCl₃) 3.07 (1H, dd, J 15.7, 1.8, C(3)H), 3.27 (1H, dd, J 15.6, 7.5, C(3)H), 3.76 (3H, s, OCH₃), 4.84 (1H, dd, J 7.5, 1.7, C(4)H), 6.82 – 6.89 (2H, m, 2 × C(4)ArC(2)H), 7.19 – 7.31 (5H, m, ArH), 7.41 (2H, t, J 7.6, 2 × C(6)ArC(3)H), 7.72 – 7.81 (2H, m, 2 × C(6)ArC(2)H), 7.89 (1H, t, J 7.5, 2 × C(4)ArC(1)H), 8.09 (1H, s, C(2)O); δC (126 MHz, CDCl₃) 37.0 (C(3)H₂), 39.7 (C(4)H), 55.4 (OCH₃), 108.0 (C(5)), 110.6 (C(5)benzoxazoleC(7)H), 114.7 (2 × C(4)ArC(2)H), 120.0 (C(5)benzoxazoleC(4)H), 124.6 (C(5)benzoxazoleC(6)H), 125.4 (C(5)benzoxazoleC(5)H), 128.1 (2 × ArCH), 128.3 (2 × ArCH), 130.5 (C(6)ArC(4)H), 131.4 (C(6)ArC(1)H), 132.7 (C(4)ArC(4)), 141.6 (C(5)benzoxazoleC(4a)), 150.3 (C(5)benzoxazoleC(7a)), 155.9 (C(6)), 159.2 (C(4)ArC(1)OCH₃), 161.1 (C(5)benzoxazoleC(2)), 166.5 (C(2)O); m/z (NSI⁺) 398 ([M+H]⁺, 25%), 420 ([M+Na]⁺, 100%), 436 ([M+K]⁺, 10%); HRMS (NSI⁺) C₂₅H₂₀NO₄ ([M+H]⁺) requires 398.1387, found 398.1381 (–1.5 ppm).

(R)-5-(benzo[d]oxazol-2-yl)-4-(3-bromophenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (280)

The title compound was prepared according to General Procedure H from (E)-3-bromocinnamic anhydride (436 mg, 1.00 mmol) and 2-phenacyl benzoxazole (171 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (20% EtOAc/petrol) to give 280 as a colourless solid (251 mg, 78%); mp 148–149 °C; [α]D²⁰ +17.7 (C 1.0, CH₂Cl₂); chiral HPLC analysis, ChiralPak OD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR major: 12.9 min, tR minor: 9.3 min, 99% ee; νmax (film)/cm⁻¹ 3013 (C-H), 1761 (C=O), 1651 (C=N), 1452 (C=C); δH (500 MHz, CDCl₃) 3.06 (1H, dd, J 15.8, 1.8, C(3)H), 3.28 (1H, dd, J 15.8, 7.6, C(3)H), 4.85 (1H, dd, J 7.6, 1.8, C(4)H), 7.16 – 7.21 (2H, m, ArH), 7.22 – 7.30 (3H, m, ArH), 7.36 – 7.43 (3H, m, ArH), 7.46 – 7.51 (2H, m, ArH), 7.51 – 7.56 (2H, m, ArH), 7.61 – 7.67 (1H, m, benzoxazoleC(4)H); δC (101 MHz, CDCl₃) 36.5 (C(3)H₂), 40.0 (C(4)H), 106.9 (C(5)), 110.6 (benzoxazoleC(7)), 120.0 (benzoxazoleC(4)H), 123.4
(C(4)ArC(1)Br), 124.7 (C(4)ArC(4)H), 125.4 (benzoxazoleC(5,6)), 125.5 (benzoxazoleC(5,6)), 128.3 (2 × C(6)PhC(3)H), 129.1 (2 × C(6)PhC(2)H), 130.3 (ArCH), 130.7 (ArCH), 130.9 (ArCH), 131.2 (ArCH), 130.3 (benzoxazoleC(7a)), 156.5 (C(6)), 160.6 (benzoxazoleC(2)), 165.8 (C(2)O); m/z (APCI+) 446 ([M+H]+, 100%); HRMS (APCI+) C24H17Br79NO3 ([M+H]+) requires 446.0386, found 446.0386 (–0.1 ppm).

(S)-5-(benzo[d]oxazol-2-yl)-4-methyl-6-phenyl-3,4-dihydro-2H-pyran-2-one (284)

The title compound was prepared according to General Procedure H from (E)-crotonic anhydride (154 mg, 1.00 mmol), and 2-phenacylbenzoxazole (171 mg, 0.72 mmol), EtN(iPr)2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (CH2Cl2→10% EtOAc/CH2Cl2) to give 284 as a white solid (169 mg, 77%); mp 107–109 °C; [α]20D +82.8 (c 1.0 in CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1.0 mL min−1, 211 nm, 30 °C), tR: major: 15.3 min, tR minor: 9.1 min, 93% ee; νmax (film)/cm−1 2974 (C-H), 2914 (C-H), 1761 (C=O), 1639 (C=C); δH (400 MHz, CDCl3) 1.36 (3H, d, J 7.1 C(3)H3), 2.81 (1H, dd, J 15.8, 2.1, C(3)H2), 3.01 (1H, dd, J 15.7, 6.6, C(3)H2), 3.68 (1H, pd, J 7.1, 2.1, C(4)H), 7.23 – 7.36 (3H, m, ArH), 7.36 – 7.42 (2H, m, 2 × C(6)PhC(3)H), 7.43 – 7.50 (3H, m, ArH), 7.70 – 7.76 (1H, m, benzoxazoleC(7)H); δC (101 MHz, CDCl3) 19.1 (C(3)), 29.8 (C(4)H), 35.6 (C(3)H2), 109.9 (C(5)), 110.5 (benzoxazoleC(7)H), 119.8 (benzoxazoleC(4)H), 124.6 (benzoxazoleC(6)H), 125.3 (benzoxazoleC(5)H), 128.1 (2 × C(6)PhC(3)H), 129.0 (2 × C(6)PhC(2)H), 130.2 (C(6)PhC(4)H), 132.8 (C(6)PhC(1)), 141.5 (benzoxazoleC(4a)), 150.2 (benzoxazoleC(7a)), 154.9 (C(6)), 161.1 (benzoxazoleC(2)), 167.0 (C(2)O); m/z (NSI+) 346 ([M+MeCN]+, 100%), 603 ([M+H]+, 20%); HRMS (NSI+) C19H16NO3 ([M+H]+) requires 306.1125, found 306.1124 (–0.2 ppm).
6. Experimental

(S)-5-(benzo[d]oxazol-2-yl)-4-(furan-2-yl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (281)

The title compound was prepared according to General Procedure H from (E)-3-(furan-2-yl)acrylic anhydride (258 mg, 1.00 mmol), and 2-phenacylbenzoxazole (171 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (CH₂Cl₂→10% EtOAc/CH₂Cl₂) to give 281 as a brown/green solid (214 mg, 83%); mp 114-116 °C; [α]D²⁰ +85.2 (c 1.0 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), tₘ major: 10.9 min, tₘ minor: 7.7 min, 97% ee; δmax (film)/cm⁻¹ 2972 (C-H), 2926 (C-H), 1782 (C=O), 1645 (C=C), 1531 (furan), 1452 (furan); δH (400 MHz, CDCl₃) 3.17 (1H, dd, J 15.9, 6.9, C(3)H₂), 3.27 (1H, dd, J 15.9, 2.0, C(3)H₂), 4.96 (1H, dd, J 6.9, 1.9, C(4)H), 6.23 – 6.27 (2H, m, furylC(3)H and furylC(4)H), 7.21 – 7.36 (4H, m, ArH), 7.37 – 7.42 (2H, m, 2 × C(6)PhC(3)H), 7.44 – 7.50 (1H, m, benzoxazoleC(7)H), 7.50 – 7.54 (2H, m, 2 × C(6)PhC(2)H), 7.69 – 7.76 (1H, m, benzoxazoleC(4)H); δc (101 MHz, CDCl₃) 33.4 (C(3)H₂), 34.2 (C(4)H), 105.6 (C(5)), 106.8 (furylC(4)H), 110.4 (furylC(3)H), 110.5 (benzoxazoleC(7)H), 119.9 (benzoxazoleC(4)H), 124.6 (benzoxazoleC(6)H), 125.4 (benzoxazoleC(5)H), 128.1 (2 × C(6)PhC(3)H), 129.0 (2 × C(6)PhC(2)H), 130.5 (C(6)PhC(4)H), 132.5 (C(6)PhC(1)), 141.4 (benzoxazoleC(4a)), 142.8 (furylC(5)H), 150.2 (benzoxazoleC(7a)), 152.1 (furylC(2)), 156.2 (C(6)), 160.8 (benzoxazoleC(2)), 165.9 (C(2)O); m/z (NSI⁺) 358 ([M+H]⁺, 20%), 375 ([M+NH₄]⁺, 75%), 390 ([M+CH₃OH+H]⁺, 100%); HRMS (NSI⁺) C₂₂H₁₆NO₄ ([M+H]⁺) requires 358.1074, found 358.1079 (+1.4 ppm).
(R)-5-(benzo[d]oxazol-2-yl)-4-(furan-3-yl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (282)

The title compound was prepared according to General Procedure H from (2E)-3-(furan-3-yl)prop-2-enoic anhydride (258 mg, 1.00 mmol) and 2-phenacyl benzoazole (171 mg, 0.72 mmol), EtN(iPr)_2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (20% EtOAc/petrol) to give 282 as a yellow oil (30 mg, 12%); [α]_D^{20} +89.1 (c 1.5, CHCl₃); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), t_R major: 11.2 min, t_R minor: 8.4 min, 95% ee; ν_max (film)/cm⁻¹ 2961 (C-H), 2930 (C-H), 1778 (C=O), 1647 (C=N), 1452 (C=C); δ_H (300 MHz, CDCl₃) 3.10 (1H, dd, J 15.8, 2.5, C(3)H), 3.18 (1H, dd, J 15.7, 6.3, C(3)H), 4.76 (1H, ddd, J 6.4, 2.5, 0.9, C(4)H), 6.36 (1H, dd, J 1.8, 0.9, furylC(4)H), 7.18 – 7.32 (3H, m, ArH), 7.32 – 7.42 (4H, m, ArH), 7.42 – 7.50 (3H, m, ArH), 7.66 – 7.72 (1H, m, benzoazoleC(4)H); δ_C (126 MHz, CDCl₃) 31.7 (C(4)H), 35.3 (C(3)H), 107.9 (C(5)), 109.3 (furylC(4)H), 110.6 (benzoazoleC(7)H), 120.0 (benzoazoleC(4)H), 124.1 (furylC(3)), 124.7 (benzoazoleC(6)H), 125.5 (benzoazoleC(5)H), 128.3 (2 × C(6)PhC(2)H), 129.1 (2 × C(6)PhC(3)H), 130.6 (C(6)PhC(4)H), 132.6 (C(6)PhC(1)), 139.5 (furylC(2)H), 141.6 (benzoazoleC(4a)), 144.1 (furylC(5)H), 150.3 (benzoazoleC(7a)), 155.7 (C(6)), 161.0 (benzoazoleC(2)), 166.5 (C(2)O); m/z (APCI⁺) 358 ([M+H]⁺, 100%); HRMS (APCI⁺) C₂₄H₁₆O₄N ([M+H]⁺) requires 358.1074, found 358.1071 (–0.8 ppm).

(S)-5-(benzo[d]oxazol-2-yl)-6-phenyl-4-(thiophen-3-yl)-3,4-dihydro-2H-pyran-2-one (283)

The title compound was prepared according to General Procedure H from (2E)-3-(thiophen-3-yl)prop-2-enoic anhydride (290 mg, 1.00 mmol) and 2-phenacyl benzoazole (171 mg, 0.72 mmol), EtN(iPr)_2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2
mL) and purified by chromatography on silica gel (6:4 → 2 CH₂Cl₂/hexane) to give 283 as a tan solid (120 mg, 45%); mp 105–107 °C; [α]_D^20 +80.4 (c 1.0, CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tₘ major: 10.6 min, tₘ minor: 8.9 min, 98% ee; νₘₚₚ (film) cm⁻¹ 3080 (C-H), 2918 (C-H), 1773 (C=O), 1515 (C=N), 1451 (C=C), 1352 (C=C), 1247 (C=N), 1106 (benzoxazole-C(7)H); δ (126 MHz, CDCl₃) 36.8 (C(3)H₂), 108.1 (C(5)), 120.0 (benzoxazole-C(4)H), 121.7 (thiophene-C(4)H), 124.7 (benzoxazole-C(6)H), 125.5 (benzoxazole-C(5)H), 126.4 (thiophene-C(5)H), 127.2 (thiophene-C(4)H), 128.2 (2 × C(6)PhC(2)H), 129.1 (2 × C(6)PhC(3)H), 130.5 (C(6)PhC(4)H), 132.6 (C(6)PhC(1)), 139.9 (thiophene-C(3)), 141.6 (benzoxazole-C(4a)), 150.3 (benzoxazole-C(7)a), 155.7 (C(6)), 161.1 (benzoxazole-C(2)), 166.5 (C(2)O); m/z (APCI⁺) 374 ([M+H]⁺, 100%); HRMS (APCI⁺) C₂₂H₁₆O₃NS ([M+H]⁺) requires 374.0845, found 374.0846 (+0.2 ppm).

Ethyl (S)-5-(benzo[d]oxazol-2-yl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyranyl-4-carboxylate (285a) and ethyl (S)-4-benzoyl-1-oxo-2,3-dihydro-1H-benzo[4,5]oxazolo[3,2-a]pyridine-3-carboxylate (285b)

The title compounds were prepared according to General Procedure H from (E)-4-ethoxy-4-oxobut-2-enoic anhydride (270 mg, 1.0 mmol), and 2-phenacylbenzoxazole (171 mg, 0.72 mmol), EtN(iPr)₂ (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by filtration through a plug of silica gel (CH₂Cl₂) to give 285a/285b as an off-white oily solid (94:6 mixture of regioisomers, 111 mg, 43%); mp 84–93 °C; [α]_D^20 − 17.6 (c 1.0, CH₂Cl₂); νₘₚₚ (film) cm⁻¹ 2986 (C-H), 1790 (C=O), 1724 (C=O), 1647 (C=O); m/z (NSI⁺) 386 ([M+Na]⁺, 30%), plus unknown degradation peaks; HRMS (NSI⁺) C₂₁H₁₆O₅Na ([M+Na]⁺) requires 389.0999, found 389.0995 (~1.0 ppm).

285a (major): chiral HPLC analysis, ChiralPak IA (20% i-PrOH:hexane, flow rate 1.0 mL min⁻¹, 211 nm, 30 °C), tₘ major: 13.9 min, tₘ minor: 10.8 min, 66% ee; δ (400 MHz,
6. Experimental

CDCl$_3$ 1.12 (3H, t, $J$ 7.1, CH$_2$CH$_3$), 3.00 (1H, dd, $J$ 16.3, 7.3, C(3)HH), 3.27 (1H, dd, $J$ 16.2, 2.0, C(3)HH), 4.07 – 4.22 (2H, m, CH$_2$CH$_3$), 4.47 (1H, dd, $J$ 7.3, 2.0, C(4)H), 7.21 – 7.39 (5H, m, ArH), 7.41 – 7.49 (3H, m, ArH), 7.66 – 7.74 (1H, m, benzoxazoleC(4)H); $\delta$c (101 MHz, CDCl$_3$) 13.9 (CH$_2$C$_6$H$_3$), 30.7 (C(3)H$_2$), 40.6 (C(4)H), 62.1 (CH$_2$CH$_3$), 103.0 (C(5)), 110.5 (benzoxazoleC(7)H), 119.9 (benzoxazoleC(4)H), 124.7 (benzoxazoleC(6)H), 125.5 (benzoxazoleC(4)H), 128.2 (2 × C(6)PhC(2)H), 129.0 (2 × C(6)PhC(3)H), 130.6 (C(6)PhC(4)H), 132.3 (C(6)PhC(1)), 141.4 (benzoxazoleC(4a)), 150.2 (benzoxazoleC(7a)), 156.8 (C(6)), 160.7 (benzoxazoleC(2)), 165.1 (C(2)O), 170.3 (COOEt).

285b (minor): chiral HPLC analysis, ChiralPak IA (20% i-PrOH:hexane, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ major: 12.8 min, $t_R$ minor: 15.0 min, 75% ee; $\alpha$H (400 MHz, CDCl$_3$, characteristic peaks) 2.99 (1H, dd, $J$ 17.0, 7.6, C(3)H), 3.19 (H, dd, $J$ 17.1, 2.8, C(3)H), 7.95 – 8.01 (1H, m, C(4′)H); $\alpha$H (400 MHz, CDCl$_3$, characteristic peaks) (1H, dd, $J$ 17.1, 7.6, C(2)H), 3.19 (1H, dd, $J$ 17.1, 2.8, C(2)H), 7.95 – 7.99 (1H, m, C(4′)H); $\delta$c (101 MHz, CDCl$_3$, characteristic peaks) 33.4 (C(2)H$_2$), 41.9 (C(3)H), 62.1 (CH$_2$CH$_3$), 133.8 (C(4)COPhC(4)H), 135.7 (C(4a′)), 140.7 (C(4)COPhC(1)), 150.9 (C(5)), 161.2 (C(1)O), 193.2 (C(4)COPh).

tert-butyl (R)-1-oxo-3-phenyl-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carboxylate (261)

The title compound was prepared according to modified General Procedure H from (E)-cinnamic anhydride (278 mg, 1.00 mmol), and tert-butyl 2-(1,3-benzothiazol-2-yl)acetate (179 mg, 0.72 mmol), polymer-supported BEMP (2.2 mmol/g loading, 364 mg, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (10:2 CH$_2$Cl$_2$/hexane) to give 261 as a yellow solid (169 mg, 65%); mp 105–110 °C; $[\alpha]_D^{20}$ –213.6 (c 0.5 in CH$_2$Cl$_2$); chiral HPLC analysis, ChiralPak AD-H (2.5% i-PrOH:hexane, flow rate 1.0 mL min$^{-1}$, 211 nm, 30 °C), $t_R$ major: 16.3 min, $t_R$ minor: 11.0 min, 75% ee; $\nu$ max (film)/cm$^{-1}$ 2979 (C-H), 2928 (C-H), 1717 (C=O), 1668 (C=O), 1454 (C=C); $\delta$H (500 MHz, CDCl$_3$) 1.45 (9H, s, OC(CH$_3$)$_3$), 3.02 (1H, dd, $J$ 16.3, 2.0, C(2)HH), 3.26 (1H, dd, $J$ 16.3, 8.1, C(2)HH), 4.28 (1H, dd, $J$ 8.3, 2.0, C(3)H), 7.18 – 7.33 (7H, m, ArH).
6. Experimental

ArH), 7.42 – 7.47 (1H, m, C(7’)H), 8.46 (1H, d, J 8.2, C(4’)H); δc (126 MHz, CDCl3) 28.4 (3 × OC(CH3)3), 37.4 (C(2)H), 40.3 (C(3)H3), 81.3 (OC(CH3)3), 102.2 (C(4)), 117.5 (C(4’)H), 121.5 (C(7’)H), 125.6 (C(6’)H), 126.5 (C(5’)H), 126.7 (2 × C(3)ArC(2)H), 127.2 (C(7a’)), 127.3 (C(3)ArC(4)H), 128.9 (2 × C(3)ArC(3)H), 136.9 (C(4a’)), 142.0 (C(3)ArC(1)), 151.1 (C(5)), 166.1 (C(1)O), 168.5 (C(4)CO; m/z (NSI+) 346 ([M–Bu+Na]+, 100%), 380 ([M+Na]+, 25%), 418 ([M+K]+, 70%); HRMS (NSI+) C22H21O3NS ([M+H]+) requires 380.1315, found 380.1311 (–1.0 ppm).

(R)-4-(4-nitrobenzoyl)-3-phenyl-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-one (262a) and (R)-5-(benzo[d]thiazol-2-yl)-6-(4-nitrophenyl)-4-phenyl-3,4-dihydro-2H-pyran-2-one (262b)

The title compounds were prepared according to General Procedure H from (E)-cinnamic anhydride (278 mg, 1.00 mmol) and 2-(1,3-benzothiazol-2-yl)-1-(4-nitrophenyl)ethanone (215 mg, 0.72 mmol), EtN(iPr)2 (140 μL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (CH2Cl2) to give 262a as a yellow solid (141 mg, 46%) and 262b as a yellow solid (41 mg, 13%).

262a (major): mp 225–229 °C; [α]D20 –90.8 (c 0.5 in CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (40% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR major: 31.8 min, tR minor: 24.5 min, 83% ee; νmax (film)/cm⁻¹ 3111 (C=H), 3065 (C=H), 3030 (C=H), 2870 (C=H), 1717 (C=O), 1701 (C=O), 1614 (C=O), 1520 (C=O), 1495 (NO2), 1340 (NO2); δh (300 MHz, CDCl3) 3.06 (1H, dd, J 15.9, 2.2, C(2)=H), 3.33 (1H, dd, J 15.9, 7.0, C(2)=H), 4.20 (1H, dd, J 6.6, 1.8, C(3)=H), 7.00 – 7.13 (2H, m, C(3)PhC(2)=H), 7.22 – 7.47 (7H, m, ArH), 7.60 – 7.69 (1H, dd, J 3.8, 1.8, C(7)=H), 8.11 (2H, d, J 8.6 C(4)COArC(4)=H), 8.45 – 8.53 (1H, dd, J 7.5, 1.5, C(4)=H); δc (75 MHz, CDCl3) 38.7 (C(2)=H), 41.5 (C(3)=H), 106.8 (C(4)), 117.7 (C(4')=H), 122.2 (C(7')=H), 123.4 (2 × C(4)COArC(3)=H), 126.2 (C(6')=H), 126.7 (2 × C(3)PhC(2)=H), 127.3 (C(7a')), 127.5 (C(3)PhC(4)=H), 128.0 (2 × C(3)PhC(3)=H), 128.0 (C(5')=H), 129.7 (2 × C(4)COArC(2)=H), 136.0 (C(4a')), 140.5 (C(3)PhC(1)), 145.4 (C(4)COArC(1)), 148.5 (C(4)COArC(4)), 157.8 (C(5)), 167.5 (C(1)=O), 188.9 (C(4)=O); m/z
6. Experimental

262b (minor): mp 89–92 °C; [α]D⁰ = −2.6 (c 0.5 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), τr major: 36.3 min, τr minor: 41.4 min, 28% ee; νmax (film)/cm⁻¹ 3105 (C-H), 3028 (C-H), 1780 (C=O), 1520 (NO₂), 1343 (NO₂); δH (75 MHz, CDCl₃) 3.11 (1H, dd, J 15.9, 1.8, C(3)H), 3.36 (1H, dd, J 15.9, 7.6, C(3)H), 4.89 (1H, dd, J 7.6, 1.7, C(4)H), 7.24 – 7.37 (6H, m, ArH), 7.44 (1H, ddd, J 8.3, 7.3, 1.3, C(5)benzothiazoleC(5)H), 7.64 – 7.69 (1H, m, C(5)benzothiazoleC(4)H), 7.70 – 7.76 (2H, m, C(6)ArC(2)H), 7.94 (1H, d, J 7.8, C(5)benzothiazoleC(7)H), 8.19 – 8.26 (2H, m, C(6)ArC(3)H); δC (75 MHz, CDCl₃) 37.1 (C(4)H), 42.5 (C(3)H), 117.1 (C(5)), 121.8 (C(5)benzothiazoleC(7)H), 123.8 (C(5)benzothiazoleC(4)H), 124.2 (2 × C(6)ArC(3)H), 126.3 (C(5)benzothiazoleC(6)H), 126.9 (C(5)benzothiazoleC(5)H), 127.3 (C(4)PhC(4)H), 128.5 (2 × C(4)PhC(2)H), 129.8 (2 × C(4)PhC(3)H), 131.3 (2 × C(6)ArC(2)H), 135.9 (C(5)benzothiazoleC(7a)), 138.5 (C(6)ArC(1)), 139.2 (C(4)PhC(1)), 149.1 (C(5)benzothiazoleC(4a)), 151.5 (C(6)ArC(4)), 153.0 (C(6)), 163.2 (C(5)benzothiazoleC(2)), 166.0 (C(2)O); m/z (APCI⁺) 429 ([M+H]⁺, 100%); HRMS (APCI⁺) C₂₃H₁₇O₄N₂S ([M+H]⁺) requires 429.0902, found 429.0902 (–0.4 ppm).

(3S,4R)-4-benzoyl-3-methyl-3,4-dihydrobenzo[4,5]imidazo[1,2-a]pyridin-1(2H)-one and (S)-5-(1H-benzo[d]imidazol-2-yl)-4-methyl-6-phenyl-3,4-dihydro-2H-pyran-2-one (266)

The title compounds were prepared according to General Procedure H from (E)-crotonic anhydride (154 mg, 1.0 mmol), and 2-phenacylbenzimidazole (170 mg, 0.72 mmol), EtN(iPr)₂ (140 µL, 0.80 mmol) and HBTM 2.1 (11.1 mg, 0.036 mmol) in THF (2 mL) and purified by chromatography on silica gel (5% → 30% EtOAc/petroleum ether) to give a green oil that was further purified by trituration with Et₂O to give 266 as an off-white solid.
(79 mg, 36%, 87A: 4B: 9C); mp 142–144 °C; [α]20D +18.1 (c 1.0, CH2Cl2); chiral HPLC: no separation conditions found therefore ee unknown; v max (film)/cm⁻¹ 3067 (N-H), 2970 (C-H), 1719 (C=O), 1670 (C=O), 1593 (C-N); δH (300 MHz, CDCl3) 1.05 – 1.28 (3.6H, m, A, B, C-CH3), 2.54 – 2.76 (1.1H, m, A-C(2)H), 2.76 – 3.04 (1.2H, m, A-C(3)H, B-C(2)H, B-C(3)H, C-C(3)H), 3.12 (1H, dd, J 17.3, 4.6, A-C(2)H), 3.28 (0.1H, tdd, J 11.0, 8.1, 5.9, B-C(3)H, C-C(3)H), 4.95 (1H, dd, J 6.2, 2.2, A-C(4)H), 5.36 – 5.40 (0.05H, m, B-C(4)H), 7.28 – 7.44 (2H, m, ArH), 7.46 – 7.58 (3H, m, ArH), 7.58 – 7.70 (2H, m, ArH), 8.02 – 8.15 (2.1H, m, A-PhC(2)H), 8.19 – 8.31 (1.1H, m, A-C(4)H, B-C(4)H); δC (101 MHz, CDCl3) 18.3 (B-CH3), 19.9 (A-CH3), 21.9 (C-CH3), 27.9 (C-C(4)H), 31.3 (A-C(3)H), 31.6 (B-C(3)H), 37.7 (B-C(2)H), 38.7 (A-C(2)H), 40.9 (C-C(3)H), 45.7 (B-C(4)H), 50.0 (A-C(4)H), 97.8 (C-C(5)), 115.2 (B-C(4)H), 115.6 (A-C(4)H), 115.7 (ArCH), 116.9 (ArCH), 119.7 (B-C(7)H), 119.9 (A-C(7)H), 124.6 (ArCH), 125.4 (A-C(5,6')H), 125.5 (B-C(5,6')H), 125.5 (A-C(5,6')H), 125.7 (B-C(5,6')H), 127.7 (ArCH), 128.6 (ArCH), 129.1 (2 × A-PhC(2,3)H), 129.1 (2 × A-PhC(2,3)H), 129.7 (ArCH), 130.3 (ArCH), 131.1 (A-C(4a')), 131.4 (B-C(4a')), 134.2 (A-PhC(4)H), 134.3 (ArCH), 136.0 (A-PhC(1)), 137.1 (ArC), 140.0 (ArC), 142.6 (B-C(4a')), 142.8 (A-C(4a')), 151.6 (A-C(5)), 152.1 (B-C(5)), 153.7 (C-C(6)), 167.7 (A-C(1)), 168.2 (B-C(1)), 168.6 (C-C(2)), 196.7 (A-COPh), 196.9 (B-COPh); m/μ (NSI⁺) 305 [M+H⁺, 100%], 327 [M+Na⁺, 60%], 343 [M+K⁺, 55%], 631 [2M+Na⁺, 55%], 647 [2M+K⁺, 100%]; HRMS (NSI⁺) C19H17N3O2 ([M+H⁺]⁺ requires 305.1285, found 305.1284 (−0.2 ppm).

4-benzoyl-3,3-dimethyl-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-one (305)

The title compound was prepared according to General Procedure H from 3-methylbut-2-enolic anhydride (91 mg, 0.50 mmol), and 2-phenacylbenzothiazole (91 mg, 0.36 mmol), EtN/(Pr)2 (70 µL, 0.40 mmol) and HBTM 2.1 (3.4 mg, 0.018 mmol) in THF (1 mL) and purified by chromatography on silica gel (10% EtOAc/petroleum ether) to give 305 as a yellow solid (75 mg, 62%); mp 110–113 °C; v max (film)/cm⁻¹ 2928 (C-H), 2870 (C-H), 1719 (C=O), 1593 (C=O); δH (300 MHz, CDCl3) 1.26 (6H, s, C(3)(CH3)2), 2.70 (2H, s C(2)H2), 7.14 – 7.32 (3H, m, ArH), 7.41 – 7.57 (3H, m, ArH), 7.59 – 7.66 (2H, m, 2 × C(4)COPh(2)H), 8.43 – 8.50 (1H, m, C(4')H); δC (126 MHz, CDCl3) 26.7 (2 ×...
6. Experimental

C(3)(CH₃)₂, 35.1 (C(3)(CH₃)₂), 49.4 (C(2)H₂), 117.3 (C(4)), 117.6 (C(4')H), 121.3 (C(7')H), 125.7 (C(6')H), 126.7 (C(5')H), 126.9 (C(7a)), 128.1 (2 × C(4)COPhC(2)H), 128.9 (2 × C(4)COPhC(3)H), 131.6 (C(4)COPhC(4)H), 136.4 (C(4a)'), 140.7 (C(4)COPhC(1)), 150.4 (C(5)), 168.9 (C(1)O), 194.4 (C(4)COPh); m/z (NSI +) 336 ([M+H] +, 30%), 374 ([M+K] +, 100%); HRMS (NSI +) C₂₀H₁₈O₂NS ([M+H] +) requires 336.1053, found 336.1048 (–1.4 ppm).

(R)-4-benzoyl-3-methyl-3-((trifluoromethyl)-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridin-1-one (310) and (E)-2-(benzo[d]thiazol-2-yl)-6,6,6-trifluoro-5-methyl-1-phenylhex-4-ene-1,3-dione (311)

The title compounds were prepared according to General Procedure H from (2Z)4,4,4-trifluoro-3-methylbut-2-enoic anhydride (406 mg, 1.40 mmol) and 2-phenacylbenzothiazole (253 mg, 1.00 mmol), EtN(iPr)₂ (190 μL, 1.10 mmol) and HBTM 2.1 (15.4 mg, 0.05 mmol) in THF (2.5 mL) and purified by chromatography on silica gel (10:2 CH₂Cl₂/hexane) to give 74a/b as a yellow solid (75:25 mixture of isomers, 163 mg, 42%). The mixture was separated by Et₂O trituration to give 310 as a yellow solid (50 mg, 13%) and 311 as a yellow oil which was solidified by hexane trituration (110 mg, 28%).

310 (1,4-addition): mp 145–150 °C; [α]D²⁰ –18.0 (c 0.5 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (10% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tₘajor: 18.1 min, tₘinor: 16.4 min, 96% ee; v_max (film)/cm⁻¹ 3019 (C-H), 1721 (C=O), 1638 (C-O); δ_H (500 MHz, CDCl₃) 2.96 (1H, d, J 16.8, C(2)H), 7.20 – 7.25 (1H, m, C(5')H), 7.29 – 7.35 (2H, m, ArH), 7.43 – 7.49 (2H, m, 2 × C(4)COPhC(3)H), 7.49 – 7.55 (1H, m, C(7')H), 7.57 – 7.63 (2H, m, 2 × C(4)COPhC(2)H), 8.42 – 8.49 (1H, m, C(4')H); δ_C (126 MHz, CDCl₃) 21.1 (CH₃), 41.8 (C(2)H₂), 43.8 (q, J_CF 26.9, C(3)CF₃), 105.3 (C(4)), 117.8 (C(4')H), 121.4 (C(7')H), 126.1 (C(6')H), 126.4 (C(7a'')), 127.2 (C(5')H), 127.6 (q, J_CF 286.1, CF₃), 128.1 (2 × C(4)COPhC(2)H), 128.8 (2 × C(4)COPhC(3)H), 131.4 (C(4)COPhC(4)H), 136.0 (C(4a')), 140.7 (C(4)COPhC(1)), 150.4 (C(5)), 168.9 (C(1)O), 194.4 (C(4)COPh); m/z (NSI +) 336 ([M+H] +, 30%), 374 ([M+K] +, 100%); HRMS (NSI +) C₂₀H₁₈O₂NS ([M+H] +) requires 336.1053, found 336.1048 (–1.4 ppm).
6. Experimental

6.6 Cascade Substrates

**General Procedure I: Enone-Malonate Synthesis**

![Diagram of enone-malonate synthesis](image)

Allylation procedure from Han and Widenhoefer.\textsuperscript{158} NaH (60% in mineral oil, 1 equiv) was suspended in DMF (0.35 M) at 0 °C. A solution of dicarbonyl (1 equiv) in DMF (1 M) was added, and the flask stirred at 0 °C for 2 h. A solution of allylbromide (1 equiv) in DMF (1 M) was added dropwise and the flask stirred at 0 °C to rt for 16 h. Water (xx mL) was

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140.0 (C(4)COPh(1)), 156.0 (C(5)), 166.1 (C(1)O), 193.0 (C(4)COPh); δ\textsubscript{F} (470 MHz, CDCl\textsubscript{3}) -75.64; m/z (NSI\textsuperscript{+}) 390 ([M+H]\textsuperscript{+}, 100%); HRMS (NSI\textsuperscript{+}) C\textsubscript{20}H\textsubscript{15}F\textsubscript{3}O\textsubscript{2}NS ([M+H]\textsuperscript{+}) requires 390.0770, found 390.0766 (–1.1 ppm).

311 (1,2-addition): mp 196–198 °C; ν\textsubscript{max} (film)/cm\textsuperscript{-1} 3023 (C–H), 1537 (C=O?), 1499 (C=O?), 1450 (C=N?) highly conjugated system, carbonyl peaks very low; δ\textsubscript{H} (500 MHz, CDCl\textsubscript{3}) 1.98 (6H, s, br, C\textsubscript{H}\textsubscript{3}), 6.08 (1H, dt, J\textsubscript{3.0}, 1.6, 1-keto-C(4)H), 6.18 (1H, dt, J\textsubscript{3.1}, 1.7, 1-enol-C(4)H), 7.37 – 7.44 (6H, m, ArH), 7.47 – 7.56 (8H, m, ArH), 7.63 (2H, t, J 8.0, benzothiazoleC(7)H), 7.85 (2H, d, J 7.9, benzothiazoleC(4)H), 14.72 (1H, s, 1-keto-OH), 14.98 (1H, s, 1-enol-OH); δ\textsubscript{C} (126 MHz, CDCl\textsubscript{3}) 12.4 (C\textsubscript{H}\textsubscript{3}), 12.4 (C\textsubscript{H}\textsubscript{3}), 108.9 (C(2)), 109.1 (C(2)), 114.2 (benzothiazoleC(7)H), 114.4 (benzothiazoleC(7)H), 122.5 (benzothiazoleC(4)H), 123.4 (q, J\textsubscript{CF} 274.0, CF\textsubscript{3}), 123.5 (q, J\textsubscript{CF} 274.0, CF\textsubscript{3}), 125.2 (benzothiazoleC(5)H), 125.2 (benzothiazoleC(5)H), 127.7 (benzothiazoleC(6)H), 127.8 (benzothiazoleC(6)H), 128.2 (2 × C(1)PhC(2)H), 128.2 (2 × C(1)PhC(2)H), 128.5 (2 × C(1)PhC(3)H), 128.5 (2 × C(1)PhC(3)H), 128.9 (q, J\textsubscript{CF} 21.5, C(5)CF\textsubscript{3}), 130.4 (q, J\textsubscript{CF} 5.7, 1-keto-C(4)H), 130.9 (q, J\textsubscript{CF} 5.7, 1-enol-C(4)H), 131.6 (C(1)PhC(4)H), 131.7 (C(1)PhC(4)H), 132.0 (C(1)PhC(1)), 132.1 (C(1)PhC(1)), 137.9 (benzothiazoleC(4a)), 138.1 (benzothiazoleC(4a)), 141.7 (benzothiazoleC(7a)), 142.0 (benzothiazoleC(7a)), 168.8 (benzothiazoleC(2)), 169.2 (benzothiazoleC(2)), 187.3 (1-keto-C(3)OH), 187.6 (1-enol-C(3)O), 193.2 (1-enol-C(1)OH), 194.1 (1-keto-C(1)O); δ\textsubscript{F} (470 MHz, CDCl\textsubscript{3}) -70.96, -70.95; m/z (NSI\textsuperscript{+}) 390 ([M+H]\textsuperscript{+}, 100%); HRMS (NSI\textsuperscript{+}) C\textsubscript{20}H\textsubscript{15}F\textsubscript{3}O\textsubscript{2}NS ([M+H]\textsuperscript{+}) requires 390.0770, found 390.0766 (–1.8 ppm).
added and the mixture extracted with ether (xx mL × 2). The combined organic layers were washed with brine (xx mL × 3), dried over MgSO₄, filtered and concentrated in vacuo to give the crude allyl ester (used without further purification).

The allyl ester was dissolved in a solution of methyl vinyl ketone (3 equiv) in CH₂Cl₂ (0.5 M) in a sealable tube and the solution degassed by sparging with argon for 10 minutes. Metathesis catalyst M2 (2 mol%) was added, the tube sealed and heated at 50 °C for 48 h. After cooling to rt the solution was concentrated in vacuo and purified by silica chromatography (passed through silica twice to remove Ru residues) to afford enonemalonates.

**Diethyl (E)-2-(4-oxopent-2-en-1-yl)malonate (370)**

![Chemical structure of Diethyl (E)-2-(4-oxopent-2-en-1-yl)malonate (370)](image)

The title compound was prepared according to general procedure I from diethylmalonate (2.30 mL, 15.0 mmol in DMF, 15 mL), allylbromide (1.30 mL, 15.0 mmol in DMF, 15 mL) and NaH (60% in mineral oil, 0.60 g, 15.0 mmol) in DMF (40 mL). Aqueous work-up afforded crude allylmalonate which was dissolved in CH₂Cl₂ (40 mL) and methyl vinyl ketone (3.65 mL, 45.0 mmol) and M2 (285 mg, 0.3 mmol) added. The residue was purified by silica chromatography (20% EtOAc/hexane, twice) to afford 370 as a pale yellow oil (820 mg, 23%) {Lit.¹⁵⁹ oil}; νmax (film)/cm⁻¹ 2982 (C-H), 2940 (C-H), 1728 (C=O), 1674 (C=O), 1630 (C=C); δH (400 MHz, CDCl₃) 1.26 (6H, t, J 7.1, 2 × CO₂CH₂CH₃), 2.22 (3H, s, CO₂CH₃), 2.79 (2H, td, J 7.2, 1.5, CH₂CH=CH), 3.49 (1H, t, J 7.3, CHCO₂Et), 4.20 (4H, qd, J 7.1, 2.2, 2 × CO₂CH₂CH₃), 6.11 (1H, dt, J 15.9, 1.5, CH₂CH=CH), 6.73 (1H, dt, J 16.0, 7.0, CH₂CH=CH). Data in agreement with the literature.¹⁵⁹
Dimethyl (E)-2-(4-oxopent-2-en-1-yl)malonate (391)

The title compound was prepared according to general procedure I from dimethylmalonate (1.14 mL, 10.0 mmol in DMF, 10 mL), allylbromide (0.87 mL, 10.0 mmol in DMF, 10 mL) and NaH (60% in mineral oil, 0.40 g, 10.0 mmol) in DMF (40 mL). Aqueous work-up afforded crude allylmalonate which was dissolved in CH$_2$Cl$_2$ (20 mL) and methyl vinyl ketone (2.43 mL, 30.0 mmol) and M2 (190 mg, 0.2 mmol) added. The residue was purified by silica chromatography (10→30% EtOAc/hexane) to afford 391 as an orange oil (522 mg, 23%); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3005 (C-H), 2957 (C-H), 1732 (C=O), 1674 (C=O), 1630 (C=C); $\delta$H (300 MHz, CDCl$_3$) 2.20 (3H, s, COC$_2$H$_3$), 2.78 (2H, td, $J$ 7.1, 1.5, C$_2$H$_2$), 3.52 (1H, t, $J$ 7.3, C$_2$HCO$_2$CH$_3$), 3.72 (6H, s, 2 × OC$_2$H$_3$), 6.09 (1H, dt, $J$ 16.0, 1.5, CH=CHCOCH$_3$), 6.69 (1H, dt, $J$ 16.0, 7.0, CH=CHCOCH$_3$); $\delta$C (75 MHz, CDCl$_3$) 27.2 (C$_2$HCO$_2$CH$_3$), 52.9 (2 × OCH$_3$), 133.2 (CH=CHCOCH$_3$), 142.6 (CH=CHCOCH$_3$), 168.8 (2 × CO$_2$CH$_3$), 198.1 (COCH$_3$); $m/z$ (NSI$^+$) 237 ([M+Na]$^+$, 100%), 215 ([M+H]$^+$, 70%); HRMS (NSI$^+$) C$_{10}$H$_{15}$O$_5$ ([M+H]$^+$) requires 215.0914, found 215.0914 (+0.0 ppm).

Diisopropyl (E)-2-(4-oxopent-2-en-1-yl)malonate (389)

The title compound was prepared according to general procedure I from diisopropylmalonate (1.90 mL, 10.0 mmol in DMF, 10 mL), allylbromide (0.87 mL, 10.0 mmol in DMF, 10 mL) and NaH (60% in mineral oil, 0.40 g, 10.0 mmol) in DMF (40 mL). Aqueous work-up afforded crude allylmalonate which was dissolved in CH$_2$Cl$_2$ (20 mL) and methyl vinyl ketone (2.43 mL, 30.0 mmol) and M2 (190 mg, 0.2 mmol) added. The residue was purified by silica chromatography (10→20% EtOAc/hexane) to afford 389 as a pale yellow oil (526 mg, 19%); $\nu_{\text{max}}$ (film)/cm$^{-1}$ 2982 (C-H), 2938 (C-H), 1724 (C=O), 1676 (C=O), 1632 (C=C); $\delta$H (300 MHz, CDCl$_3$) 1.24 (12H, dd, $J$ 6.2, 1.5, 2 × CH(CH$_3$)$_2$), 2.23
(3H, s, COCH₂), 2.78 (2H, td, J 7.2, 1.6, CH₂), 3.43 (1H, t, J 7.3, CHCO₂Pr), 5.06 (2H, hept, J 6.3, CH(CH₃)₃), 6.12 (1H, dt, J 16.0, 1.5, CH=CHCOCH₃), 6.75 (1H, dt, J 16.0, 7.0 CH=CHCOCH₃); δC (75 MHz, CDCl₃) 21.7 (2 × CH(CH₃)₃), 27.1 (COCH₃), 31.3 (CH₂), 51.1 (CHCO₂Pr), 69.5 (2 × CH(CH₃)₃), 133.2 (CH=CHCOCH₃), 143.2 (CH=CHCOCH₃), 168.0 (2 × CO₂Pr), 198.2 (COCH₃); m/z (NSI⁺) 288 ([M+NH₄]⁺, 100%), 271 ([M+H]⁺, 55%); HRMS (NSI⁺) C₁₄H₂₃O₅ ([M+H]⁺) requires 271.1540, found 271.1543 (+1.1 ppm).

Dibenzyl (E)-2-(4-oxopent-2-en-1-yl)malonate (390)

The title compound was prepared according to general procedure I from dibenzylmalonate (2.50 mL, 10.0 mmol in DMF, 10 mL), allylbromide (0.87 mL, 10.0 mmol in DMF, 10 mL) and NaH (60% in mineral oil, 0.40 g, 10.0 mmol) in DMF (40 mL). Aqueous work-up afforded crude allylmalonate which was dissolved in CH₂Cl₂ (20 mL) and methyl vinyl ketone (2.43 mL, 30.0 mmol) and M2 (190 mg, 0.2 mmol) added. The residue was purified by silica chromatography (10→20% EtOAc/hexane) to afford 390 as a pale orange oil (683 mg, 19%); νmax (film)/cm⁻¹: 2982 (C-H), 2938 (C-H), 1724 (C=O), 1676 (C=O), 1632 (C=C); δH (300 MHz, CDCl₃): 2.07 (3H, s, COC₃H₃), 2.77 (2H, td, J 7.2, 1.5, CH₂), 3.55 (1H, t, J 7.3, CHCO₂Bn), 5.09 (4H, s, 2 × CO₂CH₂Ph), 5.99 (1H, dt, J 16.0, 1.5, CH=CHCOCH₃), 6.60 (1H, dt, J 16.0, 7.0, CH=CHCOCH₃), 7.14 – 7.35 (10H, m, ArH); δC (75 MHz, CDCl₃) 27.1 (COCH₃), 31.4 (CH₂), 50.7 (CHCO₂Bn), 67.6 (CH₂Ph), 128.4 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 133.4 (CH=CHCOCH₃), 135.1 (PhC(1)), 142.4 (CH=CHCOCH₃), 168.1 (2 × CO₂Bn), 198.1 (COCH₃); m/z (NSI⁺) 384 ([M+ NH₄]⁺, 100%), 367 ([M+H]⁺, 10%); HRMS (NSI⁺) C₂₂H₂₃O₅ ([M+H]⁺) requires 367.1540, found 367.1542 (+0.5 ppm).
6.7 Cascade Products

*General Procedure J: Michael-Michael-Lactonisation*

LiHMDS (1 M in THF, 1.1 equiv) was added to a solution of enonemalonate (1 equiv) in dry THF (0.05 M) at 0 °C. After 5 minutes NEt(iPr)₂ (1.4 equiv) and HBTM 2.1 (20 mol%) were added then a reflux condenser added to the setup and the flask warmed to 70 °C. A solution of acid chloride (1.4 equiv) in THF (1 M) was added and the flask heated at 70 °C for 2 h. The solution was cooled to room temperature, diluted with EtOAc and washed sequentially with 0.1 M HCl and saturated NaHCO₃ solution, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel to afford the product(s).

**Diethyl (4aS,7R,7aR)-3-methyl-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[c]pyran-6,6(1H)-dicarboxylate (371a) and diethyl 2-cinnamoyl-2-((E)-4-oxopent-2-en-1-yl)malonate (371b)**

The title compounds were prepared according to *General Procedure J* from diethyl (E)-2-(4-oxopent-2-en-1-yl)malonate (121 mg, 0.5 mmol), LiHMDS (1 M in THF, 0.55 mL, 0.55 mmol), HBTM 2.1 (30.8 mg, 0.10 mmol), EtN(iPr)₂ (0.12 mL, 0.7 mmol) in THF (9.4 mL) and cinnamoyl chloride (117 mg, 0.7 mmol) added as a solution in THF (0.6 mL) to give 371a/371b in 68:32 crude rr The mixture was purified by chromatography on silica gel (20% EtOAc/hexane) to afford 371a as a pale yellow oil (76 mg, 41%) and 371b as a pale yellow oil (40 mg, 22%).

**371a (1,4-addition):** [α]$_D^{20}$ +51.9 (c 1.07 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), $t_R$ major: 14.8 min, $t_R$ minor: 16.5 min, 82% ee; $v_{max}$ (film)/cm⁻¹ 3032 (C-H), 2982 (C-H), 1717 (C=O); $δ_{SI}$ (500 MHz,
CDCl) 0.75 (3H, t, J 7.1, CO₂CH₂CH₃), 1.25 (3H, t, J 7.0, CO₂CH₂CH₃), 1.88 (3H, dd, J 2.2, 1.1, C(3)CH₃), 2.16 (1H, dd, J 13.9, 4.0, C(5)HH), 3.03 (1H, dd, J 13.9, 7.3, C(5)HH), 3.29 – 3.46 (3H, m, CO₂CHFCH₃s, C(4a)H, C(7a)H), 3.73 (1H, dq, J 10.7, 7.1, CO₂CHHCH₃), 4.15 – 4.29 (2H, m, CO₂CH₂CH₃), 4.63 (1H, d, J 9.4, C(7)H), 4.77 (1H, dt, J 3.1, 1.2, C(4)H), 7.20 – 7.25 (1H, m, PhC(4)H), 7.25 – 7.30 (2H, m, 2 × PhC(3)H), 7.31 – 7.36 (2H, m, 2 × PhC(2)H); δc (126 MHz, CDCl) 13.4 (CO₂CH₂CH₃), 14.1 (CO₂CH₂CH₃), 18.9 (C(3)CH₃), 36.3 (C(4a)H), 41.3 (C(5)CH₃), 47.7 (C(7a)H), 53.4 (C(7)H), 61.6 (CO₂CH₂CH₃), 61.9 (CO₂CH₂CH₃), 65.0 (C(6)), 102.4 (C(4)H), 127.7 (PhC(4)H), 128.2 (2 × ArCH), 129.0 (2 × ArCH), 137.6 (PhC(1)), 148.5 (C(3)CH₃), 169.1 (C(1)O), 170.0 (CO₂Et), 171.4 (CO₂Et); m/z (NSI⁺) 390 ([M+NH₄]⁺, 100%), 373 ([M+H]⁺, 50%); HRMS (NSI⁺) C24H23O6 ([M+H]⁺) requires 373.1646, found 373.1650 (+1.2 ppm).

371b (1,2-addition): νmax (film)/cm⁻¹ 2982 (C-H), 2934 (C-H), 1728 (C=O), 1676 (C=O), 1609 (C=C); δH (400 MHz, CDCl) 1.27 (6H, t, J 7.1, 2 × CO₂CH₂CH₃), 2.22 (3H, s, COCH₃), 3.08 (2H, dd, J 7.3, 1.4, CH₂CH=CH=CH), 4.27 (4H, q, J 7.1, 2 × CO₂CH₂CH₃), 6.09 (1H, dt, J 15.9, 1.4, CH₂CH=CH=CH), 6.83 (1H, dt, J 16.0, 7.3, CH₂CH=CH=CH), 7.05 (1H, d, J 15.6, CH=CHPh), 7.33 – 7.45 (3H, m, ArH), 7.51 – 7.59 (2H, m, ArH), 7.72 (1H, d, J 15.6, CH=CHPh); δc (101 MHz, CDCl) 14.2 (2 × CO₂CH₂CH₃), 26.7 (COCH₃), 35.2 (CH₂CH=CH), 62.7 (2 × CO₂CH₂CH₃), 70.0 (C(O)CO₂Et), 122.5 (CH=CHPh), 128.8 (2 × CArH), 129.1 (2 × CArH), 131.1 (CArH), 134.3 (PhC(1)), 134.7 (CH₂CH=CH), 142.5 (CH₂CH=CH), 144.5 (CH=CHPh), 167.1 (2 × CO₂Et), 189.3 (COCH=CHPh), 198.5 (COMe); m/z (NSI⁺) 390 ([M+NH₄]⁺, 40%), 373 ([M+H]⁺, 100%); HRMS (NSI⁺) C26H23O6 ([M+H]⁺) requires 373.1646, found 373.1652 (+1.7 ppm).

Dimethyl (4aS,7R,7aR)-3-methyl-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[c]pyran-6,6(1H)-dicarboxylate (394a) and dimethyl 2-cinnamoyl-2-((E)-4-oxopent-2-en-1-yl)malonate (394b)

![Chemical Structure](image)

The title compounds were prepared according to General Procedure J from dimethyl (E)-2-(4-oxopent-2-en-1-yl)malonate (107 mg, 0.5 mmol), LiHMDS (1 m in THF, 0.55 mL, 0.55 mmol), HBTM 2.1 (30.8 mg, 0.10 mmol), EtN(Pr)₂ (0.12 mL, 0.7 mmol) in THF (9.4 mL)
and cinnamoyl chloride (117 mg, 0.7 mmol) added as a solution in THF (0.6 mL) to give 394a/394b in 75:25 crude rr The mixture was purified by chromatography on silica gel (20%→30% EtOAc/hexane) to afford 394a as a pale yellow oil (108 mg, 63%) and 394b as a pale yellow oil (40 mg, 23%).

394a (1,4-addition): [α]_D^{20} +38.0 (c 1.50 in CHCl₃); chiral HPLC analysis, ChiralPak AS-H (5% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tₘₐₗₐₜ: 13.2 min, tₘᵢₐₜ minor: 13.2 min, tᵣₑₘₐₜ: 23.6 min, 71% ee; δH (300 MHz, CDCl₃) 1.89 (3H, dd, J 2.0, 1.1, C(3)CH₃), 2.14 (1H, dd, J 13.9, 4.0 C(5)H), 3.02 (2H, m, C(4a)H, C(7a)H), 3.12 (3H, s, CO₂C₆H₃), 3.29 – 3.50 (2H, m, C(4a)H, C(7a)H), 3.75 (3H, s, CO₂C₆H₃), 4.63 (1H, d, J 9.0, C(7)H), 4.75 – 4.80 (1H, m, C(4)H), 7.00 – 7.48 (5H, m, ArH); δ C (75 MHz, CDCl₃) 18.8 (C(3)C₆H₃), 36.2 (C(4a)H), 41.2 (C(5)H), 47.4 (C(7a)H), 52.3 (CO₂C₆H₃), 53.0 (CO₂C₆H₃), 53.6 (C(7)H), 65.1 (C(6)), 102.3 (C(4)H), 127.7 (PhC(4)H), 128.2 (2 × ArCH), 128.8 (2 × ArCH), 137.4 (PhC(1)), 148.5 (C(3)), 168.9 (C(1)O), 170.3 (CO₂C₆H₃), 171.8 (CO₂C₆H₃); m/z (NSI⁺) 367 ([M+Na]⁺, 100%), 345 ([M+H]⁺, 65%); HRMS (NSI⁺) C₁₉H₂₁O₆ ([M+H]⁺) requires 345.1333, found 345.1329 (–1.1 ppm).

394b (1,2-addition): δH (300 MHz, CDCl₃) 2.22 (3H, s, COCH₃), 3.08 (2H, dd, J 7.3, 1.4, CH₂), 3.80 (6H, s, 2 × CO₂CH₃), 6.09 (1H, dt, J 16.0, 1.4, CH=CHCOCH₃), 6.81 (1H, dt, J 16.0, 7.3, CH=CHCOCH₃), 7.00 (1H, d, J 15.6, CH=CHPh), 7.41 (3H, qd, J 2.9, 1.1, ArH), 7.50 – 7.61 (2H, m, ArH), 7.73 (1H, d, J 15.6, CH=CHPh); δ C (75 MHz, CDCl₃) 26.8 (COCH₃), 35.3 (CH₂), 53.5 (2 × CO₂CH₃), 70.1 (C(CO₂CH₃), 122.1 (CH=CHPh), 128.9 (2 × ArCH), 129.1 (2 × ArCH), 131.2 (PhC(4)H), 134.2 (PhC(1)), 134.7 (CH=CHCOCH₃), 142.1 (CH=CHCOCH₃), 145.0 (CH=CHPh), 167.5 (2 × CO₂CH₃), 189.0 (COCH=CHPh), 198.4 (COCH₃); m/z (NSI⁺) 367 ([M+Na]⁺, 100%), 345 ([M+H]⁺, 20%); HRMS (NSI⁺) C₁₉H₂₁O₆ ([M+H]⁺) requires 345.1333, found 345.1330 (–0.8 ppm).
Dibenzyl (4aS,7R,7aR)-3-methyl-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[c]pyran-6,6(1H)-dicarboxylate (395a) and dibenzyl 2-cinnamoyl-2-((E)-4-oxopent-2-en-1-yl)malonate (395b)

The title compounds were prepared according to General Procedure J from dibenzyl (E)-2-(4-oxopent-2-en-1-yl)malonate (183 mg, 0.5 mmol), LiHMDS (1 M in THF, 0.55 mL, 0.55 mmol), HBTM 2.1 (30.8 mg, 0.10 mmol), EtN(iPr)2 (0.12 mL, 0.7 mmol) in THF (9.4 mL) and cinnamoyl chloride (117 mg, 0.7 mmol) added as a solution in THF (0.6 mL) to give 395a/395b in 77:23 crude r.r. The mixture was purified by chromatography on silica gel (20% EtOAc/hexane) to afford 395a as a pale yellow oil (135 mg, 54%) and 395b as a pale yellow oil (41 mg, 16%).

395a (1,4-addition): $[\alpha]_{D}^{20} +24.6$ (c 3.42 in CH$_2$Cl$_2$); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1 mL min$^{-1}$, 211 nm, 30 °C), $t_{R}$ major: 35.6 min, $t_{R}$ minor: 38.4 min, 72% ee; $v_{\text{max}}$ (film)/cm$^{-1}$ 3034 (C-H), 1749 (C=O), 1724 (C=O); $\delta$H (300 MHz, CDCl$_3$) 1.84 (3H, dd, $J_{2.1, 1.1}$, C$_3$H$_3$), 2.21 (1H, dd, $J_{13.9, 3.9}$, C(5)H)$_2$, 4.20 (1H, d, $J_{12.3}$, CO$_2$CHH), 4.64 – 4.71 (2H, m, C(4)H, C(7)H), 4.75 (1H, d, $J_{12.3}$, CO$_2$CHH), 5.06 (1H, d, $J_{12.1}$, CO$_2$CHH), 5.17 (1H, d, 2× CO$_2$CHH), 6.85 – 6.91 (2H, m), 7.16 – 7.39 (13H, m, ArH); $\delta$C (75 MHz, CDCl$_3$) 18.8 (C$_3$C$_3$H$_3$), 36.3 (C(4a)H), 41.3 (C(5)H)$_2$, 47.7 (C(7a)H), 53.7 (C(7)H), 65.2 (C(6)), 67.4 (CO$_2$CH$_2$), 67.8 (CO$_2$CH$_2$), 102.3 (C(4)H), 127.8 (ArCH), 128.0 (2× ArCH), 128.2 (ArCH), 128.4 (2× ArCH), 128.4 (2× ArCH), 128.5 (ArCH), 128.6 (2× ArCH), 129.0 (2× ArCH), 134.7 (ArC), 135.2 (ArC), 137.3 (ArC), 148.6 (C(3)), 168.9 (C(1)O), 169.7 (CO$_2$Bn), 171.0 (CO$_2$Bn); m/z (NSI$^+$) 497 ([M+H]$^+$, 100%); HRMS (NSI$^+$) C$_{31}$H$_{29}$O$_6$ ([M+H]$^+$) requires 497.1959, found 497.1944 (−2.9 ppm).

395b (1,2-addition): $v_{\text{max}}$ (film)/cm$^{-1}$ 3032 (C-H), 1730 (C=O), 1676 (C=O), 1608 (C=O); $\delta$H (300 MHz, CDCl$_3$) 2.11 (3H, s, CH$_3$), 3.12 (2H, dd, $J_{7.4, 1.3}$, CH$_2$), 5.23 (4H, d, $J_{2.0, 2}$ CO$_2$CH$_2$), 6.02 (1H, dt, $J_{16.0, 1.3}$, CH=CHCOCH$_3$), 6.76 (1H, dt, $J_{15.9, 7.3}$ CH=CHCOCH$_3$), 6.90 (1H, d, $J_{15.6}$, CH=CHPh), 7.23 – 7.33 (10H, m, ArH), 7.33 – 7.40
(5H, m, ArH), 7.69 (1H, d, J 15.6, CH=CHPh); δC (75 MHz, CDCl₃) 26.6 (CH₂), 35.2 (CH₂), 68.3 (4 × CO₂CH₃), 122.6 (CH=CHPh), 128.5 (ArCH), 128.7 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 128.9 (ArCH), 129.0 (ArCH), 131.1 (ArCH), 134.1 (ArC), 134.6 (2 × ArC), 134.8 (CH=CHCOCH₃), 142.1 (CH=CHCOCH₃), 144.8 ([CH=CHPh], 166.8 (2 × CO₂Bn), 188.7 (COCH=CHPh), 198.4 (COCH₃); m/z (NSI⁺) 497 ([M+H]⁺, 100%); HRMS (NSI⁺) C₃₁H₃₀O₆ ([M+H]⁺) requires 497.1959, found 497.1946 (−2.5 ppm).

Diisopropyl (4aS,7R,7aR)-3-methyl-1-oxo-7-phenyl-4a,5,7,7a-tetrahydrocyclopenta[c]pyran-6,6(1H)-dicarboxylate (396a) and diisopropyl 2-cinnamoyl-2-((E)-4-oxopent-2-en-1-yl)malonate (396b)

The title compounds were prepared according to General Procedure J from diisopropyl (E)-2-(4-oxopent-2-en-1-yl)malonate (135 mg, 0.5 mmol), LiHMDS (1 M in THF, 0.55 mL, 0.55 mmol), HBTM 2.1 (30.8 mg, 0.10 mmol), EtN(Pr)₂ (0.12 mL, 0.7 mmol) in THF (9.4 mL) and cinnamoyl chloride (117 mg, 0.7 mmol) added as a solution in THF (0.6 mL) to give 396a/396b in 61:39 crude ratio. The mixture was purified by chromatography on silica gel (10%→20% EtOAc/hexane) to afford 396a as a pale yellow oil (87 mg, 44%) and 396b as a pale yellow oil (isolated as a 7:3 mixture of 396b to enone-malonate 389, 71 mg, 36%).

396a (1,4-addition): [α]D²⁰ +51.0 (c 0.58 in CH₂Cl₂); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tₘₙ major: 10.2 min, tₘₙ minor: 12.0 min, 70% ee; νmax (film)/cm⁻¹ 2980 (C-H), 2924 (C-H), 1763 (C=O), 1719 (C=O); δH (300 MHz, CDCl₃) 0.48 (3H, d, J 6.3, CH(CH₃)(CH₃), 1.01 (3H, d, J 6.2, CH(CH₃)(CH₃)), 1.24 (3H, d, J 6.3, CH(CH₃)(CH₃), 1.28 (3H, d, J 6.2, CH(CH₃)(CH₃), 1.89 (3H, dd, J 2.1, 1.1 C(3)CH₃)), 2.19 (1H, dd, J 13.9, 3.5, C(5)HH), 3.03 (1H, dd, J 13.9, 7.1, C(5)HH), 3.26 – 3.48 (2H, m, C(4a)H, C(7a)H), 4.46 (1H, p, J 6.3, CH(CH₃)₂), 4.62 (1H, d, J 9.0, C(4)H), 4.75 (1H, dq, J 2.9, 1.1, C(7)H), 5.09 (1H, p, J 6.2, CH(CH₃)₂), 7.19 – 7.38 (5H, m, ArH); δC (75 MHz, CDCl₃) 18.9 (C(3)CH₃), 20.7 (CH(CH₃)(CH₃)), 21.4, (CH(CH₃)(CH₃)), 21.6 (CH(CH₃)(CH₃)), 21.8 (CH(CH₃)(CH₃)), 36.3 (C(4a)H), 41.6 (C(5)H), 48.4 (C(7a)H), 53.4 (C(7)H), 65.0 (C(6)), 69.4 (CH(CH₃)₂), 69.5 (CH(CH₃)₂), 102.4 (C(4)H), 127.7 (PhC(4)H), 128.3 (2 × ArCH), 129.2 (2 × ArCH), 137.9 (PhC(1)), 148.6 (C(3)), 169.1 (C(1)O), 169.5
(CO$_2$Pr), 171.0 (CO$_2$Pr); $m/z$ (NSI$^+$) 401 ([M+H]$^+$, 100%), 423 ([M+Na]$^+$, 65%); HRMS (NSI$^+$) C$_{35}$H$_{50}$O$_6$ ([M+H]$^+$) requires 401.1959, found 401.1949 (−2.4 ppm).

**396b (1,2-addition):** $\nu_{\max}$ (film)/cm$^{-1}$ 2982 (C-H), 1724 (C=O), 1676 (C=O), 1609 (C=O); $\delta_{\text{H}}$ (300 MHz, CDCl$_3$) 1.25 (12H, d, $J$ 6.3, 2 × CH(CH$_3$)$_2$), 2.21 (3H, s, COCH$_3$), 3.05 (2H, dd, $J$ 7.3, 1.4, CH$_2$), 5.12 (2H, p, $J$ 6.3, 2 × CHCH$_3$)$_2$, 6.09 (1H, dt, $J$ 16.1, 1.4, CH=CHCOCH$_3$), 6.83 (1H, dt, $J$ 16.0, 7.3, CH=CHCOCH$_3$), 7.06 (1H, d, $J$ 15.7, CH=CHPh), 7.39 (3H, dd, $J$ 5.1, 1.9, ArH), 7.48 – 7.59 (2H, m, ArH), 7.70 (1H, d, $J$ 15.7, CH=CHPh); $\delta_{\text{C}}$ (75 MHz, CDCl$_3$) 21.7 (CH$_3$), 70.6 (2 × CH(CH$_3$)$_2$), 122.8 (CH=CHPh), 128.7 (2 × ArCH), 129.1 (2 × ArCH), 131.0 (PhC(4)H), 134.4 (PhC(1)H), 134.7 (CH=CHCOCH$_3$), 142.7 (CH=CHCOCH$_3$), 144.0 (CH=CHPh), 166.6 (2 × CO$_2$Pr), 189.6 (COCH=CHPh), 198.5 (COCH$_3$); $m/z$ (NSI$^+$) 401 ([M+H]$^+$, 30%), 423 ([M+Na]$^+$, 100%); HRMS (NSI$^+$) C$_{35}$H$_{50}$O$_6$ ([M+H]$^+$) requires 401.1959, found 401.1949 (−2.4 ppm).

Dimethyl (4aS,7S,7aR)-3,7-dimethyl-1-oxo-4a,5,7,7a-tetrahydrocyclopenta[c]pyran-6,6(1H)-dicarboxylate (397a) and dimethyl 2-((E)-but-2-enoyl)-2-((E)-4-oxopent-2-en-1-yl)malonate (397b)

The title compounds were prepared according to General Procedure J from dimethyl (E)-2-(4-oxopent-2-en-1-yl)malonate (107 mg, 0.5 mmol), LiHMDS (1 m in THF, 0.55 mL, 0.55 mmol), HBTM 2.1 (30.8 mg, 0.10 mmol), EtN(iPr)$_2$ (0.12 mL, 0.7 mmol) in THF (9.4 mL) and crotonoyl chloride (67 μL, 0.7 mmol) added as a solution in THF (0.6 mL) to give 397a/397b in 73:27 crude rr The mixture was purified by chromatography on silica gel (20%→30% EtOAc/hexane) to afford 397a as a pale yellow oil (79 mg, 56%) and 397b as a pale yellow oil (28 mg, 20%).

**397a (1,4-addition):** $[\alpha]_{D}^{20}$ +117.4 (c 0.98 in CH$_2$Cl$_2$); chiral HPLC analysis, ChiralPak AS-H (2.5% i-PrOH:hexane, flow rate 1 mL min$^{-1}$, 211 nm, 30 °C), $t$$_r$ major: 11.9 min, $t$$_r$ minor: 27.3 min, 90% ee; $\nu_{\max}$ (film)/cm$^{-1}$ 2955 (C-H), 1726 (C=O); $\delta_{\text{H}}$ (300 MHz, CDCl$_3$) 1.14 (3H, d, $J$ 6.9, C(7)CH$_3$), 1.81 (3H, dd, $J$ 2.3, 1.1, C(3)CH$_3$), 2.00 (1H, dd, $J$ 14.0, 4.3, C(5)CHH), 2.71 (1H, ddd, $J$ 11.2, 8.7, 0.8, C(7)H), 2.77 (1H, dd, $J$ 14.0, 8.2, C(5)HH), 2.90
6. Experimental

Dibenzyl (4aS,7S,7aR)-3,7-dimethyl-1-oxo-4a,5,7a-tetrahydrocyclopenta[c]pyran-6,6(1H)-dicarboxylate (398a) and dibenzyl 2-((E)-but-2-enoyl)-2-((E)-4-oxopent-2-en-1-yl)malonate (398b)

The title compounds were prepared according to General Procedure J from dibenzyl (E)-2-(4-oxopent-2-en-1-yl)malonate (183 mg, 0.5 mmol), LiHMDS (1 mL in THF, 0.55 mL, 0.55 mmol), HBTM 2.1 (30.8 mg, 0.10 mmol), EtN(Pr)2 (0.12 mL, 0.7 mmol) in THF (9.4 mL) and crotonoyl chloride (67 μL, 0.7 mmol) added as a solution in THF (0.6 mL) to give 398a/398b in 77:23 crude rr The mixture was purified by chromatography on silica gel (20% EtOAc/hexane) to afford 398a as a pale yellow oil (118 mg, 54%) and 398b as a pale yellow oil (30 mg, 14%).

398a (1,4-addition): [α]D20 +84.2 (c 1.55 in CH2Cl2); chiral HPLC analysis, ChiralPak AD-H (5% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR major: 21.4 min, tR minor: 23.2 min, 90% ee; νmax (film)/cm⁻¹ 2955 (C-H), 1748 (C=O), 1722 (C=O); δH (400 MHz, CDCl3) 1.15 (3H, d, J 6.9, C(7)CH3), 1.79 (3H, dd, J 2.3, 1.1, C(3)CH3), 2.06 (1H, dd, J 14.0, 4.3, C(5)HH), 2.73 (1H, ddd, J 11.1, 8.8, 0.9, C(7)H), 2.81 (1H, dd, J 13.9, 8.2, C(5)HH),

398b (1,2-addition): νmax (film)/cm⁻¹ 2957 (C-H), 1732 (C=O), 1676 (C=O); δH (300 MHz, CDCl3) 1.92 (3H, dd, J 7.0, 1.7, CH=CHCH3), 2.21 (3H, s, COCH3), 3.00 (2H, dd, J 7.4, 1.4, CH3), 3.78 (6H, s, 2 × CO2CH3), 6.05 (1H, dt, J 16.0, 1.4, CH=CHCOCH3), 6.39 (1H, dq, J 15.1, 1.6, CH=CHCH3), 6.77 (1H, dt, J 16.0, 7.3, CH=CHCOCH3), 7.05 (1H, dq, J 15.2, 7.0, CH=CHCH3); δC (75 MHz, CDCl3) 18.8 (CH=CH), 26.3 (CH2), 53.4 (2 × CO2CH3), 69.7 (C(CO2CH3)2), 127.4 (CH=CHCH3), 134.7 (CH=CHCOCH3), 142.2 (CH=CHCOCH3), 145.9 (CH=CHCH3), 167.5 (2 × CO2CH3), 188.7 (COCH=CH), 198.5 (COCH3); m/z submitted; HRMS submitted.
6. Experimental

2.99 – 3.08 (1H, m, C(7a)H), 3.08 – 3.16 (1H, m, C(4a)H), 4.59 (1H, dp, J 2.1, 1.1, C(4)H), 4.98 – 5.19 (4H, m, 2 × CO₂CH₂Ph), 7.19 – 7.27 (4H, m, ArCH), 7.29 – 7.37 (6H, m, ArCH); δc (101 MHz, CDCl₃) 15.3 (C(7)C₃H₃), 18.8 (C(3)CH₂), 34.9 (C(4a)H), 41.2 (C(5)H₂), 44.2 (C(7)H), 48.4 (C(7a)H), 62.4 (C(6)), 67.5 (CO₂CH₂Ph), 67.5 (CO₂CH₂Ph), 103.1 (C(4)H), 128.3 (2 × ArCH), 128.4 (2 × ArCH), 128.5 (ArCH), 128.6 (ArCH), 128.7 (2 × ArCH), 135.0 (PhC(1)), 135.4 (PhC(1)), 147.1 (C(3)), 169.6 (C(1)O), 170.5 (CO₂Bn), 170.9 (CO₂Bn); m/z submitted; HRMS submitted.

398b (1,2-addition): νₘₐₓ (film)/cm⁻¹ 2967 (C-H), 1728 (C=O), 1694 (C=O), 1676 (C=O);
δH (400 MHz, CDCl₃) 1.79 (3H, dd, J 7.0, 1.7, CH=CHCH₃), 2.06 (3H, s, COCH₃), 3.01 (2H, dd, J 7.3, 1.4, CH₂), 5.18 (4H, d, J 1.4, 2 × CO₂CH₂Ph), 5.95 (1H, dt, J 16.0, 1.4, CH=CHCOCH₃), 6.29 (1H, dq, J 15.2, 1.7, CH=CHCH₃), 6.67 (1H, dt, J 16.0, 7.3, CH=CHCOCH₃), 6.98 (1H, dq, J 15.2, 7.0, CH=CHCH₂), 7.19 – 7.30 (4H, m, ArH), 7.30 – 7.35 (6H, m, ArH); δc (101 MHz, CDCl₃) 18.4 (CH=CHCH₃), 26.5 (CICH₂), 35.1 (CH₂), 68.2 (2 × CO₂CH₂Ph), 69.6 (C(CO₂Bn)₂), 127.7 (CH=CHCH₃), 128.6 (4 × ArCH), 128.8 (4 × ArCH), 134.7 (2 × PhC(1)), 134.8 (CH=CHCOCH₃), 142.1 (CH=CHCOCH₃), 145.6 (CH=CHCH₃), 166.8 (2 × CO₂Bn), 188.5 (COCH=CH), 198.4 (COCH₃); m/z submitted; HRMS submitted.

6.8 Misc

Methyl (3S)-4-(1,3-benzothiazol-2-yl)-5-(4-nitrophenyl)-5-oxo-3-phenylpentanoate (293)

To a solution of (E)-cinnamic anhydride (556 mg, 2.0 mmol) in THF (4 ml), was added 2-(1,3-benzothiazol-2-yl)-1-(4-nitrophenyl)ethanone (417 mg, 1.4 mmol), HBTM 2.1 (22 mg, 0.07 mmol) and NEt₂(Pr)₂ (260 µL, 1.5 mmol) at 0 °C. The reaction mixture was stirred and gradually warmed to room temperature over 18 h. DMAP (171 mg, 1.4 mmol) and MeOH (4 ml) were then added and the flask stirred at room temperature for 24 h. The solution was diluted with EtOAc and washed sequentially with 0.1 M HCl and saturated NaHCO₃.
solution, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by chromatography on silica gel (10:2 DCM/hexane → 5% EtOAc/DCM) followed by trituration with Et₂O to remove a bright yellow contaminant gave 293 as a pale yellow solid (580 mg, 90%, 5:1 dr); mp 109-112 ºC; [α]D²⁰ +7.8 (c 0.5 in CHCl₃); vmax (film) /cm⁻¹ 3028 (C-H), 2951 (C-H), 1724 (C=O, ester), 1695 (C=O, ketone), 1522 (NO₂; m/ z (NSI⁺) 461 ([M+H]+, 100%), 483 ([M+Na]⁺, 55%), 943 ([2M+Na]⁺, 30%); HRMS (NSI⁺) C₂₅H₂₁N₃O₅S ([M+H]+) requires 461.1166, found 461.1166 (+0.1 ppm).

Major diastereomer: chiral HPLC analysis; Chiralcel IB (8% i-PrOH:hexane, flow rate 1.5 mL min⁻¹, 254 nm, 30 ºC) tᵣ major: 10.5 min, tᵣ minor: 11.5 min, 66% ee; δH (400 MHz, CDCl₃) 2.82 – 2.98 (2H, m, 2 × C(2)HH), 3.55 (3H, s, CO₂CH₃), 4.29 (1H, ddt, J 8.9, 6.3, 4.4, C(3)H), 5.87 (1H, d, J 9.9, C(4)H), 7.03 – 7.24 (5H, m, C(3)Ph-ArH), 7.29 (1H, ddd, J 8.2, 7.3, 1.2, benzothiazoleC(6)H), 7.37 (1H, ddd, J 8.3, 7.2, 1.3, benzothiazoleC(5)H), 7.72 (1H, ddd, J 8.0, 1.3, 0.6, benzothiazoleC(7)H), 7.85 – 7.91 (1H, m, benzothiazoleC(4)H), 8.26 – 8.31 (2H, m, 2 × C(5)PhNO₂-C(2)H), 8.31 – 8.36 (2H, m, 2 × C(5)PhNO₂-C(3)H); δC (101 MHz, CDCl₃) 38.8 (C(2)H₂), 45.0 (C(3)H), 51.9 (CO₂CH₃), 57.1 (C(3)H), 121.7 (benzothiazoleC(7)H), 123.3 (benzothiazoleC(4)H), 124.1 (2 × C(5)ArC(3)H), 125.5 (benzothiazoleC(6)H), 126.2 (benzothiazoleC(5)H), 127.6 (C(3)PhC(4)H), 128.4 (2 × C(3)PhC(2)H), 128.7 (2 × C(3)PhC(3)H), 130.3 (2 × C(5)ArC(2)H), 135.6 (benzothiazoleC(7a)), 139.2 (C(3)PhC(1)), 140.8 (C(5)ArC(1)), 150.7 (C(5)ArC(4)), 152.4 (benzothiazoleC(4a)), 165.67 (benzothiazoleC(2)), 172.0 (CO₂CH₃), 195.3 (C(5)O).

Minor diastereomer: chiral HPLC analysis; Chiralcel IB (8% i-PrOH:hexane, flow rate 1.5 mL min⁻¹, 254 nm, 30 ºC) tᵣ major: 16.1 min, tᵣ minor: 12.4 min, 68% ee; δH (400 MHz, CDCl₃, characteristic peaks) 2.64 (1H, dd, J 15.9, 4.2, C(2)HH), 2.78 (1H, dd, J 15.9, 10.4, C(2)HH), 3.41 (3H, s, CO₂CH₃), 5.71 (1H, d, J 11.2, C(4)H), 7.51 (1H, ddd, J 8.3, 7.2, 1.3, benzothiazoleC(6)H), 7.93 – 7.98 2H, m, 2 × C(5)PhNO₂-C(2)H), 8.05 (1H, dt, J 8.3, 0.8, benzothiazoleC(4)H), 8.11 – 8.17 (2H, m, 2 × C(5)PhNO₂-C(3)H); δC (101 MHz, CDCl₃, characteristic peaks) 38.6 (C(2)H₂), 51.7 (CO₂CH₃), 58.7 (C(4)H), 122.0 (benzothiazoleC(7)H), 123.4 (benzothiazoleC(4)H), 123.9 (2 × C(5)ArC(3)H), 125.9 (benzothiazoleC(6)H), 126.6 (benzothiazoleC(5)H), 129.6 (2 × C(5)ArC(2)H), 166.1 (benzothiazoleC(2)), 171.5 (CO₂CH₃), 196.0 (C(5)O).

The corresponding racemic reaction was carried out on a gram scale from (E)-cinnamic anhydride (1.39 g, 5.0 mmol) and 2-(1,3-benzothiazol-2-yl)-1-(4-nitrophenyl)ethanone (1.07
g, 3.6 mmol), NEt(Pr){sub}_2 (700 μL, 4.0 mmol) and racemic HBTM 2.1 (55mg, 0.18 mmol) in THF (10 mL) followed by addition of DMAP (0.44 g, 3.6 mmol) and MeOH (10 mL). Purification by chromatography on silica gel (10:2 DCM/hexane → 5% EtOAc/DCM) to give 293 as a yellow solid (1.57 g, 95%, 3:1 dr); mp 148-150 °C.

Methyl (3S)-4-(1,3-benzothiazol-2-yl)-5-(4-nitrophenyl)-5-oxo-3-phenylpentanoic acid (292)

Methyl (3S)-4-(1,3-benzothiazol-2-yl)-5-(4-nitrophenyl)-5-oxo-3-phenylpentanoate (575 mg, 1.25 mmol) was added to concentrated HCl (20 ml) and heated at 60 °C for 72h. After cooling to room temperature the solution was washed with DCM × 4. The combined organic layers were dried over anhydrous MgSO_{4}, filtered and concentrated in vacuo. Purification by chromatography on silica gel (DCM → 10% MeOH/DCM) gave 292 as a yellow solid (516 mg, 92%); mp 204-207 °C; [α]_{D}^{22} +1.2 (c 0.5 in CH_{2}Cl_{2}); chiral HPLC analysis no separation conditions found therefore ee unknown; ν_{max} (film) /cm^{-1} 2906 (OH), 1709 (C=O, acid), 1689 (C=O, ketone), 1523 (NO_{2}); NMR analysis of major diasteromer A and minor B (configuration of the stereocentres unknown): δ_{H} (400 MHz, DMSO) 2.61 – 2.90 (4H, m, C(2)CH_{2}A+B), 4.04 – 4.19 (2H, m, C(3)H A+B), 6.10 (1H, d, J 10.5, C(4)H B), 6.24 (1H, d, J 10.7, C(4)H A), 6.98 – 7.40 (10H, m, ArH), 7.40 – 7.55 (4H, m, ArH), 7.78 – 7.84 (1H, m, benzothiazoleC(7)H B), 7.87 – 7.91 (1H, m, benzothiazoleC(7)H A), 8.07 – 8.13 (1H, m, benzothiazoleC(4)H A), 8.14 – 8.20 (2H, m, 2 × PhNO_{2}C(2) A), 8.21 – 8.27 (2H, m, 2 × PhNO_{2}C(3) A), 8.30 – 8.35 (2H, m, 2 × PhNO_{2}C(2) B), 8.35 – 8.42 (2H, m, 2 × PhNO_{2}C(3) B), 12.07 (2H, s, COOH A+B); δ_{C} (101 MHz, DMSO) 39.2 (C(2)H_{3}, A+B), 44.5 (C(3)H, B), 45.1 (C(3)H, A), 56.0 (C(4)H, A+B), 122.1 (ArCH), 122.4 (ArCH), 122.6 (ArCH), 122.9 (ArCH), 124.0 (4 × ArCH), 125.2 (ArCH), 125.6 (ArCH), 126.1 (ArCH), 126.5 (ArCH), 126.8 (ArCH), 126.9 (ArCH), 128.0 (2 × ArCH), 128.2 (2 × ArCH), 128.4 (2 × ArCH), 128.7 (2 × ArCH), 129.8 (2 × ArCH), 130.3 (2 × ArCH), 135.0 (C(3)PhC(1)), 135.1 (C(3)PhC(1)), 140.1 (benzothiazoleC(7a), A+B), 140.5 (PhNO_{2}C(1), A), 141.1 (PhNO_{2}C(1), B), 150.2 (PhNO_{2}C(4), A+B), 151.9 (benzothiazoleC(4a), B), 152.3
Experimental

(benzothiazoleC(4a), A), 166.1 (benzothiazoleC(2), B), 166.3 (benzothiazoleC(2), B), 172.1
(COOH, A), 172.3 (COOH, B), 195.2 (C(5)O, A+B); m/z (NSI) 445 ([M-H]−, 100%); HRMS (NSI) C_{24}H_{17}N_{2}O_{5}S ([M-H]−) requires 445.0864, found 445.0861 (-0.6 ppm).

The corresponding racemic reaction was carried out on a gram scale from Methyl (3S)-4-(1,3-benzothiazol-2-yl)-5-(4-nitrophenyl)-5-oxo-3-phenylpentanoic acid (1.57 g, 3.4 mmol) and concentrated HCl (50 ml). Purification by chromatography on silica gel (10:2 DCM/hexane → 5% EtOAc/DCM) to give 292 as a yellow solid (1.13 g, 74%); mp 200-202 °C.

Recyclisation experiments:

To a solution of methyl (3S)-4-(1,3-benzothiazol-2-yl)-5-(4-nitrophenyl)-5-oxo-3-phenylpentanoic acid (85 mg, 0.19 mmol) in THF (0.5 mL) was added NEt(Pr)_{2} (0.045 mL, 0.25 mmol) and pivaloyl chloride (0.03 mL, 0.23 mmol). After 30 minutes HBTM 2.1 (5.9 mg, 0.019 mmol) and NEt(Pr)_{2} (0.04 mL, 0.23 mmol) were added and the reaction stirred for 2 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with 0.1 M HCl, saturated aqueous NaHCO_{3} and brine, dried over MgSO_{4}, filtered and concentrated in vacuo. The regioisomeric ratio of 262a/262b was analysed by 1H NMR of the crude reaction mixture. Major N-cyclised regioisomer 262a was isolated on an analytical scale by silica chromatography (CH_{2}Cl_{2}) and analysed by chiral HPLC (ChiralPak AD-H (40% i-PrOH:hexane, flow rate 1 mL min^{-1}, 211 nm, 30 °C), t_{R} major: 31.8 min, t_{R} minor: 24.5 min), results as specified in the appropriate tables in Section 3.4.1.
Crossover experiment:

To a solution of methyl (3S)-4-(1,3-benzothiazol-2-yl)-5-(4-nitrophenyl)-5-oxo-3-phenylpentanoic acid (112 mg, 0.25 mmol) in THF (1 mL) was added NEt(Pr)2 (0.04 mL, 0.25 mmol) followed by pivaloyl chloride (0.04 mL, 0.30 mmol). After 30 minutes HBTM 2.1 (7.7 mh, 0.025 mmol) and 2-phenacylbenzothiazole (63 mg, 0.25 mmol) were added and the reaction stirred for 2 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with 0.1 M HCl, saturated aqueous NaHCO3 and brine, dried over MgSO4, filtered and concentrated in vacuo. The regioisomeric ratio analysed by 1H NMR of the crude reaction mixture (228a 11 : 228b 4 : 262a 100 : 262b 16). Major N-cyclised regioisomers were isolated on an analytical scale by silica chromatography (CH2Cl2) and analysed by chiral HPLC.

262a: Chiral HPLC analysis, ChiralPak AD-H (40% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR major: 31.8 min, tR minor: 24.5 min, 63:37 er.

228a: chiral HPLC analysis, ChiralPak AD-H (20% i-PrOH:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C), tR minor: 13.2 min, tR major: 22.5 min, 89:11 er.

(R)-3-(4'-methoxy-[1,1'-biphenyl]-3-yl)-N,N-dimethyl-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-α]pyridine-4-carboxamide (313)
6. Experimental

(R)-3-(3-Bromophenyl)-N,N-dimethyl-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-\(a\)]pyridine-4-carboxamide (128 mg, 0.30 mmol), 4-methoxyboronic acid (68 mg, 0.45 mmol), sodium carbonate (64 mg, 0.60 mmol), Pd(OAc)\(_2\) (3.4 mg, 0.015 mmol) and diphenylphosphinoferrocene (dppf, 16.6 mg, 0.03 mmol) were added to degassed dioxane/water (9:1, 3 mL) under N\(_2\) and heated in a sealed tube at 100 °C for 15 h. The reaction was then cooled to room temperature and flushed through a plug of silica with EtOAc, the collected solution was concentrated in vacuo and then purified by chromatography on silica gel (CH\(_2\)Cl\(_2\)→10% EtOAc/CH\(_2\)Cl\(_2\)) to give 313 as a pale yellow oil (103 mg, 70%); [\(\alpha\)]\(_D\)\(^{20}\); −78.7 (c 1.0, CH\(_2\)Cl\(_2\)); chiral HPLC analysis, ChiralPak AS-H (20% i-PrOH:hexane, flow rate 1 mL min\(^{-1}\), 220 nm, 30 °C), \(t_R\) major: 13.0 min, \(t_R\) minor: 26.8 min, >99% ee; \(\nu\) max (film)/cm\(^{-1}\): 2930 (C=O), 2836 (C-H), 1701 (C=O), 1580 (C=O), 1481 (C=C); \(\delta_{HI}\) (400 MHz, CDCl\(_3\)) 2.86 (6H, s, N(CH\(_3\))\(_2\)), 3.02 (1H, dd, J 16.2, 6.4, C(2)H\(_2\)), 3.20 (1H, dd, J 16.2, 7.1, C(2)H\(_2\)), 3.83 (3H, s, OCH\(_3\)), 4.26 (1H, at, J 6.7, C(3)H), 6.90 – 7.00 (2H, m, 2 × biphenylC(3")H), 7.12 – 7.36 (5H, m, ArH), 7.39 – 7.45 (2H, m, ArH), 7.45 – 7.50 (2H, m, 2 × biphenylC(2")H), 8.34 – 8.39 (1H, m, C(4")H); \(\delta_C\) (101 MHz, CDCl\(_3\)) 37.0 (2 × N(CH\(_3\))\(_2\)), 40.4 (C(3)H), 40.9 (C(4)H), 55.4 (OCH\(_3\)), 106.4 (C(4)), 114.3 (2 × biphenylC(3")H), 117.5 (C(4")H), 121.3 (C(7")H), 125.0 (ArCH), 125.3 (ArCH), 125.4 (ArCH), 125.9 (ArCH), 126.0 (C(7a"))), 126.3 (ArCH), 128.2 (2 × biphenylC(2")H), 129.5 (ArCH), 133.2 (biphenylC(1")H)), 137.2, (C(4a")), 141.4 (ArC), 141.6 (ArC), 142.3 (ArC), 159.4 (C(5)), 167.7 (C(1)O), 169.3 (CONMe\(_2\)); \(m/\zeta\) (NSI\(^{+}\)) 457 ([M+H\(^+\)], 100%), 479 ([M+Na\(^+\)], 55%), 495 ([M+K\(^+\)], 50%), 935 (2M+Na\(^+\), 55%), 951 (2M+K\(^+\), 50%); HRMS (NSI\(^{+}\)) \(C_{27}H_{23}O_4N_S ([M+H])^+\) requires 457.1580, found 457.1577 (−0.7 ppm).

Methyl (R,E)-3-(3-(4-(dimethylcarbamoyl)-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-\(a\)]pyridin-3-yl)phenyl)acrylate (316)
6. Experimental

216

triethylamine (52 μL, 0.38 mmol), Pd(OAc)$_2$ (3.4 mg, 0.015 mmol) and P(o-tolyl)$_3$ (9.1 mg, 0.03 mmol) were added to degassed DMF (2 mL) under N$_2$ and heated in a sealed tube at 125 °C for 15 h. The reaction was then cooled to room temperature and flushed through a plug of silica with EtOAc, the collected solution was concentrated in vacuo and redissolved in Et$_2$O (20 mL). This solution was washed with brine (4 × 20 mL), dried over MgSO$_4$, filtered and concentrated in vacuo. The crude oil obtained was then purified by chromatography on silica gel (10% EtOAc/CH$_2$Cl$_2$ → 20% EtOAc/CH$_2$Cl$_2$) to give 316 as a pale yellow oil (115 mg, 89%) plus recovered starting material (14 mg, 11%); [α]$_D^{20}$ –81.6 (c 1.0, CH$_2$Cl$_2$); chiral HPLC analysis: no separation conditions found therefore ee unknown; $\nu_{max}$ (film)/cm$^{-1}$ 3007 (C-H), 2947 (C-H), 1701 (C=O), 1616 (br, 2 × C=O), 1581 (C=N), 1487, (C=C); $\delta$_H (400 MHz, CDCl$_3$) 2.86 (6H, s, N(CH$_3$)$_2$), 2.96 (1H, dd, J 16.3, 6.1, C(2)H$_2$), 3.18 (1H, dd, J 16.3, 7.1, C(2)H$_2$), 3.78 (3H, s, OC$_2$H$_3$), 4.22 (1H, at, J 6.6, C(3)H$_2$), 6.39 (1H, d, J 16.0, ArCH=CHCO$_2$Me), 7.09 – 7.36 (5H, m, ArH), 7.40 – 7.44 (1H, m, C(7')H), 7.62 (1H, d, J 16.0, ArCH=CHCO$_2$Me), 8.33 – 8.36 (1H, m, C(4')H); $\delta$_C (126 MHz, CDCl$_3$) 36.9, 40.1, 40.7, 51.8, 105.6, 117.6, 118.4, 121.3, 125.8, 126.4, 126.8, 126.9, 128.7, 129.8, 135.2, 137.1, 141.8, 142.5, 144.4, 167.3, 167.4, 169.1; m/z (NSI$^+$) 435 ([M+H]$^+$, 100%), 457 ([M+Na]$^+$, 60%), 891 (2M+Na$^+$, 30%); HRMS (NSI$^+$) C$_{24}$H$_{23}$O$_4$N$_2$S ([M+H]$^+$) requires 435.1373, found 435.1369 (~0.9 ppm).

Methyl (R,E)-3-(3-(5-(benzo[d]oxazol-2-yl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-4-yl)phenyl)acrylate (317a) and methyl (R,E)-3-(3-(4-benzoyl-1-oxo-2,3-dihydro-1H-benzo[4,5]oxazolo[3,2-a]pyridin-3-yl)phenyl)acrylate (317b)

(R)-5-(benzo[d]oxazol-2-yl)-4-(3-bromophenyl)-6-phenyl-3,4-dihydro-2H-pyran-2-one (134 mg, 0.3 mmol), methyl acrylate (34 μL, 0.375 mmol), triethylamine (52 μL, 0.375 mmol), Pd(OAc)$_2$ (3.4 mg, 0.015 mmol) and P(o-tolyl)$_3$ (9.1 mg, 0.03 mmol) were added to degassed DMF (2 mL) under N$_2$ and heated in a sealed tube at 125 °C for 15 h. The reaction was then cooled to room temperature and flushed through a plug of silica with EtOAc, the collected solution was concentrated in vacuo and redissolved in Et$_2$O (20 mL).
This solution was washed with brine (4 × 20 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude oil obtained was then purified by chromatography on silica gel (CH₂Cl₂→2% EtOAc/CH₂Cl₂) to give 317a as a pale yellow oil (56 mg, 41%), 317b as an off-white solid (15 mg, 11%) and recovered starting material (8 mg, 6%).

317a (major): [α]₂³⁰^D +0.9 (c 1.0, CH₂Cl₂); no separation conditions found therefore ee unknown; ν_max (film)/cm⁻¹ 2949 (C-H), 1778 (C=O), 1707 (C=O), 1637 (C=N), 1450 (C=C); δ_H (400 MHz, CDCl₃) 3.07 (1H, dd, J 16.0, 1.8, C(3)H), 3.38 (3H, s, OCH₃), 4.90 (1H, dd, J 7.6, 1.8, C(4)H), 6.40 (1H, d, J 16.0, ArCH=CHCO₂Me), 7.16 – 7.29 (3H, m, ArH), 7.31 – 7.43 (5H, m, ArH), 7.45 – 7.56 (4H, m, ArH), 7.62 – 7.65 (1H, m, benzoxazoleC(4)H), 7.64 (1H, d, J 16.1, ArCH=CHCO₂Me); δ_C (101 MHz, CDCl₃) 36.6 (C(3)H), 40.2 (C(4)H), 51.9 (OCH₃), 107.2 (C(5)), 110.6 (benzoxazoleC(7)H), 118.6 (ArCH=CHCO₂Me), 120.0 (benzoxazoleC(4)H), 124.7 (ArCH), 125.5 (ArCH), 127.1 (ArCH), 127.4 (ArCH), 128.3 (2 × C(6)PhC(2)H), 128.7 (ArCH), 129.1 (2 × C(6)PhC(3)H), 130.0 (ArCH), 130.7 (ArCH), 132.5 (C(6)PhC(1)), 135.5 (C(3)ArC(1)CH=), 140.4 (ArC), 141.5 (ArC), 144.4 (ArCH=CHCO₂Me), 150.3 (benzoxazoleC(7a)H), 156.4 (C(6)), 160.8 (benzoxazoleC(2)), 166.0 (C(2)O), 167.3 (CO₂Me); m/z (NSI⁺) 452 ([M+H]^⁺, 100%), 474 ([M+Na]^⁺, 50%), 925 (2M+Na]^⁺, 30%); HRMS (NSI^+) C₁₂H₁₂O₃N ([M+H]^⁺) requires 452.1492, found 452.1484 (−1.9 ppm).

317b (minor): mp 120-123 °C; [α]₂³⁰^D −179.4 (c 0.35, CH₂Cl₂); no separation conditions found therefore ee unknown; ν_max (film)/cm⁻¹ 2949 (C-H), 1715 (C=O), 1660 (C=O), 1637 (C=O), 1595 (C=N), 1476 (C=C); δ_H (400 MHz, CDCl₃) 3.08 (1H, dd, J 16.9, 2.6, C(2)H), 3.24 (1H, dd, J 16.9, 7.6, C(2)H), 3.79 (3H, s, OCH₃), 4.70 (1H, dd, J 7.6, 2.6, C(3)H), 6.38 (1H, d, J 16.0, ArCH=CHCO₂Me), 6.92 – 6.97 (1H, m, C(5')H), 7.14 – 7.24 (2H, m, ArH), 7.29 – 7.35 (2H, m, ArH), 7.38 – 7.45 (4H, m, ArH), 7.48 – 7.55 (1H, m, ArH), 7.58 – 7.68 (3H, m, C(7')H, ArCH=CHCO₂Me, ArH), 7.95 – 8.01 (1H, m, C(4')H); δ_C (101 MHz, CDCl₃) 36.5 (C(3)H), 39.4 (C(2)H), 51.9 (OCH₃), 93.7 (C(4)), 110.1 (C(7)H), 115.2 (C(4')H), 118.2 (ArCH=CHCO₂Me), 125.0 (ArCH), 125.7 (ArCH), 126.7 (ArCH), 126.9 (ArCH), 126.9 (C(4a)'), 128.1 (4 × C(4)COPhC(2,3)H), 128.5 (ArCH), 129.7 (ArCH), 131.3 (C(4)COPhC(4)H), 135.2 (C(3)ArC(1)CH=), 140.8 (C(4)COPhC(1)), 142.8 (C(3)ArC(3)CH), 144.8 (ArCH=CHCO₂Me), 146.7 (C(7a)'), 155.9 (C(5)), 166.9 (CO₂Me), 167.5 (C(1)O), 191.5 (COPh); m/z (NSI⁺) 452 ([M+H]^⁺, 100%), 474 ([M+Na]^⁺, 70%), 925
(Z)-3-oxo-1,3-diphenylprop-1-en-1-yl cinnamate (203)

EtN(\text{i}Pr)\text{\textsubscript{2}} (5.4 mL, 31.2 mmol) was added to a solution of 1,3-diphenylpropane-1,3-dione (5.6 g, 25.0 mmol) in THF (25 mL). After 30 min stirring at room temperature, trans-cinnamoyl chloride (5.0 g, 30.0 mmol) was added and the flask heated at 50 °C for 16 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with 2M HCl (50 mL) followed by saturated aqueous NaHCO\text{\textsubscript{3}} (50 mL), dried over MgSO\text{\textsubscript{4}} and concentrated in vacuo. The residue was purified by column chromatography (5% → 10% Et\text{\textsubscript{2}}O/Petrol) to afford a 3:1 mixture of unreacted cinnamoyl chloride to product (3.5 g, 40%) plus cinnamate 203 as an off-white fluffy solid (665 mg, 8%); mp 109-111 °C \{Lit.\textsuperscript{62} 111-112 °C\}; δ\text{\textsubscript{\text{H}}} (300 MHz, CDCl\text{\textsubscript{3}}) 6.69 (1H, d, J 16.0, PhCH=CHCO), 7.30 (1H, s, C(2)\text{\textsubscript{H}}), 7.38 – 7.64 (11H, m, Ar\text{\textsubscript{H}}), 7.74 (2H, d, J 7.7, Ar\text{\textsubscript{H}}), 7.87 (1H, d, J 16.0, PhCH=CHCO), 7.98 (2H, d, J 7.6, Ar\text{\textsubscript{H}}). Data in agreement with the literature.\textsuperscript{62}
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**Method shorthand:** M06-2X/6-31+G(d,p)/PCM(THF)//M06-2X/6-1G(d)/PCM(THF)


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