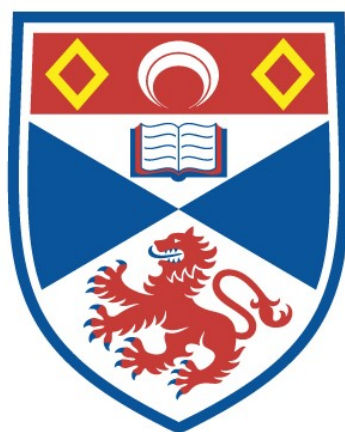


PYRROLE ACETIC ACID DERIVATIVES IN LEWIS BASE CATALYZED
ENANTIOSELECTIVE FORMAL [4+2] CYCLOADDITIONS

Shuyue Zhang

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



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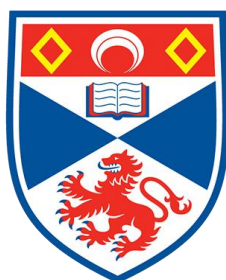
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Pyrrole Acetic Acid Derivatives in Lewis Base
Catalyzed Enantioselective Formal [4+2]
Cycloadditions

Shuyue Zhang



University of
St Andrews

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

October 2019

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Abstracts

This thesis describes the use of C(1) ammonium enolate chemistry with Lewis base isothioureia catalysis in Michael addition-lactonization/lactamization between 2-pyrrolyl acetic acid derivatives and various Michael acceptors.

Chapter 2 proved the principle that amino esters protected as benzophenone Schiff base could be α -functionalized using Lewis base catalysis.

Chapter 3 described the use of 2-pyrrolyl acetic acid in enantioselective Michael addition-lactonization with CCl_3 enone. After *in situ* ring-opening, a range of 30 diesters and diamides in up to 98% yield, >95:5 dr and >99:1 er. Further demonstration of the synthetic utility of these ring-opening derivatives was achieved with an intramolecular Friedel-Crafts acylation utilizing the electron-rich nature of pyrrole to afford dihydroindolizinone derivatives in up to 90% yield with no erosion in stereoselectivity.

Chapter 4 described the use of either α,β -unsaturated trifluoromethyl ketones or α -keto- β,γ -unsaturated esters with 2-pyrrolyl acetic acid to synthesize tetrahydroindolizine derivatives in one-pot, with up to 98% yield, >95:5 dr and >99:1 er.

Chapter 5 described the synthesis of dihydropyridinones from chalcone-derived N-Ts ketimine and unsaturated cyclic sulfonamide derived from saccharin in up to 97% yield, >95:5 dr and >99:1 er.

Chapter 6 described the synthesis of tetrasubstituted pyridines using a variety of unsaturated ketimines bearing esters with DHPB catalyst in up to 66% yield. Further derivatization was demonstrated via transforming 2-pivaloyloxy group into 2-OTs group in a two-step process, enabling the Pd-catalyzed cross coupling and reduction.

Acknowledgements

First of all, I would like to thank my supervisor, Prof. Andrew Smith for giving me this great opportunity to work in his research group and for all his support and guidance throughout the whole PhD and in the preparation of this thesis. I am also grateful for the help of Dr. James Taylor, currently at the University of Bath, for all his professional contribution towards analyzing results from Chapter 3 and preparing the manuscripts.

I would also like to thank all members of the Smith Group past and present, in particular Mark Greenhalgh and Claire Young, for assisting me in preparing the thesis and providing guidance throughout my PhD degree.

Lastly, I would like to thank all the important person in my life for supporting me and staying with me during the four-year journey.

List of abbreviations

Ac	Acetyl
aq	Aqueous
app.	Apparent
Ar	Aromatic
ASAP	Atmospheric solid analysis probe
Bn	Benzyl
br	Broad
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	tert-Butyloxycarbonyl protecting group
Bz	Benzoyl
BTM	Benzotetramisole
Cat.	Catalyst
Cbz	Carboxybenzyl
Cy	Cyclohexyl
d	Doublet
DCC	Dicyclohexylcarbodiimide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dba	Dibenzylideneacetone
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane
dd	Doublet of doublet
DMC	Dimethylcarbonate
DMF	Dimethylformamide
DHPB	3,4-Dihydro-2 <i>H</i> -pyrimido[2,1- <i>b</i>]benzothazole
dp	Doublet of quartets

dr	Diastereomeric ratio
E	Electrophile
EDG	Electron donating group
ee	Enantiomeric excess
equiv./eq.	Equivalent(s)
er	Enantiomeric ratio
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
Fmoc	Fluorenylmethyloxycarbonyl
HBTM	Homobenzotetramisole
HyperBTM	HyperHomobenzotetramisole
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared
ITU	Isothioureas
<i>J</i>	Coupling constant
LB	Lewis base
LG	Leaving group
Lit	Literature
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
Me	Methyl
MHz	Megahertz
mp	Melting point

MS	Mass spectrometry
<i>NHC</i>	<i>N</i> -heterocyclic carbene
NMR	Nuclear Magnetic Resonance
NSI	Nanospray ionisation
Nu	Nucleophile
<i>o</i>	<i>Ortho</i>
<i>o/n</i>	Overnight
<i>p</i>	<i>Para</i>
ppm	Parts per million
Ph	Phenyl
Piv	pivalaloyl
PNP	<i>Para</i> -nitrophenyl
PS	Polymer supported
PTC	Phase transfer catalysis
pin	pinacolato
Pr	Propyl
q	Quartet
quant.	Quantitative
R	General substituent
rt	Room temperature
s	Singlet
sept	Septet
t	Triplet
<i>t</i> -Bu	Tertiary Butyl
T	Temperature
Tf	Triflate
TS	Transition state

Ts	<i>p</i> -toluenesulfonyl
TMS	Trimethylsilane
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TFFA	Trifluoroacetic anhydride
Ts	Tosyl

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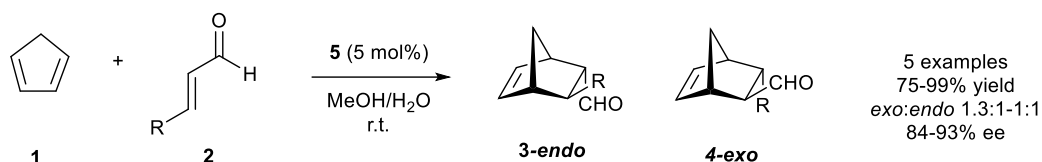
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Chapter 1: Introduction

1.1. Organocatalysis Overview

Catalysis is highly important throughout synthetic organic chemistry, ranging from the discovery of new reactions and processes to the large-scale production of complex organic molecules. Many chemists aim to develop chiral catalysts that can promote enantioselective transformations in order to prepare chiral molecules as a single enantiomer. An ideal catalyst should not contain any precious elements to avoid prohibitive cost and reduce resource depletion,¹ as well as being both selective and recyclable. Moreover, it should enable reactions to be carried out using relatively simple operational procedures. Organocatalysts are small organic molecules that are capable of selectively promoting enantioselective transformations and are often inspired by enzymatic transformations. Most organocatalysts are generally bench-stable, and often use operationally simple procedures in reaction processes, avoiding the need for a strict inert atmosphere (glove-box chemistry) and other complex apparatus. Compared to metal catalysts, they are sometimes regarded as eco-friendly due to their relatively low toxicity to living creatures.¹ From a synthetic viewpoint, an ideal catalyst should be relatively cheap to make in large quantities either from chiral pool reagents or through enantioselective transformations of starting materials. Enantioselective organocatalysis has become a fast-expanding field of study, as well as a powerful synthetic methodology which is complementary to metal-catalysis. The increasing focus on asymmetric organocatalytic transformations was triggered by a key report by MacMillan in 2000.² A Diels-Alder reaction was achieved using chiral Lewis base organocatalysts to give products with excellent enantioselectivity, proceeding through an iminium ion intermediate (Scheme 1.1). The condensation between a secondary amine **5** and an α,β -unsaturated aldehyde **2** generates the activated iminium ion species **6** which has a lower energy LUMO compared with that of the corresponding α,β -unsaturated aldehyde **2**. Reaction of **6** with cyclopentadiene **1** in a [4+2] cycloaddition furnished products **3** and **4** with good enantioselectivity.²



Scheme 1.1: MacMillan's work on iminium ion catalysis

The major defining feature of MacMillan's work was the realization of the full potential of using small organic molecules to access novel activation modes which had previously not been widely applied in the organic synthesis community. This realization underlined the potential benefits of organocatalysts, hinting at a promising synthetic future for the use of organocatalysts to access complex molecules asymmetrically. Since the publication of MacMillan's historic work, many advances have been made in developing organocatalysis across a range of four broad classes of organocatalysts: Brønsted acid catalysis, Lewis acid catalysis, Brønsted base catalysis and Lewis base catalysis. Selected examples of each type will be discussed herein.

1.2. Brønsted acid catalysis

Brønsted acid catalysts activate a carbon-heteroatom double bond such as a carbonyl or imine via partial or complete protonation. Thus, the LUMO energy of the substrate is lowered, rendering it more electrophilic.³ There are two distinct approaches for activation with Brønsted acid catalysts (Fig. 1.1). The first approach can be referred to as a general or neutral Brønsted acid catalysis, and relies on hydrogen bonding (H-bonding) between the substrates (H-bond acceptor) and the chiral catalysts (H-bond donor). Another approach generally utilizes the relative acidities between the substrates and the chiral catalysts to protonate the substrate, forming a tight ion-pair between the substrate and catalyst, which is recognized as specific or stronger Brønsted acid catalysis. The tight ion-pair is able to impart stereocontrol via the

influence of the chiral backbone of the catalyst, guiding nucleophilic attack on the bound substrate.

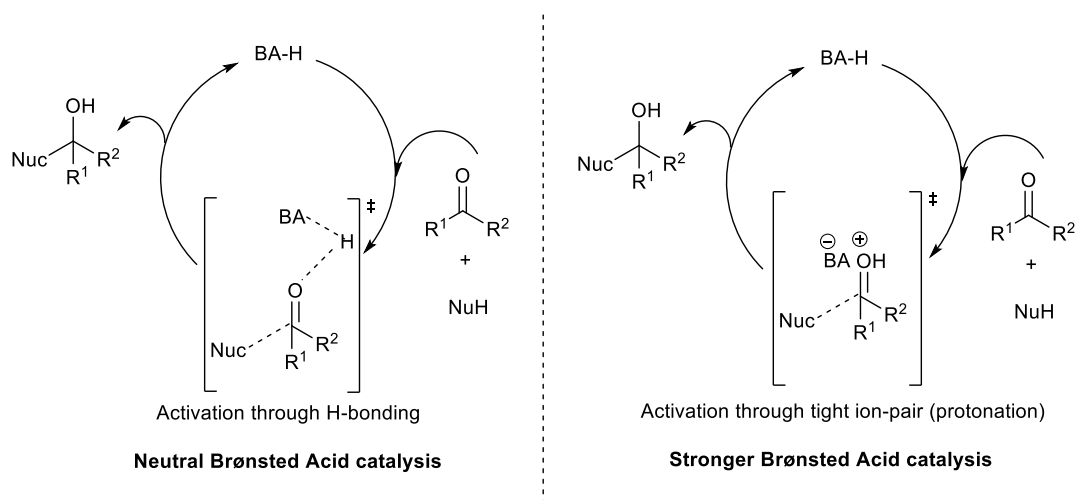


Fig. 1.1: General activation modes of Brønsted acid catalysis

1.2.1. Neutral Brønsted acid catalysis

H-bonding catalysis plays an important role in biological systems,⁴ especially in enzymatic reactions. Modern applications of neutral H-bonding catalysis in asymmetric synthesis have focused mainly on three types of catalysts, namely chiral ureas/thioureas **7**, chiral diols **8** and BINOL derivatives **9** (Fig. 1.2).

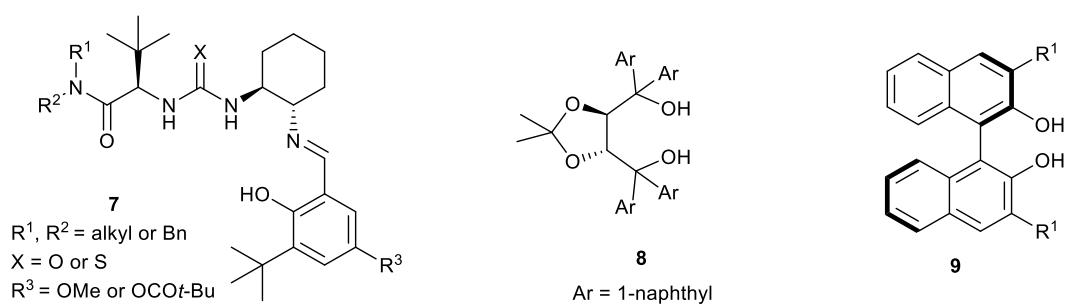
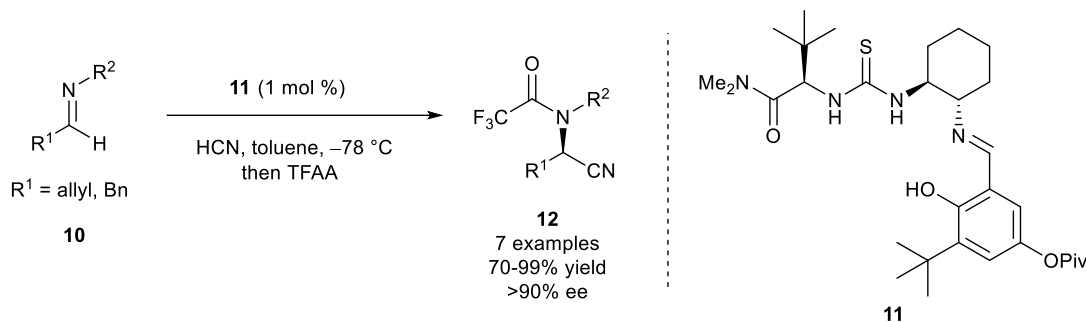


Fig. 1.2: Modern chiral H-bonding catalysts

Pioneering work by Jacobsen and co-workers used chiral ureas and thioureas as H-bonding catalysts to build a compound library⁵ via enantioselective Strecker reactions. Further work showed that, starting from an allyl or benzyl imine **10**, chiral thiourea **11** catalysed the formation of a cyanide-containing amide **12** with excellent yield and enantiomeric access (Scheme 1.2).⁶ Building upon these promising results, enantioselective additions to a range of functionally different electrophiles employing this catalytic strategy have been reported by

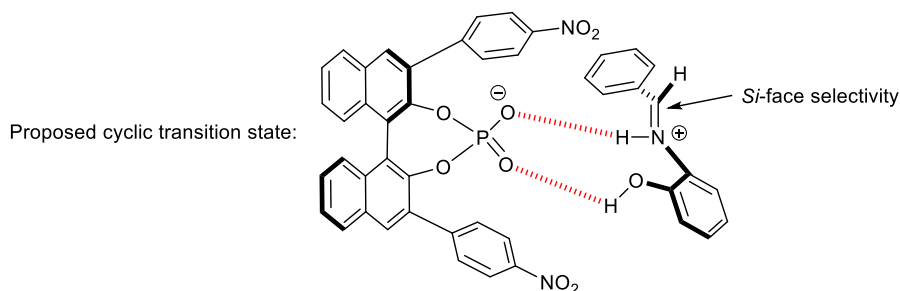
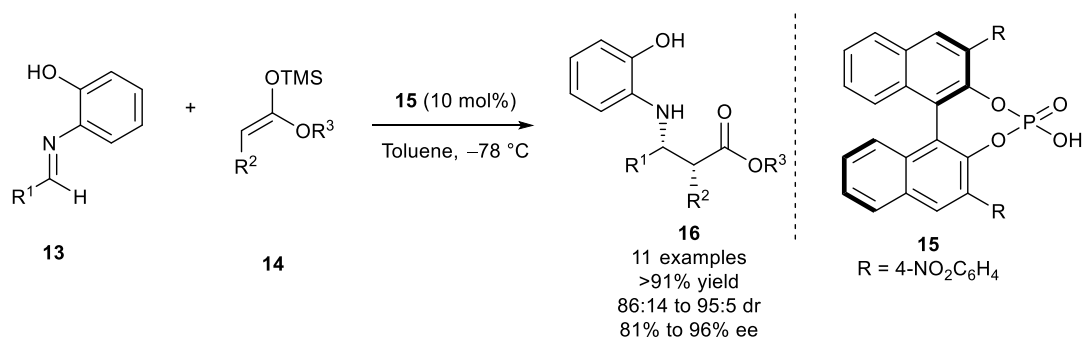
Jacobsen and co-workers, including asymmetric Mannich⁷ and aza-Baylis-Hillman reactions.⁸ Other applications within this area includes the use of chiral diol derivative **8** in asymmetric Diels-Alder reaction by Rawal,⁹ and asymmetric variant of Morita-Baylis-Hillman reactions developed using BINOL derived H-bonding catalyst **9**.¹⁰



Scheme 1.2: Thiourea-catalyzed asymmetric Strecker reaction

1.2.2. Stronger Brønsted acid catalysis

Differing from neutral Brønsted acid catalysts, strong Brønsted acid catalysts can be fully deprotonated by a substrate, generating a tight ion pair with strong charge-controlled interactions (Fig. 1.1). Akiyama¹¹ and Terada¹² developed a range of BINOL-derived phosphoric acid catalysts **15** (Scheme 1.3). These catalysts are specially designed with rigid binaphthol backbones with tuneable R groups which can be used to optimize selectivity and reactivity. Well known examples of their use include Yamamoto's Diels-Alder reaction¹³ between vinyl ketones and silyoxydienes, and Akiyama's Mannich reaction (Scheme 1.3), in which amino esters **16** are generated from imines **13** and silyl enol ethers **14** with excellent enantioselectivity and in excellent yields.¹¹ Based on theoretical calculations, a transition state is proposed, which features two key interactions between the imine and the deprotonated catalyst, resulting in overall *Re*-facial selectivity for the subsequent nucleophilic attack.



Scheme 1.3: Enantioselective Mannich reaction using stronger Brønsted acid catalysts

1.3. Lewis acid catalysis

Historically, metal-based Lewis acids have been extensively used in substrate activation, but some are associated with toxicity towards living creatures, harmful effects towards the environment and instability to air and moisture. Therefore, alternative novel organic Lewis acids have been developed in recent years. Normally a Lewis acid will accept an electron pair from the substrate to form a Lewis acid-substrate complex. If the Lewis acid is chiral, subsequent reactions can potentially generate enantioenriched product. Phase transfer catalysis (PTC) is an example of Lewis acid organocatalysis.¹⁴ Typically, a PTC system is designed to have two coexisting phases, one organic phase and one either aqueous or solid phase. Due to the biphasic nature of the system, it is often difficult to investigate mechanisms in detail. One mechanism proposed by Starks¹⁵ suggests that the phase-transfer catalyst (Q) moves between the aqueous phase and the organic phase, generating a hydroxide species (Q⁺HO⁻) in reaction with an organic phase insoluble base (MOH). The hydroxide species (Q⁺HO⁻) can then transfer to the organic phase where it can deprotonate an organic phase soluble nucleophile (NuH) to give a reactive carbanionic species (Q⁺Nuc⁻) (Fig. 1.3). The key to a successful PTC reaction is the generation of the tight ion pair Q⁺Nuc⁻, in which the chiral catalyst can influence the selectivity of the subsequent reactions, and result in an enantioselective transformation.

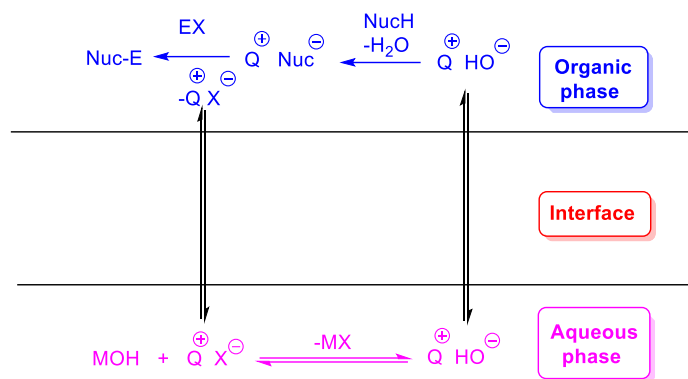
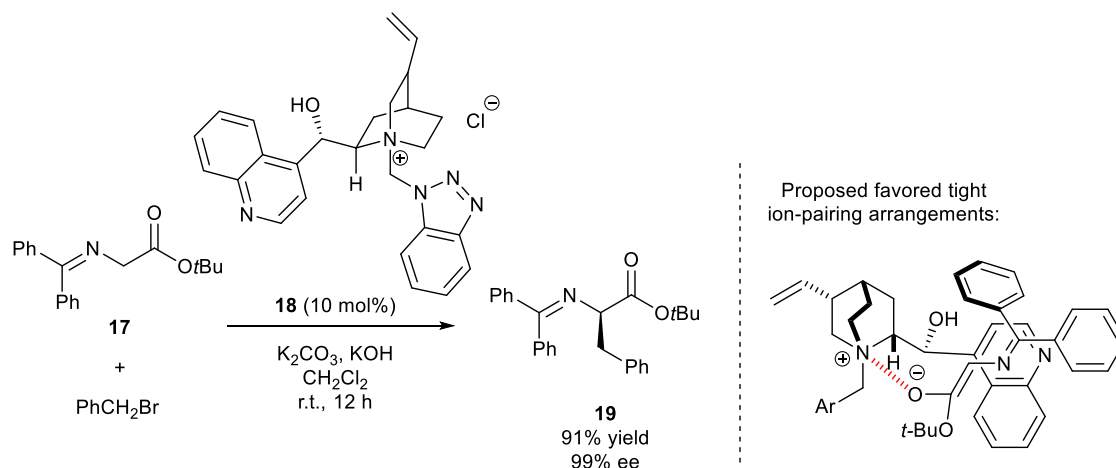


Fig. 1.3: General mechanism of phase-transfer catalysis

One area of interest where chiral PTC has been widely applied is the synthesis of optically active α -amino acids using a prochiral glycine ester protected as a Schiff base. Using cinchonine-derived catalyst **18**, Zhang and co-workers reported the asymmetric benzylation of *tert*-butyl glycine ester Schiff base **17** to synthesise phenylalanine derivative **19** with high enantioselectivity and in excellent yield (Scheme 1.4).¹⁶ A tight ion pair model has been proposed to account for the stereochemical rationale, where the enolate oxygen interacts closely with the ammonium catalyst **18** (Scheme 1.4).¹⁷ In addition to this, kinetic resolution of secondary alkyl halides,¹⁸ conjugate additions¹⁹ and Mannich reactions²⁰ have also been investigated using similar cinchonine-derived catalysts.

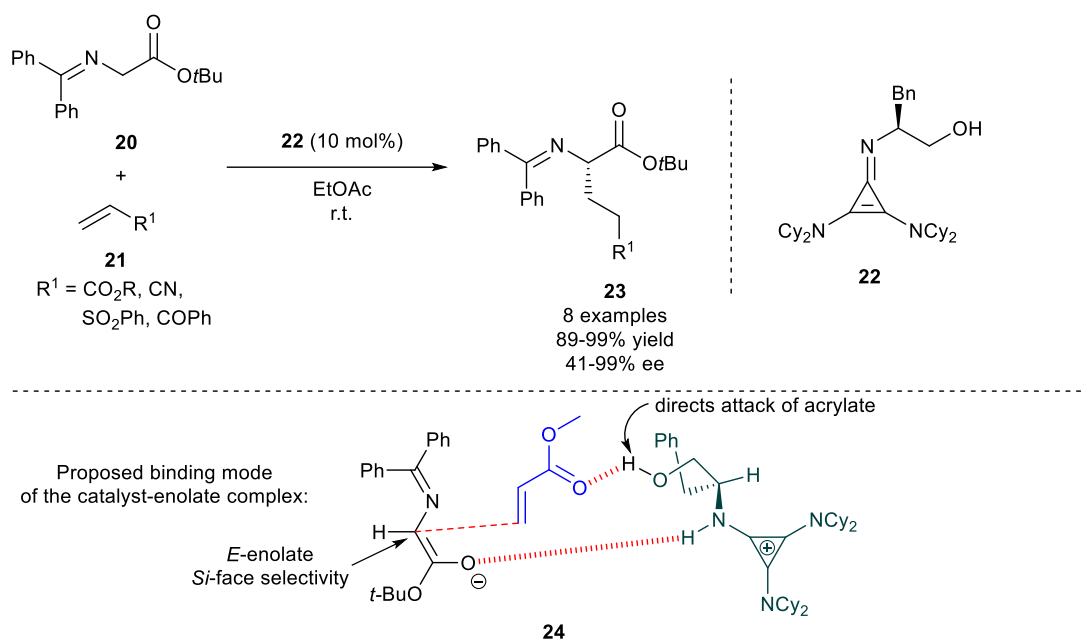


Scheme 1.4: Synthesis of optically active α -amino derivatives using chiral PTC

1.4. Brønsted base catalysis

Brønsted bases are characterised by their ability to deprotonate substrates and can be used to catalyse many carbon-carbon and carbon-heteroatom bond forming reactions. When a chiral base is used, generation of a tight ion pair between the deprotonated nucleophilic

species and the protonated chiral Brønsted base catalyst can introduce enantioselectivity. Catalysts usually include highly basic nitrogen-based functional groups which are easily accessible from chiral pool reagents. One state of the art example was reported by Lambert, using highly basic cyclopropenimine Brønsted base catalyst **22** in a Michael addition of deprotonated glycine ester Schiff base **20** into Michael acceptors **21**. The observed high stereocontrol was proposed to arise through the lowest energy binding mode **24** between the catalyst and the enolate by computational calculations²¹ (Scheme 1.5). The relative ease of preparing catalyst **22** and the scalability of the reaction - up to 25 g scale (97% yield, 99% ee) - highlight the huge potential of chiral Brønsted base catalysts in asymmetric transformations.²²



Scheme 1.5: Michael addition involving cyclopropenimine as Brønsted base catalyst

1.5. Lewis base catalysis

Lewis base catalysis is one of the biggest areas of organocatalysis in terms of applications. In a simplified model, Lewis base catalysis can be defined as the donation of a lone pair of electrons to an electrophilic substrate, leading to a formal increase in the electron density on the activated substrate (Fig. 1.4).²³ Subsequent transformations of the activated adduct form intermediates that can act as either electrophiles or nucleophiles. In the past decade many activation modes have been accessed using Lewis base catalysts and selected examples

focusing on nucleophilic enolate equivalents generated through secondary or tertiary amines will be briefly discussed herein.

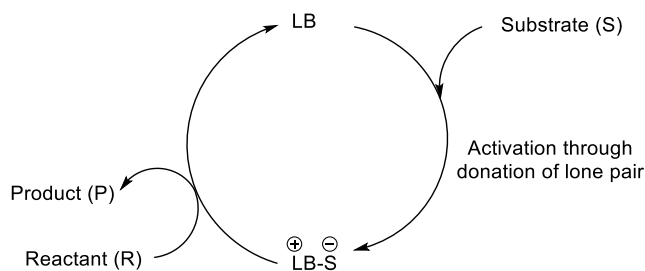
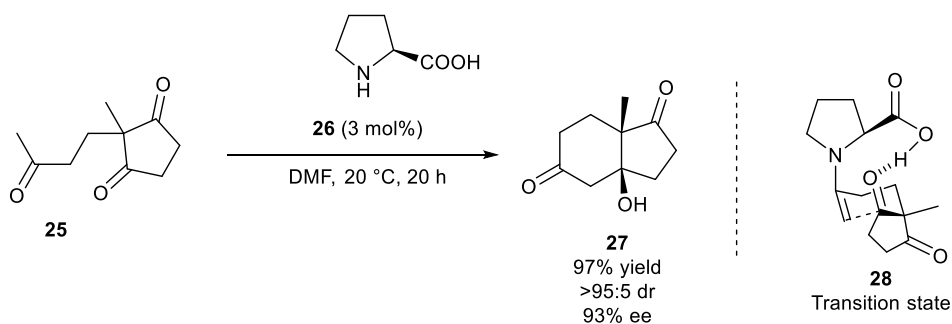


Fig. 1.4: General activation mode of Lewis base catalysis

1.5.1. Enamine catalysis from secondary amines

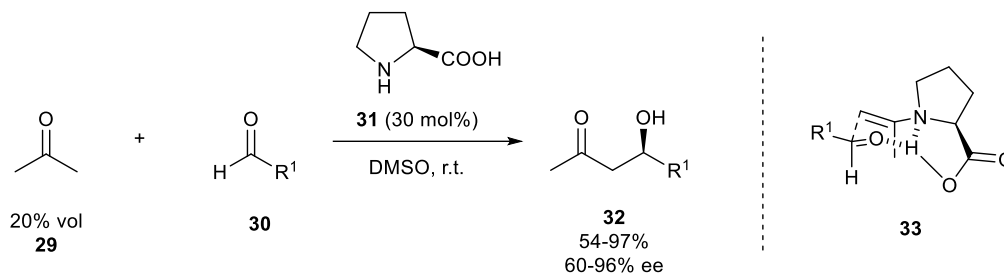
Enamine intermediates derived from chiral secondary amines and ketones or aldehydes react analogously to nucleophilic enolate equivalents. A higher energy HOMO makes them more reactive. One of the earliest examples of this type of catalysis appeared in 1971, when Hajos reported the enantio- and diastereoselective Hajos-Parrish-Eder-Sauer-Wiechert cyclization using proline as a catalyst.²⁴ Intramolecular aldol reaction between triketone **25** and chiral proline catalyst **26** gave bicyclic product **27** with excellent stereoselectivity and in excellent yield (Scheme 1.6). It has been proposed that the transition state involved a six-membered ring structure **28** and that the stereoselectivity is directed by a H-bonding interaction between the carboxylic acid and the ketone moiety.



Scheme 1.6: Hajos' work on Hajos-Parrish-Eder-Sauer-Wiechert cyclisation

It took modern chemists more than 30 years to begin to build on Hajos' earlier discovery of asymmetric organocatalysis. In 2000, List published an asymmetric proline-catalyzed intermolecular aldol reaction between acetone and benzaldehydes. The reaction was postulated to proceed through a chair-like closed transition state **33** with H-bonding

controlling the selectivity, giving β -hydroxy ketones **32** in moderate to excellent yield and with good to high enantioselectivity (Scheme 1.7).²⁵

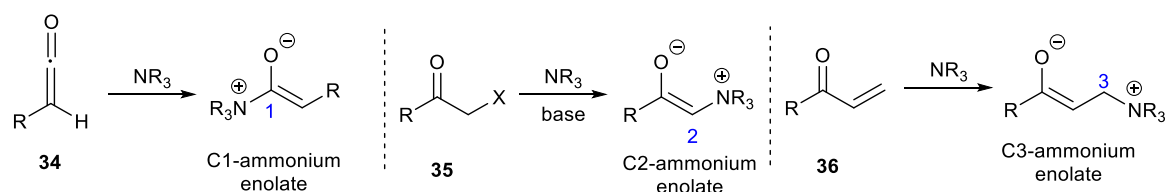


Scheme 1.7: Asymmetric aldol reaction

Since List's publication, further applications of enantioselective enamine catalysis have been documented, including Mannich reaction,^{26,27} α -oxygenation of aldehydes and ketones,²⁸ α -halogenation of aldehydes,^{29,30} conjugate additions^{31,32} and enamine alkylations.³³

1.5.2. Ammonium enolates from tertiary amines

Ammonium enolates are a class of C-based nucleophilic species generated from chiral tertiary amine catalysts.³⁴ Depending on the site of nucleophilic attack, C1-, C2- or C3-ammonium enolates can be produced and are classically accessed through reaction with ketenes **34**, α -halocarbonyls **35** and α,β -unsaturated carbonyls **36** respectively (Scheme 1.8). For the purpose of this thesis, C1-ammonium enolates will be selectively discussed thereafter.



Scheme 1.8: C1, C2 and C3 ammonium enolates

Historically, cinchona alkaloids, which were first isolated from bark, have represented an important class of tertiary amine catalysts to generate C1-ammonium enolates, due to their Lewis basic quinuclidine nitrogen atom presented in a chiral environment (Fig. 1.5).

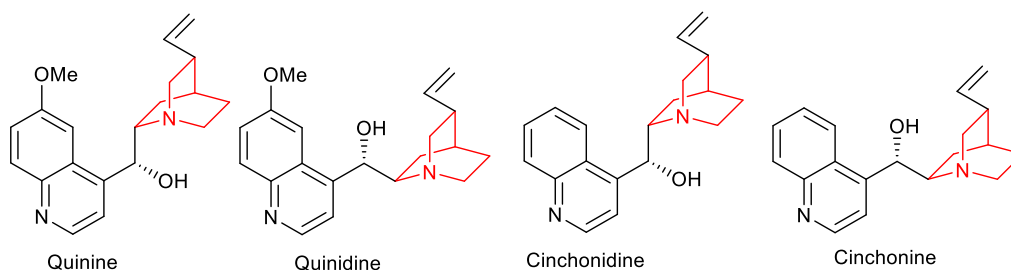
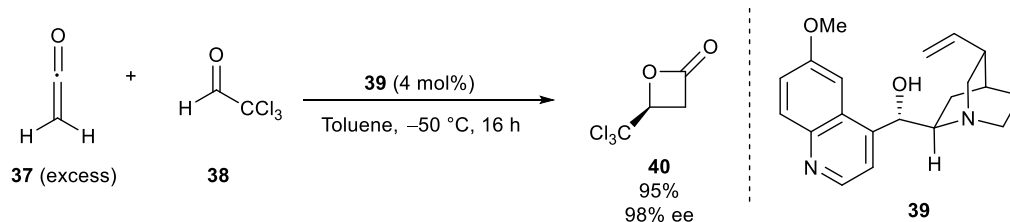


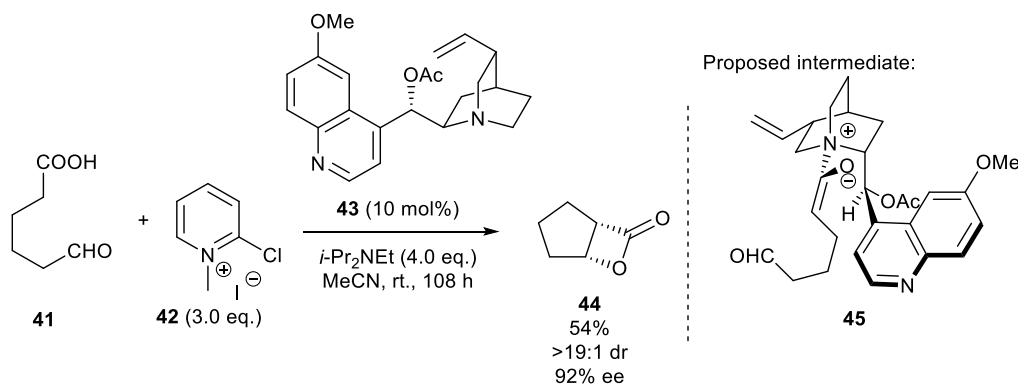
Fig. 1.5: Commonly encountered cinchona alkaloids

In 1982, Wynberg reported the use of catalytic tertiary amine cinchona alkaloid **39** in the enantioselective formation of β -lactone **40** via a C1-ammonium enolate.³⁵ Highly reactive ketene **37** and trichloroacetaldehyde **38** starting materials were required to give the β -lactone **40** in 95% yield and 98% ee (Scheme 1.9).



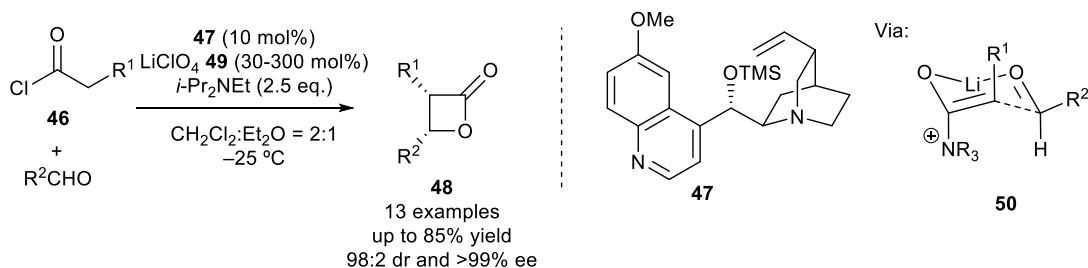
Scheme 1.9: Synthesis of β -lactone by Wynberg

Due to the significant limitations associated with the highly reactive ketenes generated either *in situ* or pre-formed, the C1-ammonium enolates have also been accessed from other bench stable precursors, such as acid chlorides, homoanhydrides and carboxylic acids. For example, Romo successfully demonstrated the use of simple keto-acid **41** as C1-ammonium enolate precursor in diastereo- and enantioselective cinchona-alkaloid catalyzed aldol lactonization reactions to access bicyclic β -lactones **44** in 54% yield, >19:1 dr and 92% ee via **45** (Scheme 1.10).³⁶

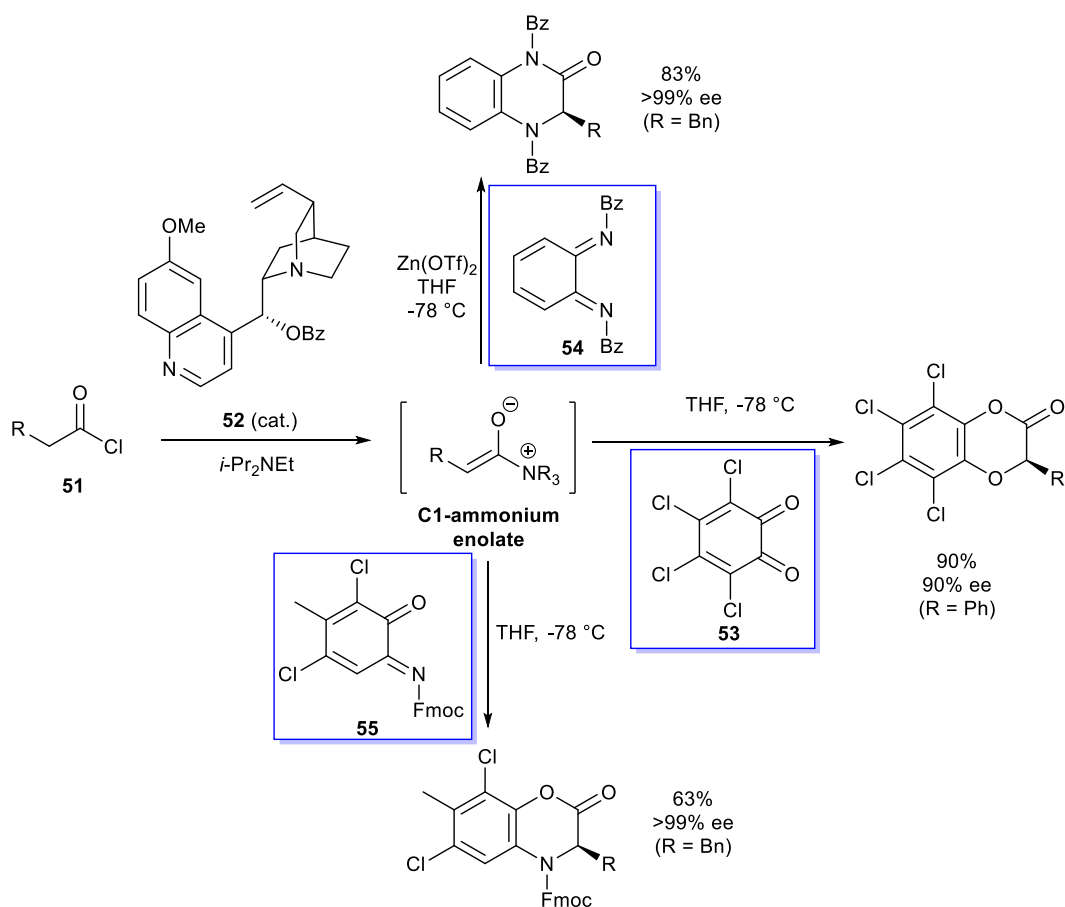


Scheme 1.10: Keto-acids as C1-ammonium enolate precursors

Acid chlorides have also been demonstrated as the C1-ammonium enolate precursors. As an example, in the report by Nelson, a Lewis acid co-catalyst was used to promote the aldol process between the Li ammonium enolate and an aldehyde in an intermolecular process via a proposed closed Zimmerman-Traxler transition state **50** (Scheme 1.11). The β -lactones **48** could be obtained, under this protocol, in good yields and excellent diastereo- and enantioselectivity with a broad scope of aldehydes.³⁷

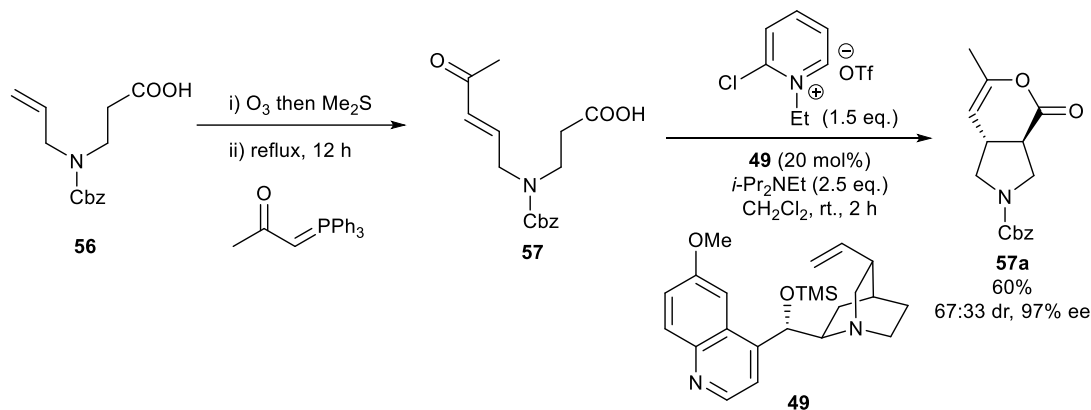
Scheme 1.11: Acid chlorides in LiClO₄ promoted aldol lactonization

Application of ammonium enolates generated from cinchona alkaloids was extended further into formal [4+2] cycloaddition as a powerful strategy to construct 6-membered rings in a catalytic enantioselective fashion.³⁸ For example, C1-ammonium enolates generated from **51** *in situ* (via a ketene intermediate) can participate in enantioselective [4+2] cycloadditions with highly reactive substrates, such as *o*-quinone **53**,³⁹ *o*-quinone diimide **54**⁴⁰ and quinone imide **55**⁴¹ (Scheme 1.12). Excellent enantioselectivity and good yields were obtained, but the successful transformations were limited only to highly reactive cycloaddition partners.



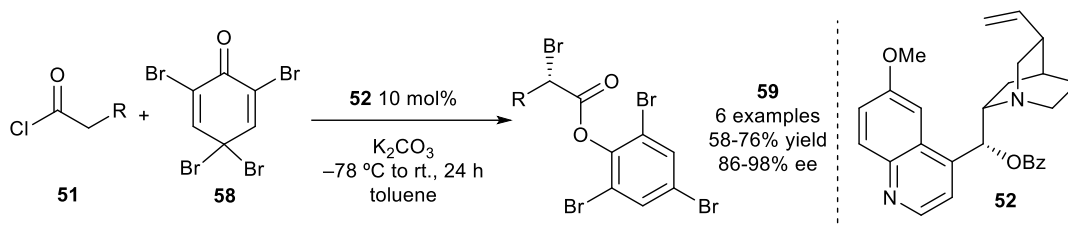
Scheme 1.12: C1-ammonium enolates in formal [4+2] cycloaddition

To overcome the requirement for highly reactive reaction partners in ammonium enolate chemistry, an intramolecular protocol was developed by Smith in 2013.⁴² Ozonolysis and subsequent Wittig reaction of alkene **56** furnished the enone acid **57**. Treatment of enone acid **57** with pivaloyl chloride to form a reactive anhydride intermediate, followed by chiral cinchona alkaloid derivative **49** furnished the Michael addition-lactonization product **57a** in 60% yield, moderate dr of 67:33 and an excellent 97% ee (Scheme 1.13).



Scheme 1.13: Intramolecular formal [4+2] cycloaddition

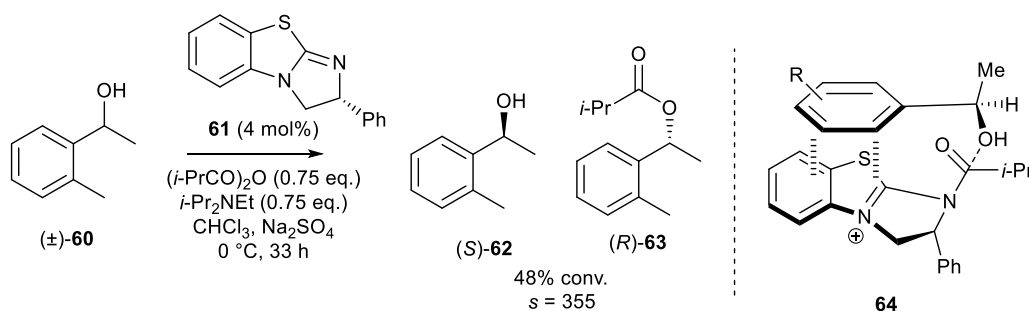
Enantioselective α -halogenation with a suitable electrophilic halogen source was also achieved using cinchona alkaloid derived catalysts **52**. For example, Lectka reported the bromination of ammonium enolates (generated *in situ* from acid chloride **51**, K_2CO_3 and benzoyl quinone **52** via a ketene intermediate) using polybrominated *p*-quinone **58**. Up to 98% excellent ee and a good yield of up to 76% was achieved (Scheme 1.14).⁴³ In this particular example, a turnover of the catalyst was achieved with the help of the aryloxide generated *in situ* from the brominating agent **58**, unlike the previous catalyst turnover with tethered nucleophiles. Similarly, a chlorination procedure was also reported by the same group using a perchloroquinone derived reagent.⁴⁴



Scheme 1.14: α -bromination catalyzed by benzoyl quinone

1.6. Development of Lewis basic isothioureas in organocatalysis

Isothioureas (ITUs) are nitrogen-based organocatalysts that show increasing popularity in the field of enantioselective catalysis. Their first appearance in asymmetric synthesis was in the kinetic resolution of secondary benzylic alcohols reported by Birman and co-workers in 2006.⁴⁵ Using chiral benzotetramisole **61** (BTM) as catalyst and isobutyric anhydride as acylating reagent, a maximum selectivity factor of 355 was achieved for the acylative kinetic resolution of secondary alcohols (Scheme 1.15). The reaction was proposed to proceed through a pre-TS assembly **64**. A combination of a π - π stacking interaction and minimized steric interaction between the alcohol and acylating reagent are responsible for the selective acylation of racemic alcohol **60** to enantioenriched alcohol (*S*)-**62** and ester (*R*)-**63**.⁴⁵



Scheme 1.15: Birman's kinetic resolution of secondary alcohol

Since Birman's report, isothiourea catalyst **61** has been used to catalyze O-Si, C-N and C-C bond forming reactions, leading to the synthesis of complex molecules in high enantiopurity.⁴⁶ Multiple bond forming reactions have also been achieved via domino reactions and formal cycloadditions. New ITUs such as HBTM and its derivative, HyperBTM have been designed, and in many cases have enhanced catalytic reactivity and selectivity (Fig. 1.6).

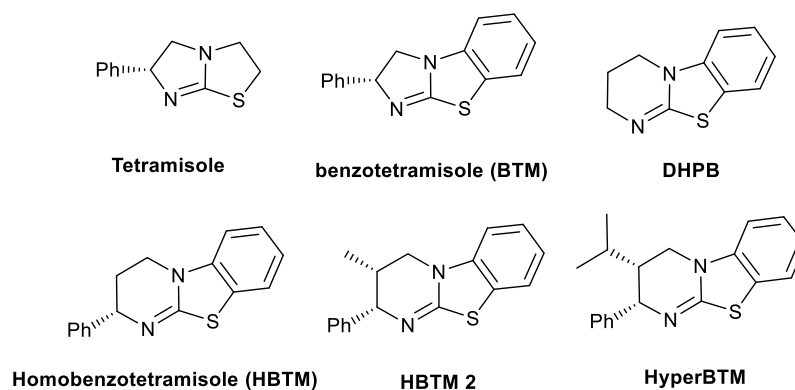
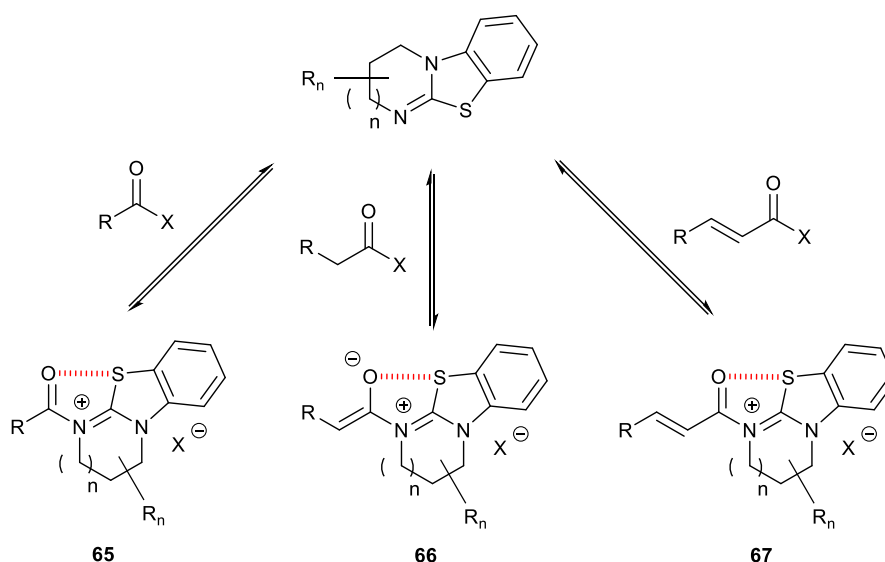


Fig. 1.6: Common isothiourea catalysts

Typically, ITUs can react with anhydrides, acyl halides, or aryl esters to access three main types of intermediates, namely acyl ammonium **65**, ammonium enolate **66** and α,β -unsaturated acyl ammonium **67** (Scheme 1.16). The acyl ammonium species act as electrophiles and enable enantioselective acyl transfer, whilst C1-ammonium enolates are nucleophilic at the α -position. The α,β -unsaturated acyl ammonium can act as a Michael acceptor in conjugate additions, or a dienophile in hetero-Diels-Alder reactions.⁴⁶ Within all three intermediates, a non-covalent 1,5-S---O interaction is proposed to be responsible for locking the conformation of the carbonyl oxygen co-planar to sulfur,⁴⁷ with the catalyst stereodirecting groups responsible for generating the facial selectivity.

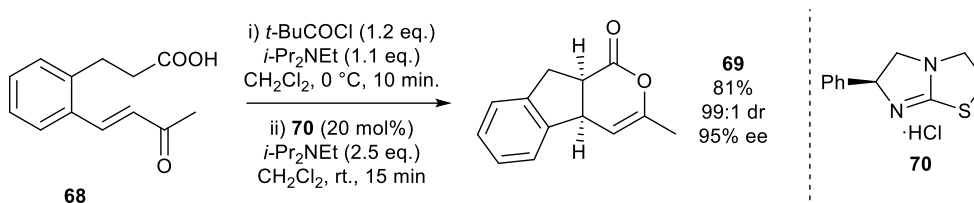


Scheme 1.16: Three main types of ITU-activated intermediates

For the purpose of this thesis, C1-ammonium enolates derived from isothiurea catalysis will be the focus and selected examples will be discussed herein.

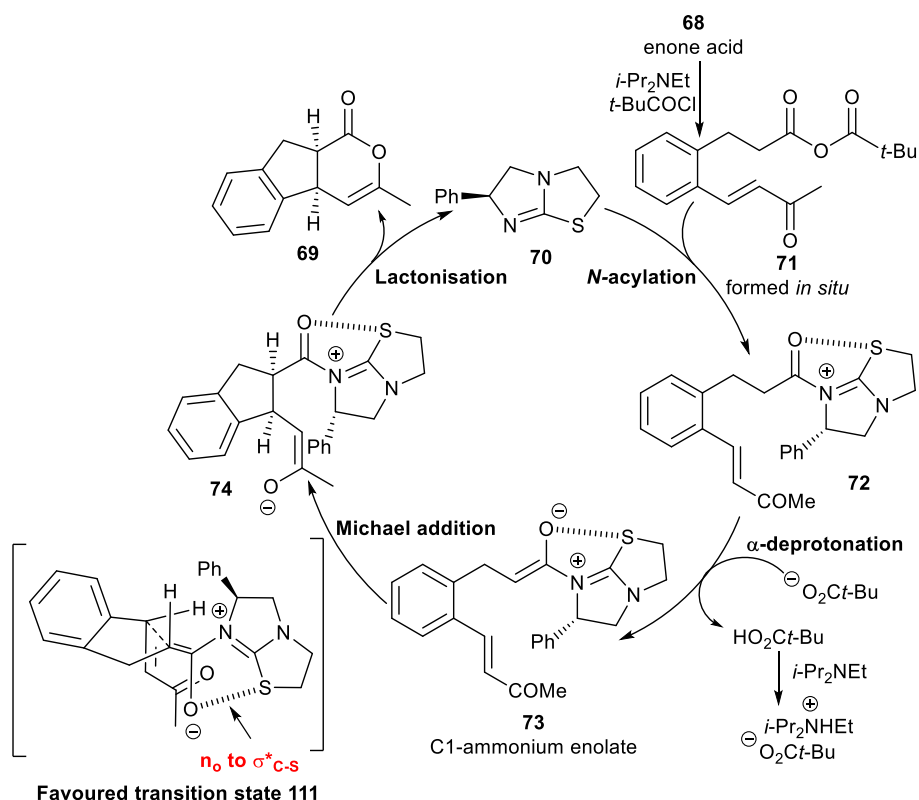
1.6.1. Isothiureas in formal [4+2] cycloadditions

Building upon previous work on using cinchona alkaloids to access enantioenriched 6-membered lactones via formal [4+2] cycloaddition (Scheme 1.13), in 2011, Smith demonstrated intramolecular enantioselective formal [4+2] cycloadditions catalyzed by isothiureas. In this report, commercially available Lewis base catalyst tetramisole hydrochloride **70** was used to access the C1-ammonium enolate intermediate from enone acid **68**, following by Michael addition-lactonization to furnish the highly enantioenriched tricyclic lactone **69** in 81% yield, 99:1 dr and 95% ee (Scheme 1.17).⁴⁸



Scheme 1.17: Intramolecular formal [4+2] cycloadditions

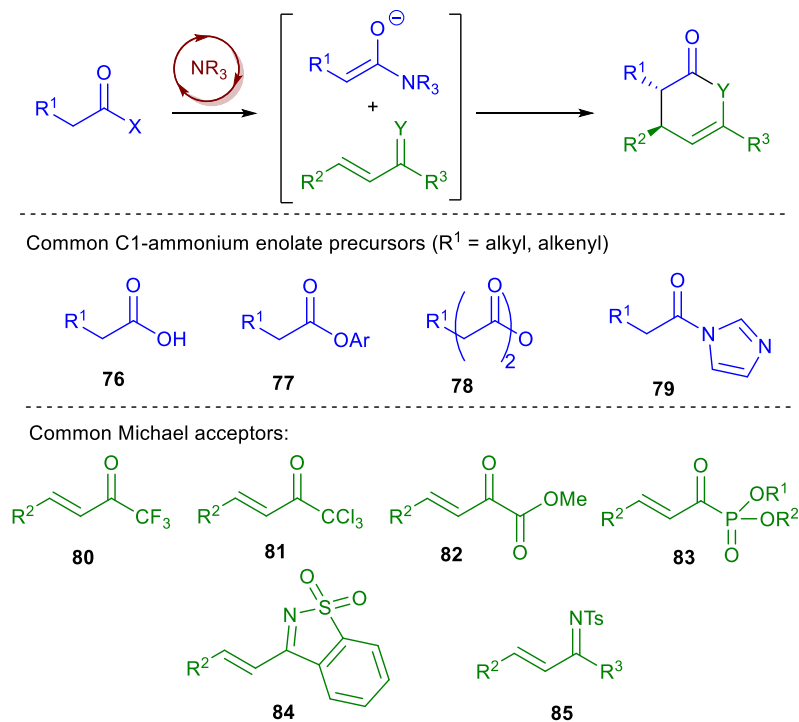
A possible catalytic cycle was also proposed. Starting with the mixed anhydride **71** generated from enone acid **68**, *i*-Pr₂NEt and pivaloyl chloride, *N*-acylation with the isothiourea catalyst, followed by α -deprotonation, gives C1-ammonium enolate **73**. Subsequent intramolecular Michael addition generates acyl ammonium intermediate **74** through a transition state **75** where the two prochiral centres adopt an approximately staggered conformation to minimize unfavourable non-bonding interactions.⁴⁸ Subsequent lactonization allows turnover of the catalyst while releasing the product **69** (Scheme 1.18).



Scheme 1.18: Possible catalytic cycle for intramolecular formal [4+2]

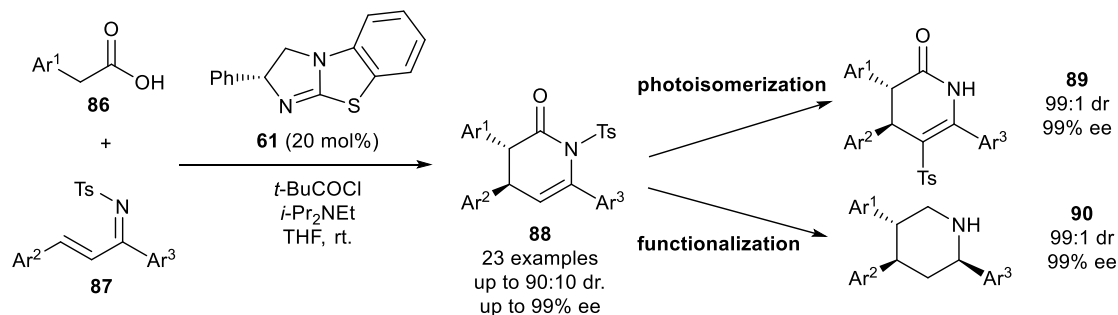
The corresponding intermolecular Michael addition-lactonization process has also been studied and developed extensively with isothiourea catalysis. A wide range of C1-ammonium enolate precursors with various aryl or alkenyl substituents (R^1) have been reported, such as

carboxylic acids **76**,⁴⁹ aryl esters **77**,⁵⁰ homoanhydrides **78**⁵¹ and acyl imidazoles **79**.⁵² Meanwhile, different Michael acceptors (**80-85**) have been employed to access enantioenriched δ -lactones^{48,51-54} or lactams,^{55,56} as well as their ring-opened derivatives (Scheme 1.19).



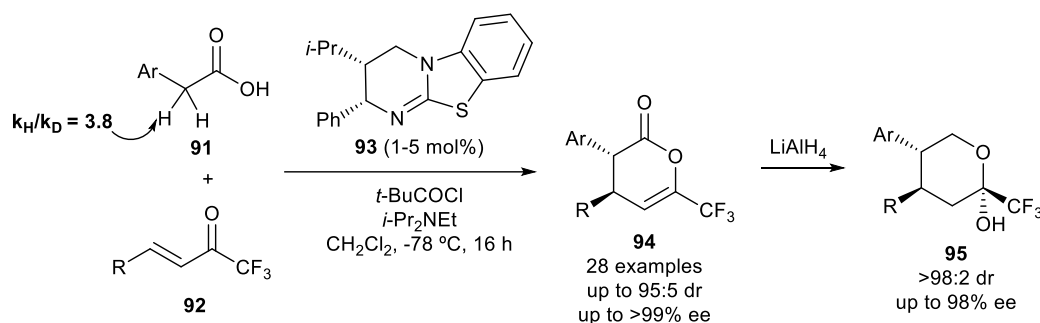
Scheme 1.19: An overview of intermolecular formal [4+2]

For example, in 2012, the isothiourea catalyzed intermolecular Michael addition-lactamization between carboxylic acids **86** and *N*-tosyl- α,β -unsaturated ketimines **87** was developed to access enantioenriched 6-membered lactams **88** in good diastereoselectivity and with excellent enantioselectivity (Scheme 1.20). The lactam products **88** undergo *N*- to *C*- sulfonyl photoisomerization to give **89** without erosion in diastereo- and enantioselectivity, or can be derivatized further into stereodefined trisubstituted piperidines **90**.⁵⁷



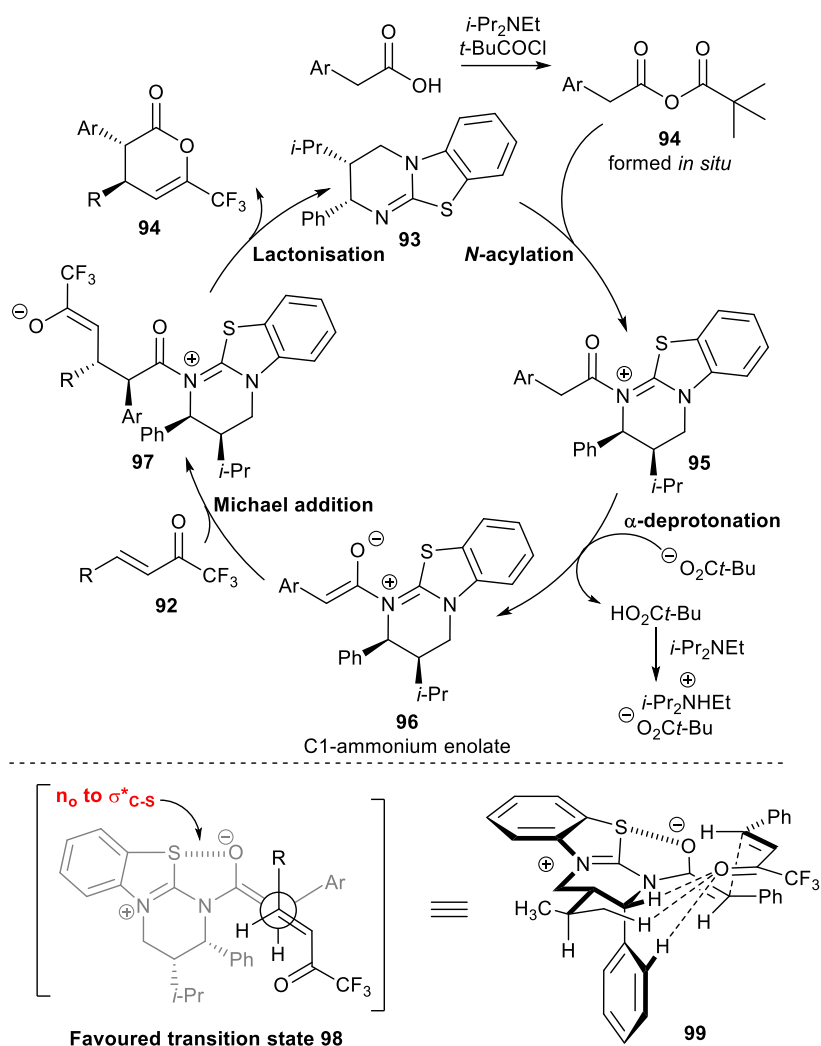
Scheme 1.20: Synthesis of δ -lactams via intermolecular Michael addition-lactonization

This one-pot strategy was also applied in later work published by Smith in 2013. Starting from commercially available aryl acetic acids **91**, *in-situ* activation followed by Michael addition-lactonization with electron-deficient trifluoromethyl enones **92** afforded 6-membered lactones **94** with excellent diastereoselectivity and enantioselectivity (Scheme 1.21). Further derivatization afforded diverse building blocks **95** with trifluoromethyl stereogenic centres. A detailed mechanistic study, including the observation of a primary kinetic isotope effect ($k_H/k_D = 3.8$) is consistent with the rate determining step of this transformation being the α -deprotonation of the acyl ammonium intermediate.⁴⁹



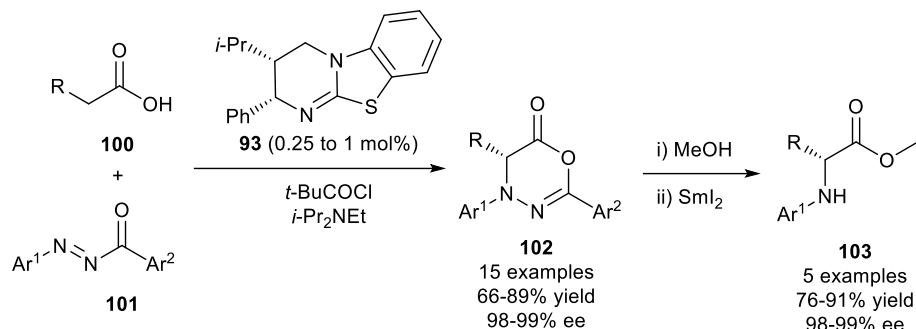
Scheme 1.21: Michael-lactonisation of trifluoromethylenones

A similar mechanism, compared with the intramolecular version, was proposed. Formation of a mixed anhydride, *N*-acylation, deprotonation, Michael addition and lactonization furnished the lactone **94** with high level of stereocontrol (Scheme 1.22).⁴⁸ A preferred transition state **98**, analogous to Heathcock's model,⁵⁸ was proposed. The stabilizing n_o to $\sigma^*_{\text{C-S}}$ interaction within the (*Z*)-ammonium enolate **96** positions both sulfur atom and the enolate oxygen coplanar.⁵⁹ The key to explain the observed stereoselectivity includes the isothiuronium heterocycle **99** adopting a half-chair conformation, with minimization of 1,2-strain leading to the Ph group sitting in a pseudoaxial position with the *i*-Pr group pseudoequatorial. Several stabilizing non-classical C-H \cdots O interactions between the catalyst backbone and the incoming Michael acceptors (NCH \cdots O 2.09 Å, PhH \cdots O 2.27 Å and *i*-PrH \cdots O 2.16 Å) were identified, via computational study of the transition state structure **99**, to impart the high stereoselectivity for the observed stereoisomer of the lactone **94**.⁶⁰

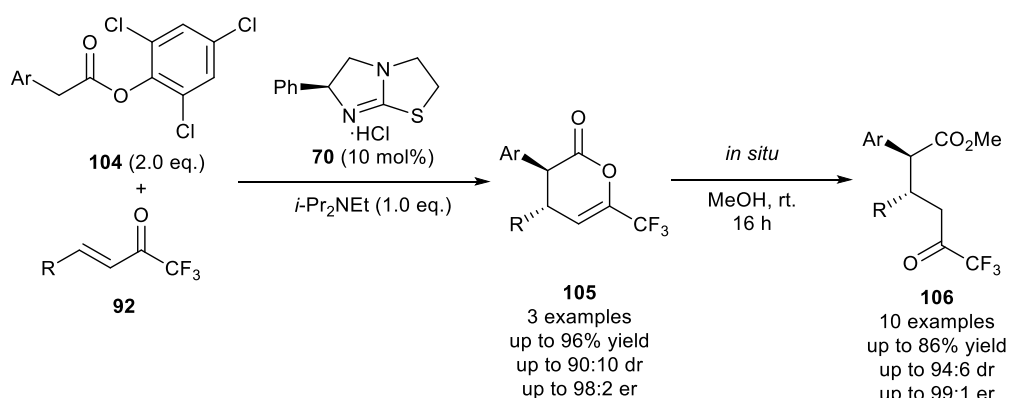


Scheme 1.22: Possible catalytic cycle for intermolecular formal [4+2]

Instead of generating a carbon-carbon bond, isothiourea catalyzed asymmetric α -amination of carboxylic acids with *N*-aryl-*N*-aroyldiazenes **101** was also demonstrated. At low catalyst loading, this procedure gave either 1,3,4-oxadiazin-6-ones **102** in good yield and excellent enantioselectivity. Upon ring-opening and cleavage of the N-N bond using Sml_2 , enantioenriched α -amino acid derivatives **103** could be obtained in overall good yield with no erosion in the enantioselectivity (Scheme 1.23).⁶¹

Scheme 1.23: Isothiourea catalyzed asymmetric α -amination

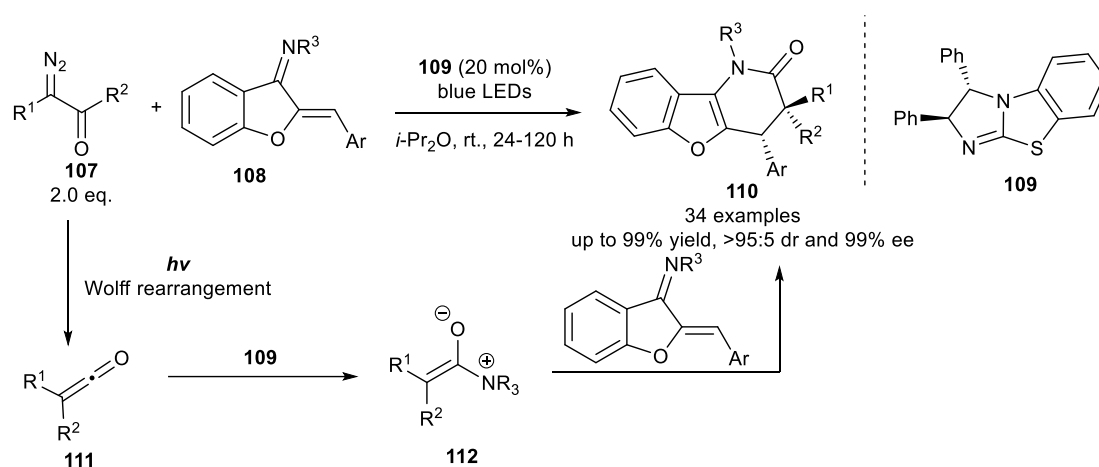
To avoid both the difficulties in removing the side product (mostly pivalic anhydride) generated using the *in-situ* activation strategy with pivaloyl chloride and $i\text{-Pr}_2\text{NEt}$, as well as the use of excess reagents, pre-formed acyl transfer agents, such as homoanhydrides **78** and acyl imidazoles **79**, have been used as the C1-ammonium enolate precursors instead of carboxylic acids. However, the first species formally require the use of two equivalents carboxylic acids, while the latter species require a high catalyst loading (20 mol%) and longer reaction times. Recently, the use of aryl esters as the bench-stable C1-ammonium enolate precursors in asymmetric Michael addition-lactonization reaction was developed. This strategy allows the use of electron-deficient aryl esters, such as 2,4,6-trichlorophenyl esters **104**, with the HCl salt of the isothiourea catalyst **70**, to access 6-membered lactones **105** and their ring-opening derivatives **106** in excellent yield, good diastereoselectivity and excellent enantioselectivity (Scheme 1.24).⁵⁰



Scheme 1.24: Bench-stable aryl esters in Michael addition-lactonization

Besides commonly encountered C1-ammonium enolate precursors described above, the use of α -diazoketones **107** were also explored. In recent work published by Song, a sequential photoactivation/isothiourea catalyzed Michael addition-lactamization was developed

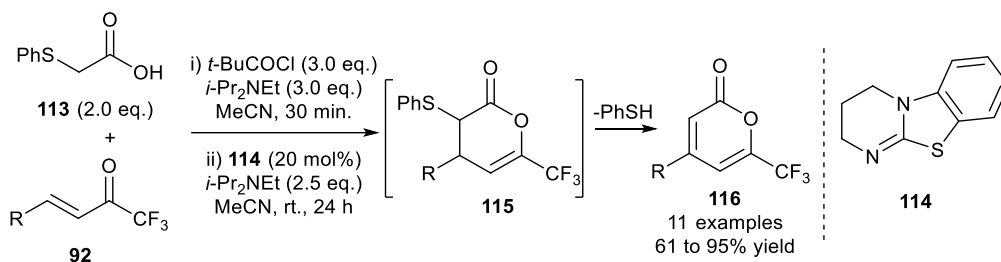
(Scheme 1.25). In the presence of isothiurea catalyst **109**, light-induced Wolff rearrangement of α -diazoketones **107** afforded the corresponding disubstituted C1-ammonium enolates **112** via ketenes **111**. Subsequent Michael addition with auronederived α,β -unsaturated imines followed by lactamization afforded the tricyclic lactams **110** in excellent yield and with excellent diastereo- and enantioselectivity.⁶² By merging visible-light chemistry with isothiurea catalysis, this procedure solved the reactivity problems with disubstitution on traditional C1-ammonium enolate precursors **76-79**, and enabled access to the 6-membered dihydropyridone **110** with quaternary stereocentre.



Scheme 1.25: Michael addition-lactonization with α -diazoketones

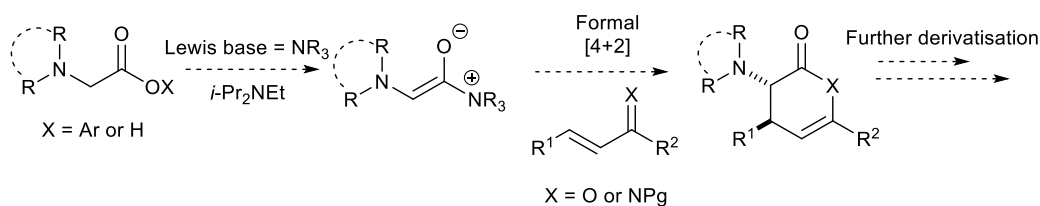
1.7. Aims and objectives

This chapter highlights the importance of modern development of organocatalysis in synthetic organic chemistry. Among the four common types of organocatalysts, Lewis base organocatalysts have been extensively utilized to perform catalytic enantioselective transformations, such as ammonium enolate chemistry and formal [4+2] cycloadditions.⁴⁶ Despite all the efforts so far, the scope of this formal [4+2] cycloaddition process has been limited by the nature of the carbon-based substituents that could be installed on the ammonium enolate precursors, with aryl and alkenyl substituents extensively demonstrated in intermolecular processes at the onset of this thesis. Only the thiophenyl group has been successfully incorporated into ammonium enolate precursors to access dihydropyranone **115**, but leads to a facile base-promoted elimination to afford trifluoromethyl substituted 2-pyrones **116** in good to excellent yield (Scheme 1.26).⁶³

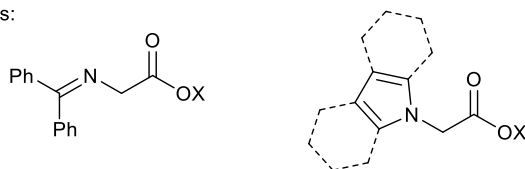


Scheme 1.26: Incorporation of thiophenyl into formal [4+2] cycloaddition

This thesis aims to broaden the scope of ITU-catalyzed enantioselective formal [4+2] cycloadditions by employing novel substituents onto ammonium enolate precursors. Efforts will focus on designing and evaluating nitrogen-based substituents to synthesize enantioenriched unnatural α -amino acid derivatives (Scheme 1.27), with subsequent derivatization using the chemistry of nitrogen-based substituents to afford synthetically useful building blocks.



Potential substrates:



Scheme 1.27: Proposed formal [4+2] cycloaddition with nitrogen-based enolate precursors

1.8. References

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Chapter 2: Glycine-derived Schiff bases in formal [4+2] cycloadditions

2.1. Overview

Unnatural α -amino acids are attracting more attention in modern drug design not only because of their biological activities, but also due to their role as probes in studying bioactive transformations of peptides, and the mechanisms underlying enzymatic transformations.¹ Examples of potential drug candidates containing unnatural α -amino acid groups include Atazanavir (a highly active azapeptide inhibitor of the HIV protease)² and Tuftsin (a macrophage/microglial activator)³ (Fig. 2.1).

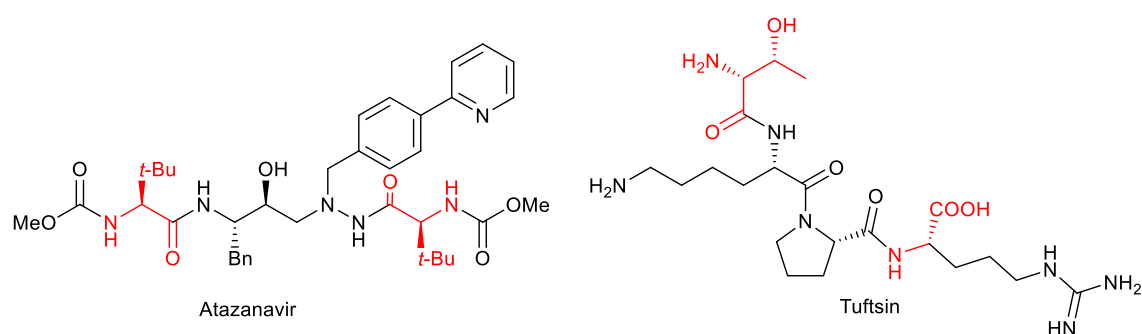
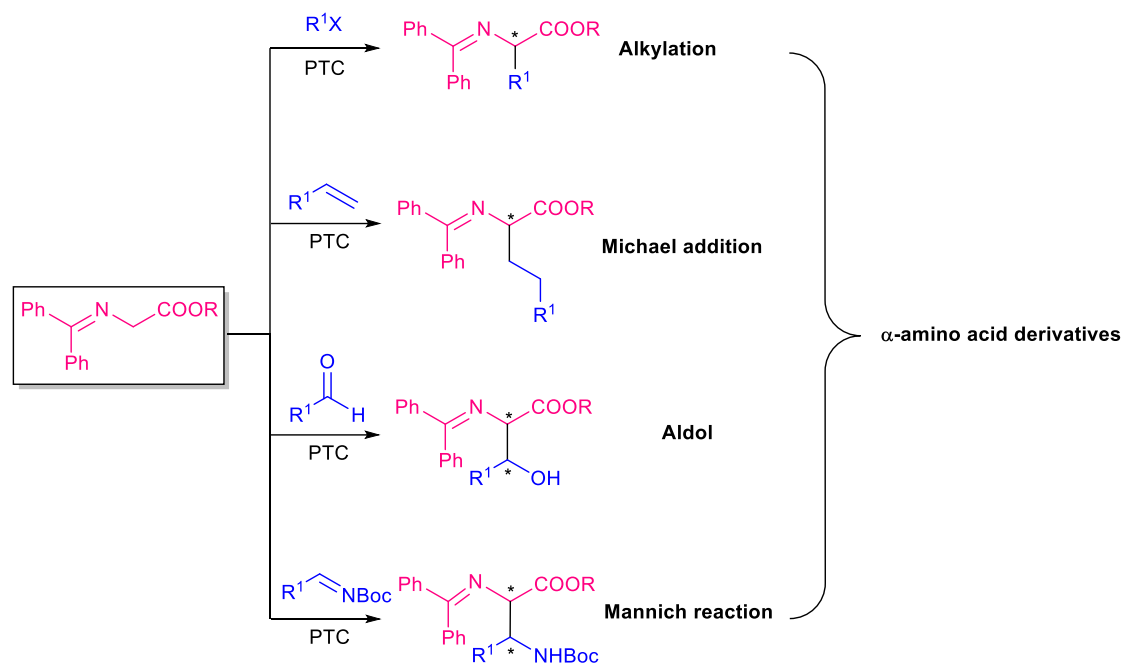


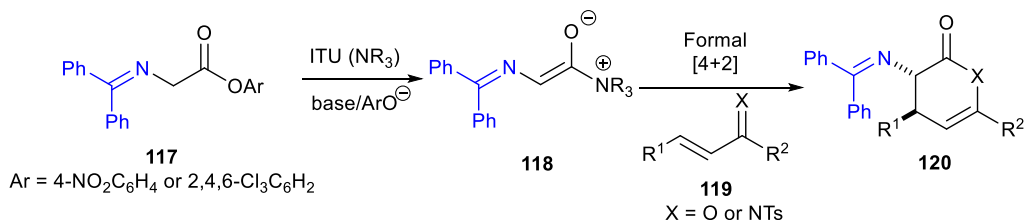
Fig. 2.1: Structure of potential drug candidates

The increasing demand for unnatural α -amino acids has made it necessary to develop new methodologies to access them particularly in enantio-pure form. Historically, glycine esters protected as benzophenone Schiff bases have frequently been used as equivalents of α -anionic amino acids in asymmetric synthesis.⁴ The benzophenone-derived imines of glycine esters were first applied in the catalytic phase-transfer alkylations to make amino acid derivatives by O'Donnell in 1978.⁵ Since then, a wide variety of methods to access enantiopure α -amino acid derivatives have been developed using this class of substrates, including phase transfer catalyzed alkylations,⁶⁻⁸ Michael,⁹⁻¹⁴ aldol,^{15,16} and Mannich¹⁷⁻²⁰ reactions (Scheme 2.1).



Scheme 2.1: Reactions of Schiff base imine of glycine esters²¹

Building upon the precedent for α -functionalization of Schiff base imines of glycine esters, this chapter will focus on expanding the reactivity to include isothiurea-catalyzed Michael addition-lactonization reactions between glycine aryl esters **117** and Michael acceptors **118** (Scheme **2.2**).



Scheme 2.2: Isothiurea catalyzed formal [4+2] with Schiff base imines

2.2. Choice and synthesis of enolate precursors

As suggested by previous computational and mechanistic studies, the leaving group from ammonium enolate precursor not only initiates the catalytic cycle with Lewis base catalysis, but also deprotonates the *N*-acyl ammonium intermediate.²² In the case of acid-labile Schiff base imines, alternative ammonium enolate precursors other than carboxylic acids need to be considered. Historically, electron poor aryl esters have been successfully applied as effective acylating agents²³ and been evaluated as C1-ammonium and azolium enolate precursors.^{24,25} Following previous experience of using bench-stable aryl esters as C1-ammonium enolate

precursors (Scheme 1.24),²⁶ both *para*-nitrophenol (PNP) and 2,4,6-trichlorophenol (TCP) esters were selected as potential substrates to be tested in catalytic transformations using Lewis basic isothioureas (Fig. 2.2).

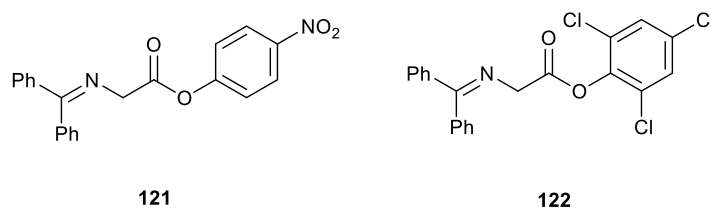
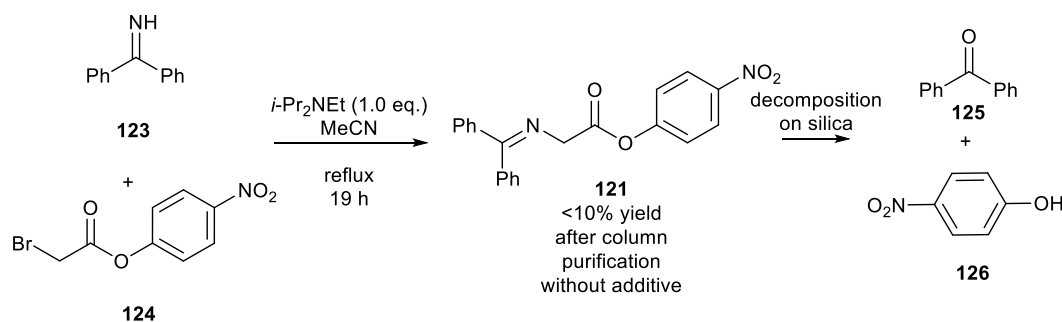


Fig. 2.2: Suggested glycine-derived Schiff base esters

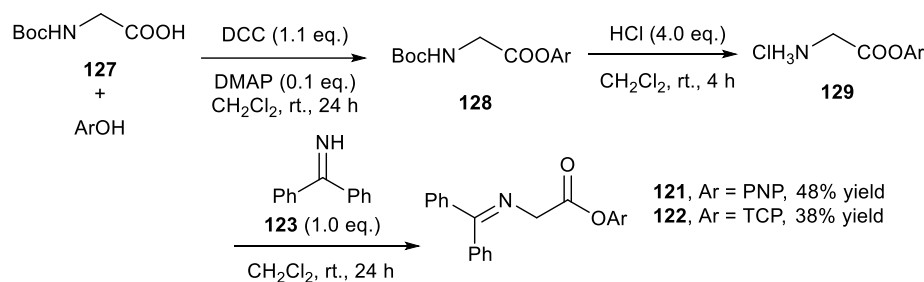
Initial attempts towards the synthesis of PNP ester benzophenone Schiff base using PNP bromoacetate **124** and benzophenone imine **123** under reflux conditions in MeCN gave full conversion to imine ester **121** (as determined by ¹H NMR analysis of crude mixture). However, less than 10% yield was isolated after purification by flash column chromatography, with decomposition products benzophenone **125** and *para*-nitrophenol **126** isolated (Scheme 2.3).²⁷ Using eluents containing 1% Et₃N as an additive still led to full decomposition of the product **121**. This suggested that **121** is not only unstable under acidic conditions, but also potentially incompatible with the non-nucleophilic base triethylamine. With purification proving difficult, alternative routes to synthesize **121** were sought that would avoid flash chromatography.



Scheme 2.3: Initial attempts on the synthesis of **121**

A successful procedure in synthesizing various aromatic Schiff base esters was reported by the Pan Group in 2014.²⁸ This three-step procedure proceeds through initial DCC-mediated esterification of *N*-Boc-protected glycine **127**, followed by Boc-deprotection using HCl to give glycine aryl esters **129** as their hydrochloride salts. Final transimination with benzophenone imine **123** affords the corresponding glycine aryl esters, which are readily separated from the

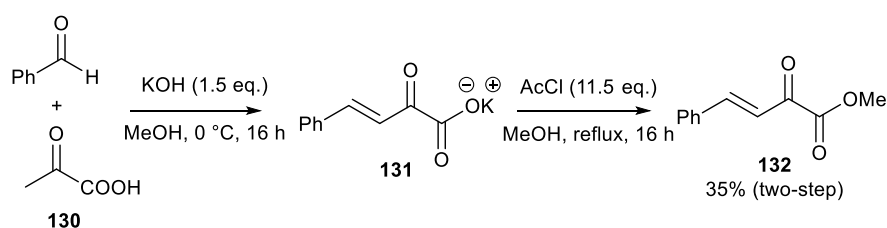
solid ammonium chloride side product via filtration (Scheme 2.4). Following this procedure, PNP ester Schiff base **121** was isolated, after trituration with ether to wash off any PNP and benzophenone impurities, as white needles in 48% yield over three steps. However, TCP ester Schiff base **122** has similar solubility in ether compared with benzophenone impurity, so had to be purified by column chromatography giving the product with 38% yield over three steps.



Scheme 2.4: Improved synthetic procedure

2.3. Formal [4+2] cycloadditions with α -keto- β,γ -unsaturated esters

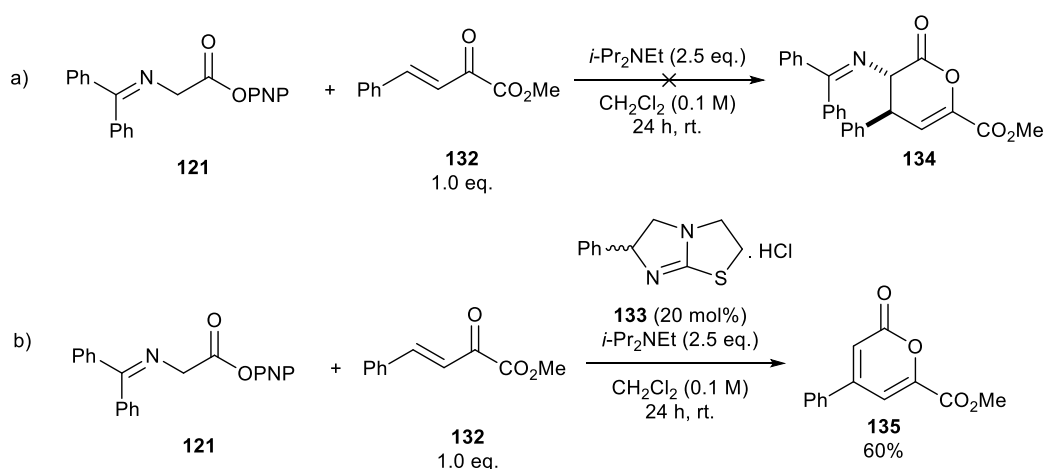
With the required substrates in hand, attention was turned to evaluating a model isothioureacatalyzed Michael addition-lactonization. α -Keto- β,γ -unsaturated ester was selected as a model Michael acceptor because it serves as a highly reactive electron deficient 4π system in formal [4+2] cycloadditions.²⁹ It was synthesized in a simple two-step procedure, starting with the base-mediated aldol reaction between benzaldehyde and pyruvic acid **130** to afford potassium salt **131**. Methylation with MeOH and acetyl chloride gave the desired ester **132** in 35% yield over two-steps (Scheme 2.5).



Scheme 2.5: Synthesis of Michael acceptors **132**

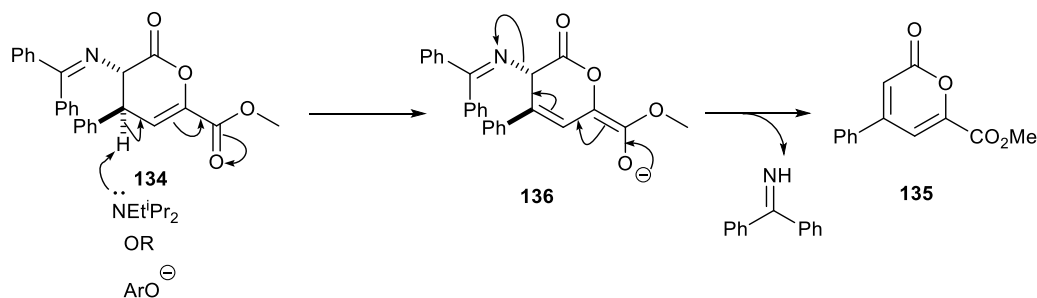
The formal [4+2] cycloadditions were then tested using keto-ester **132** and racemic ITU catalysts. An initial control experiment using *i*-Pr₂NEt as base without any isothioureacatalyst showed no observable conversion, returning the PNP ester starting material **121** and the Michael acceptor **132** (Scheme 2.6 (a)). However, using 20 mol% tetramisole hydrochloride **133** as the catalyst, PNP ester **121** was fully consumed within 24 hours, but the desired product **134** could not be found upon ¹H NMR analysis of the crude material. Instead, compound **135**

was found to be the only product that was isolated in 60% yield (Scheme 2.6 (b)), suggesting complete elimination of the imine functionality from the proposed lactone product **134**.



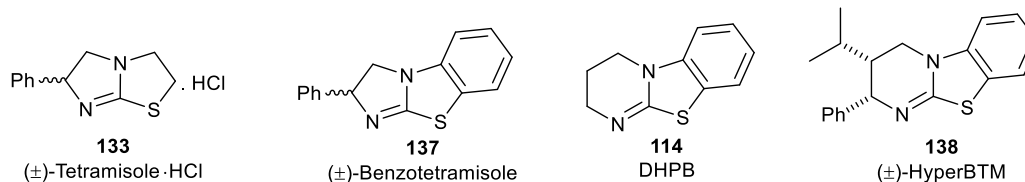
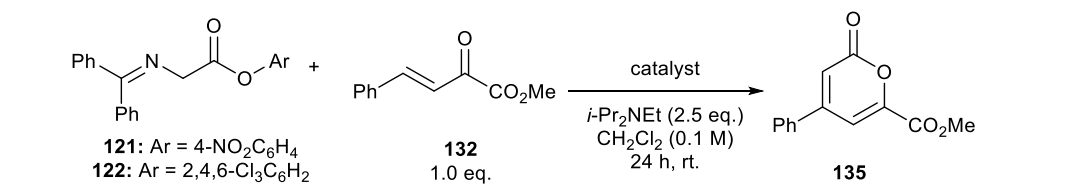
Scheme 2.6: Initial proof of concept study

A possible elimination pathway for the benzophenone imine is proposed, assuming initial Michael addition/lactonization of the ammonium enolate and enone to give **134** (Scheme 2.7). Deprotonation at C(4) leads to the intermediate **136**, with subsequent elimination of the benzophenone imine generating the final product **135**. The eliminated imine is further hydrolyzed to benzophenone and NH_3 upon aqueous work-up.



Scheme 2.7: Possible elimination pathway for the Schiff base imine

Several attempts were made to avoid the formation of this elimination product (Table 2.1). Lower catalyst loading resulted in a decrease in the isolated yield of **135** (entry 1-2). Carrying out the reaction at -78°C with 10 mol% catalyst loading did not prevent the elimination from happening, with **135** isolated in 45% yield (entry 3). Changing the catalyst from tetramisole hydrochloride **133** to either benzotetramisole, DHPB or HyperBTM still resulted in the isolation of **135** (entry 4-6). A final test reaction with TCP ester **122** and tetramisole hydrochloride **133** also gave **135** in 38% yield (entry 7).



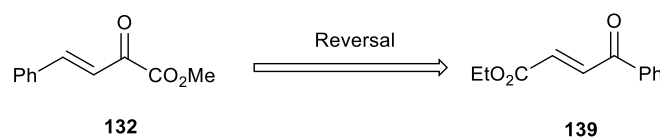
Entry	Ar	Temp.	Catalyst (loading)	Yield of 135*
1	121	rt.	133 (10 mol%)	51%
2	121	rt.	133 (5 mol%)	34%
3	121	-78 °C	133 (10 mol%)	45%
4	121	rt.	137 (10 mol%)	20%
5	121	rt.	114 (10 mol%)	49%
6	121	rt.	138 (10 mol%)	44%
7	122	rt.	133 (10 mol%)	38%

*Isolated yield.

Table 2.1: Reaction condition screening of Michael acceptor 132

2.4. Formal [4+2] cycloadditions with electron deficient ketones

Given the potential problems observed in the elimination of the Schiff base lactone **134**, we decided to investigate if reversing the position of the phenyl and ester functionalities would lead to different products (Scheme 2.8). Enone **139** is commercially available and has been successfully applied by Ye and co-workers in NHC-catalyzed formal [4+2] cycloadditions.³⁰

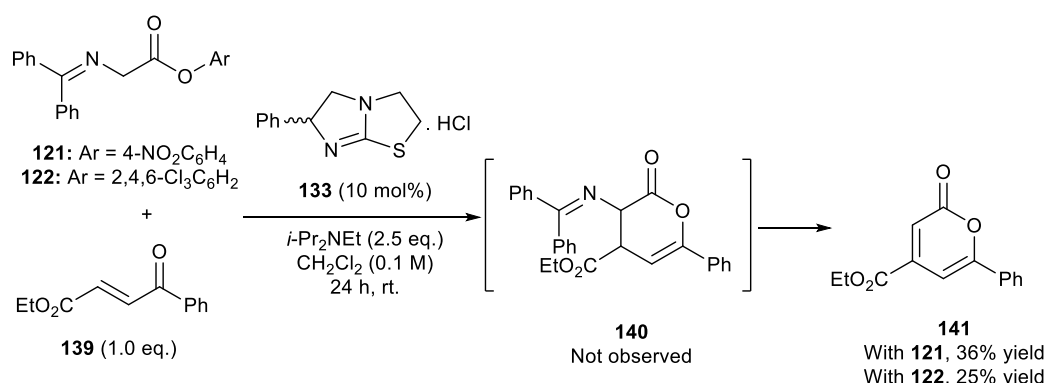


Scheme 2.8: Proposed Michael acceptor

2.4.1. Reactivity with β-ester enone

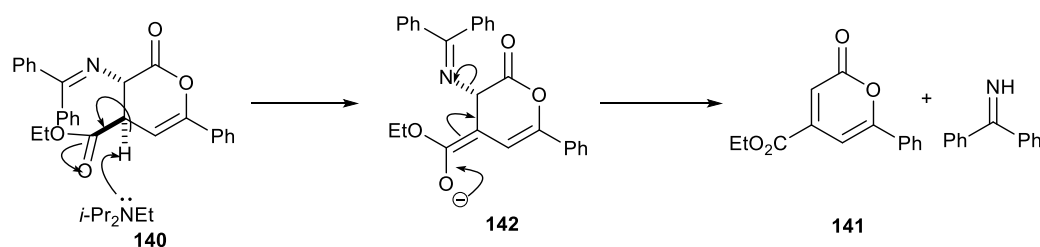
Under our catalytic conditions using **133**, enone **139** did not lead to the formation of the desired Schiff base lactone **140** according to the ¹H NMR analysis of the crude reaction mixture.

Instead, elimination of the imine was again observed, with substituted pyranone **141** isolated in 36% and 25% yield from PNP ester **121** and TCP ester **122** respectively (Scheme 2.9).



Scheme 2.9: Test reactions with ketoenone

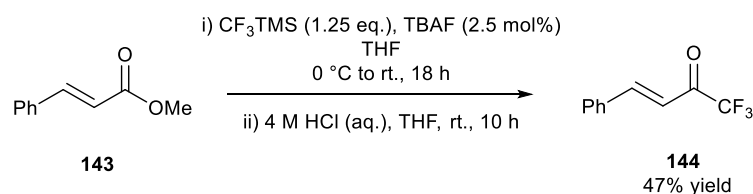
In this case, an E1cB mechanism is proposed to explain the formation of **141**, again assuming initial Michael addition-lactonization of the enolate and enone (Scheme 2.10).



Scheme 2.10: Mechanistic explanations for the elimination process

2.4.2. Reactivity with trifluoromethyl enones

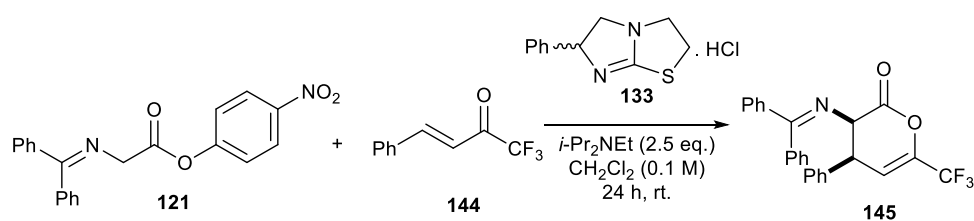
To reduce the risk of possible elimination, further studies used trifluoromethyl enones as these Michael acceptors have been successfully applied in a wide range of formal cycloadditions involving either ITU or NHC redox catalysis.^{31,32} CF₃ enone Michael acceptor was synthesized via a one-step procedure published by Pedro.³³ Reaction of commercially available α,β -unsaturated methyl ester **143** with trifluoromethyltrimethylsilane, followed by acidic hydrolysis, gave the desired enone **144** in 47% yield (Scheme 2.11).



Scheme 2.11: Synthesis of trifluoromethyl enone

2.4.2.1. Base-mediated Michael addition-lactonizations

With the CF₃ enone **144** in hand, the formal cycloadditions were attempted using racemic tetramisole hydrochloride catalyst **133** with PNP ester **121** (Table 2.2). At room temperature with 20 mol% catalyst loading and 2.5 equivalents of *i*-Pr₂NEt, full consumption of the trifluoromethyl enone **144** was observed, and the desired lactone product **145** observed in 52:48 dr (*syn:anti*) (determined by ¹H NMR analysis of the crude material), although the isolated yield for the lactone **145** was only moderate (40%) (entry **1**). No elimination product was identified in the crude reaction mixture, consistent with our hypothesis that switching to the trifluoromethyl group would prevent unwanted elimination. The catalytic reaction was then screened using different catalyst loadings at room temperature (15 mol% and 10 mol%) (entry **2-3**). An overall incomplete conversion of CF₃ enone was detected by TLC analysis of the reaction mixture after 24 h with lower catalyst loadings, giving isolated yields of 25% and 10% respectively. Meanwhile, consistently low diastereoselectivity (dr close to 50:50) was observed for the catalytic transformations performed at room temperature. To probe this, a control experiment in the absence of catalyst but using *i*-Pr₂NEt was performed, showing about 30% conversion of enone **144** into the lactone product **145** with a dr. of 74:26 (*syn:anti*) and an isolated yield of 14% (entry **4**). This is consistent with a base-mediated background reaction at room temperature in CH₂Cl₂ and may contribute to the observed low diastereoselectivity in entries **1-3**.

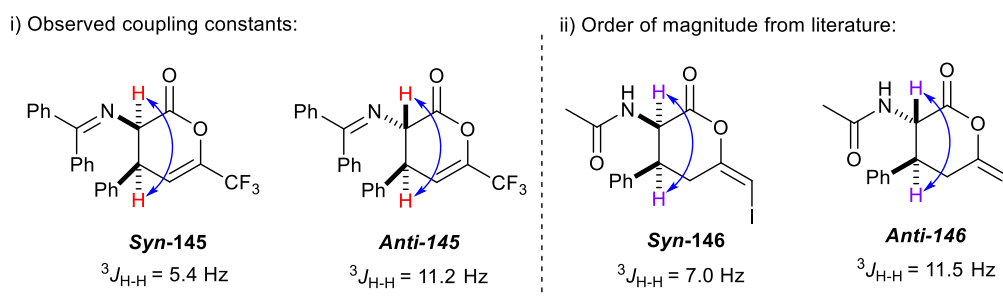


Entry	Catalyst loading	d.r. (<i>syn:anti</i>)*	Yield**
1	20 mol%	52:48	40%
2	15 mol%	56:44	25%
3	10 mol%	55:45	10%
4	None	74:26	14%

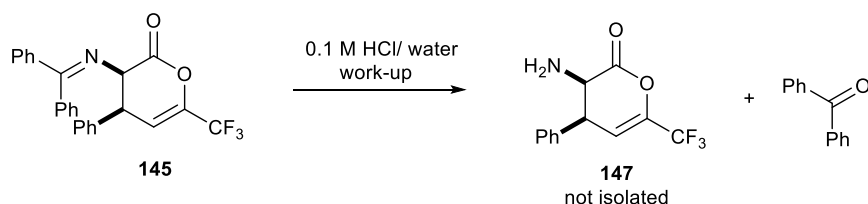
*Ratio determined from ¹H NMR of crude reaction mixture **Yield refers to isolated yield of the combined diastereoisomers.

Table 2.2: Proof of concept study with CF₃ enone

The relative configuration of the [4+2] cycloaddition lactone product was assigned by comparing the observed coupling constants to those of similar δ -lactones **146** reported in the literature (Fig. 2.3). When the protons attached to C(3) and C(4) are *syn*- to each other, a literature coupling constant of 7.0 Hz was reported for *syn*-**146**,³⁴ while a similar coupling constant of 5.4 Hz was observed for one of the diastereoisomers of **145**; this was therefore assigned as the *syn*-diastereoisomer. Likewise, a coupling constant of 11.5 Hz was reported in the literature for *anti*-**146**,³⁴ which is consistent with the observed coupling constant of 11.2 Hz for the other diastereoisomer, assigned as *anti*-**145**.

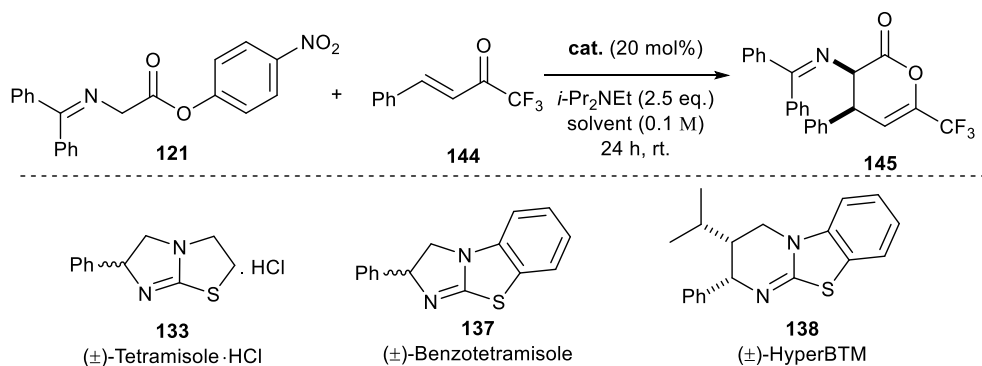
**Fig. 2.3: Assigning the relative stereochemistry**

It was noticed that upon treating the crude with typical work-up procedure (0.1 M HCl or water), hydrolysis of the imine occurred, leading to the detection of benzophenone in the crude material. Benzophenone could also be released in the process of flash column chromatography, due to instability in the presence of slightly acidic silica gel. Both hydrolysis processes would give the lactone product **147** with a free amine group. The observed low isolation yield could be explained by **147** remaining either in the aqueous layer during work-up, or on the silica gel during column chromatography (Scheme 2.12).

**Scheme 2.12: Possible explanation for low isolation yield**

To avoid the problem of hydrolyzing the imine motif in **145**, the crude reaction mixture from entry **1** (Table 2.2) was quickly passed through a silica column after removing the solvent. The

filtrate showed a greatly reduced amount of benzophenone. Upon purification by column chromatography, a slightly improved isolated product yield of 52% was obtained. Encouraged by the improved result, this new procedure was used in all subsequent catalytic transformations below to record the isolated yield. In an attempt to improve diastereoselectivity, a solvent and catalyst screening were performed, and NMR yield (by using 1,4-dinitrobenzene as the internal standard) was taken into consideration to avoid inaccurate results caused by decomposition during column chromatography (Table 2.3). Dichloromethane gave 60% NMR yield and low 52:48 dr with tetramisole **133** (entry 1). Changing the solvent from dichloromethane to either toluene or MeCN did not show any improvement in the diastereoselectivity, but the NMR yield dropped to 55% and 50% respectively (entry 2 and 3). An increased diastereoselectivity of 70:30 was noticed when changing the solvent to THF, but a poor NMR yield of 20% was observed (entry 4). With benzotetramisole **137** as the catalyst in CH₂Cl₂, NMR yield increased to 68%, but the diastereoselectivity remained similarly low (45:55) (entry 5). While HyperBTM **138** showed a reduced NMR yield of 45%, a slight increase in the dr to 66:34 was observed (entry 6).

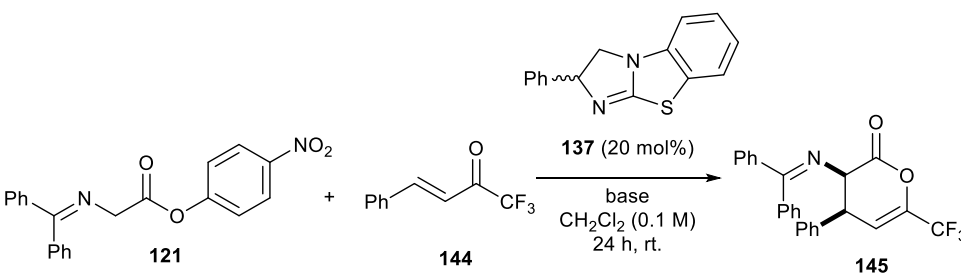


Entry	Catalyst	Solvent	d.r. (<i>syn:anti</i>)*	NMR Yield**
1	133	CH ₂ Cl ₂	52:48	60%
2	133	Toluene	54:46	55%
3	133	MeCN	57:43	50%
4	133	THF	70:30	20%
5	137	CH ₂ Cl ₂	45:55	68%
6	138	CH ₂ Cl ₂	66:34	45%

*Ratio determined from ¹H NMR of reaction mixture. **Yield from ¹H NMR using 1,4-dinitrobenzene as the internal standard.

Table 2.3: Solvent and catalyst screening

Using benzotetramisole **137** in dichloromethane, the effect of the auxiliary base was explored (Table 2.4). When reducing the amount of *i*-Pr₂NEt from 2.5 to 1.0 eq., NMR yield increased to 78%, however the diastereoselectivity still remained the same at 48:52 (entry 2). 2,6-Lutidine gave a slight improvement in both diastereoselectivity to 38:62 and NMR yield to 77% (entry 3). Satisfyingly, pyridine also gave the lactone **145** in 20:80 dr., together with an NMR yield of 68% (entry 4).

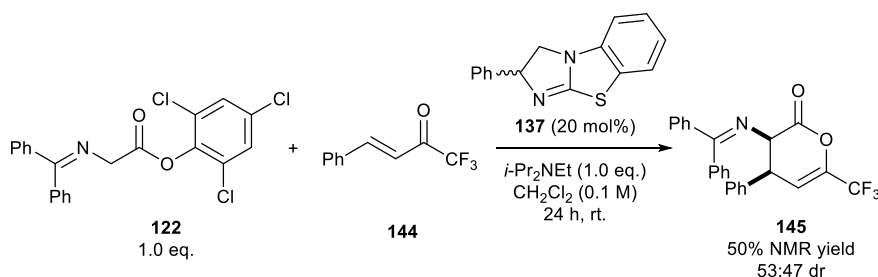


Entry	Base	Equivalents	d.r. (<i>syn:anti</i>)*	NMR Yield**
1	<i>i</i> -Pr ₂ NEt	2.5	45:55	68%
2	<i>i</i> -Pr ₂ NEt	1.0	48:52	78%
3	2,6-lutidine	1.0	38:62	77%
4	pyridine	1.0	20:80	68%

*Ratio determined from ¹H NMR of reaction mixture. **Yield from ¹H NMR using 1,4-dinitrobenzene as the internal standard.

Table 2.4: Base Optimization

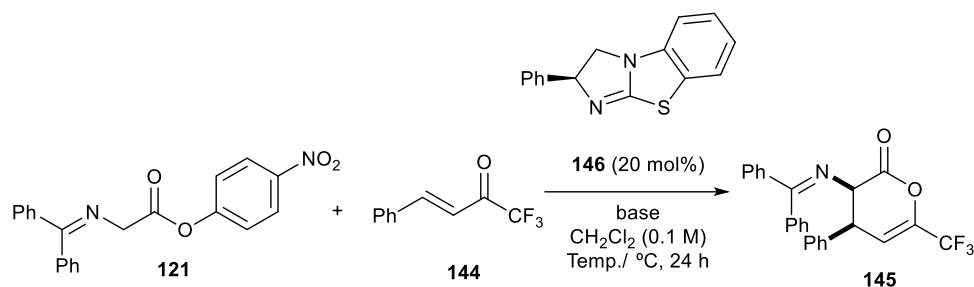
Trichlorophenyl ester **122** was also tested using 1 equivalent *i*-Pr₂NEt and 20 mol% benzotetramisole catalyst **137**. A good NMR yield of 50%, but poor diastereoselectivity of 53:47 was observed (Scheme 2.13).



Scheme 2.13: Reactivity with trichlorophenyl ester **122**

With the racemic reaction giving a good NMR yield albeit with a variable degree of diastereoselectivity, the enantioselectivity of this reaction was explored. At room temperature with 1 equivalent of 2,6-lutidine as a base, high NMR yield of 74% was obtained along with a

moderate dr of 38:62 but a poor er of 48:52 (Table 2.5, entry 1). Pyridine gave similar diastereoselectivity of 20:80 dr, 66% NMR yield and similar er of 54:46 (entry 2). Similar to pyridine and lutidine, 2.5 equivalents of *i*-Pr₂NEt also gave a poor enantioselectivity of 53:47 er with a good NMR yield of 67% (entry 3). A significant increase in er for both diastereoisomers to 71:29 was observed when 1.0 equivalent of *i*-Pr₂NEt was employed (entry 4). Lowering the reaction temperature to 0 °C slightly improved the dr to 62:38 (entry 5). However, the NMR yield dropped to 60% and the er was maintained at 72:28. Further lowering the reaction temperature to -78 °C showed an improved er to 78:22 and an improved dr of 75:25, but the NMR yield dropped significantly to 53% (entry 6).



Entry	Base (eq.)	Temp.	d.r. (<i>syn:anti</i>)*	NMR Yield**	er***
1	2,6-lutidine (1.0)	rt.	38:62	74% (45%)	48:52 (<i>anti</i>) 48:52 (<i>syn</i>)
2	Pyridine (1.0)	rt.	20:80	66% (37%)	49:51 (<i>anti</i>) 54:46 (<i>syn</i>)
3	<i>i</i> -Pr ₂ NEt (2.5)	rt.	45:55	67% (34%)	53:47 (<i>anti</i>) 53:47 (<i>syn</i>)
4	<i>i</i> -Pr ₂ NEt (1.0)	rt.	48:52	78% (37%)	71:29 (<i>anti</i>) 73:27 (<i>syn</i>)
5	<i>i</i> -Pr ₂ NEt (1.0)	0 °C	62:38	60% (20%)	72:28 (<i>anti</i>) 72:28 (<i>syn</i>)
6	<i>i</i> -Pr ₂ NEt (1.0)	-78 °C	75:25	53% (15%)	75:25 (<i>anti</i>) 78:22 (<i>syn</i>)

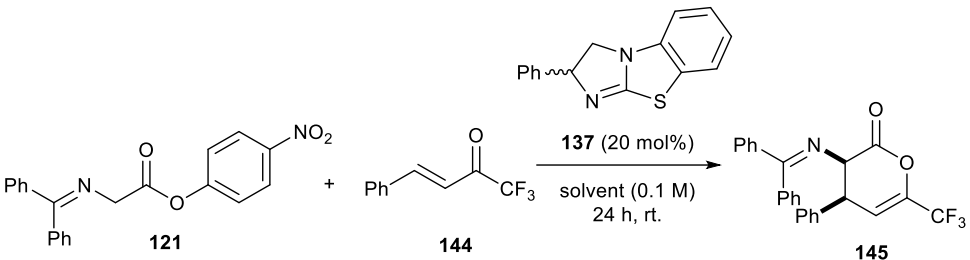
*Ratio determined from ¹H NMR of reaction mixture. **Yield from ¹H NMR using 1,4-dinitrobenzene as the internal standard, isolated yield in parentheses. ***Determined from chiral HPLC analysis of a mixture of dr.

Table 2.5: Screening on conditions with chiral catalyst

2.4.2.2. Base-free Michael addition-lactonizations

With the publication of a recent paper exploring the use of aryloxide as the base in C1-ammonium enolate chemistry,³⁵ the same idea was applied into the Michael addition-

lactonization reactivity with substrate **121**. At room temperature and using racemic BTM **137**, polar aprotic solvents DMF, MeCN and isopropyl acetate gave nearly quantitative NMR yield with 1 equivalent aryl ester **121**, but the diastereoselectivity was close to 50:50 (Table **2.6**, entry **1-3**). When switching to a relatively non-polar solvent CH₂Cl₂, a dr of 17:83 was observed for **145**, favouring the *anti*-diastereomer (entry **4**). To push the conversion, 2.0 equivalents of aryl ester **121** were employed, leading to an NMR yield of 75% and a similar diastereoselectivity of 15:85 (entry **6**).

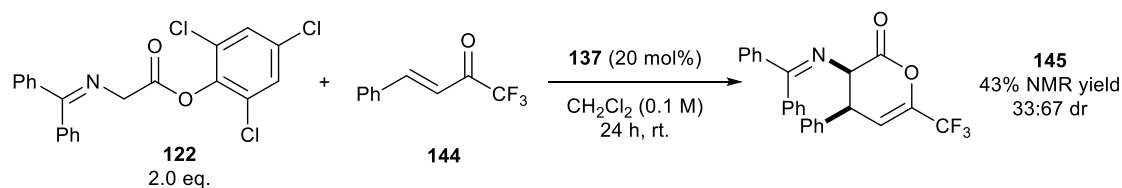


Entry	Eq. of 121	Solvent	d.r. (<i>syn:anti</i>)*	NMR Yield**
1 [#]	1.0	DMF	45:55	>99%
2 [#]	1.0	MeCN	53:47	>99%
3 [#]	1.0	Isopropyl acetate	51:49	97%
4	1.0	CH ₂ Cl ₂	17:83	55%
5	1.5	CH ₂ Cl ₂	13:87	63%
6	2.0	CH ₂ Cl ₂	15:85	75%

*Ratio determined from ¹H NMR of reaction mixture. **Yield from ¹H NMR using 1,4-dinitrobenzene as the internal standard. [#]Reaction at 10 hours.

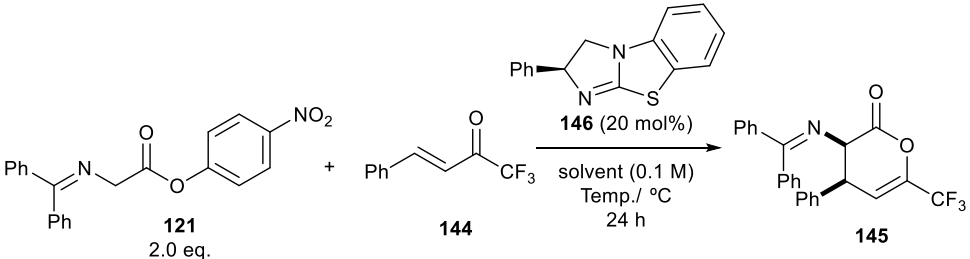
Table 2.6: Optimizations with base-free process

Next, the same base-free reactivity was investigated with TCP ester **122**. Using 2 equivalents ester **122** and CH₂Cl₂ at room temperature, a much reduced reactivity of 43% NMR yield was observed with moderate dr (33:67) (Scheme **2.14**), compared with the PNP ester under the same conditions (Table **2.6**, entry **6**). Therefore, the use of TCP ester was not evaluated further.



Scheme 2.14: Base-free reaction with TCP ester

Following on the promising reactivity observed with the base-free process, the enantioselective was explored. At room temperature using CH₂Cl₂ as the solvent, a low 42:58 er was observed for the major *anti*-diastereoisomer, while the minor *syn*-diastereoisomer was racemic (49:51 er) (Table 2.7, entry 1). Interestingly, when lowering the temperature to –10 °C and –78 °C, the *syn*-diastereoisomer was favoured, and a dr of 60:40 and 66:34 was observed at –10 and –78 °C respectively (entry 2 and 3). Lowering the temperature resulted in no change in the er of *syn*-diastereoisomer (52:48), but an increase in the er of *anti*-diastereoisomer to 34:66 (entry 2). As a comparison between different solvent systems, when the reaction is performed in the polar aprotic solvent DMF at low temperature of –40 °C, a poor diastereoselectivity of close to 50:50 was still observed, with a very promising NMR yield of 98% (entry 4). Interestingly, an enantioselectivity of 87:13 er was observed for the *anti*-diastereoisomer, but a much lower er of 62:38 was noticed for the *syn*-diastereoisomer.



Entry	Solvent	Temp.	d.r. (<i>syn:anti</i>)*	NMR Yield**	er***
1	CH ₂ Cl ₂	rt.	13:87	77% (40%)	42:58 (<i>anti</i>) 49:51 (<i>syn</i>)
2	CH ₂ Cl ₂	–10 °C	60:40	64% (33%)	34:66 (<i>anti</i>) 52:48 (<i>syn</i>)
3	CH ₂ Cl ₂	–78 °C	65:35	31% (10%)	n/d.
4 [#]	DMF	–40 °C	53:47	98% (55%)	87:13 (<i>anti</i>) 62:38 (<i>syn</i>)

*Ratio determined from ¹H NMR of reaction mixture. **Yield from ¹H NMR using 1,4-dinitrobenzene as the internal standard, isolated yield in parentheses. ***Determined from chiral HPLC analysis of reaction mixture. [#]Reaction with 1.0 eq. **121** and 10 mol% **146** after 16 h.

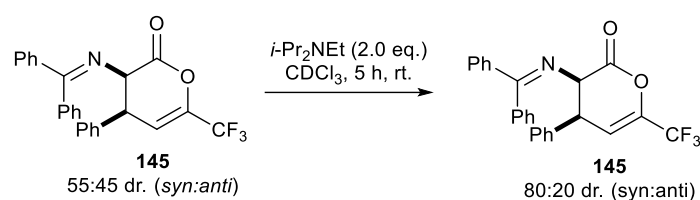
Table 2.7: Enantioselectivity for base-free reactions

In-situ derivatizations were investigated to facilitate the isolation of stable derivatives of the Michael addition-lactonization product **145**. Unfortunately, no desired product was isolated following either hydrolysis of imine with citric acid or ring-opening of the lactone with MeOH.

The former resulted in the isolation of benzophenone as the only product, and the latter gave full decomposition of the desired lactone **145** without observing any benzophenone.

2.4.2.3. Control reactions

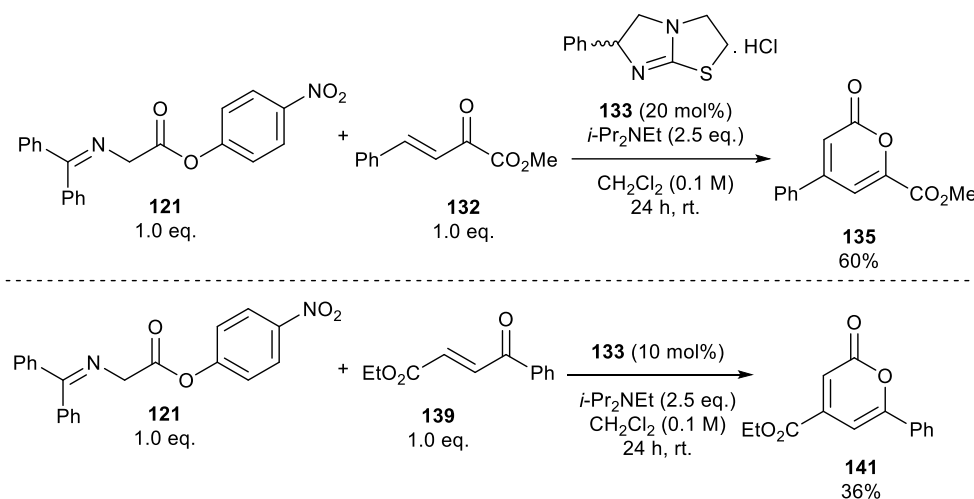
Analysis of all these results indicated that product diastereo- and enantioselectivity varied significantly with the reaction conditions, including solvent, temperature and base. The absolute configuration of the *syn*- and *anti*-diastereoisomers of the lactone **145** could not be unambiguously confirmed. Their configuration is arbitrarily assigned as direct analogy to the well-studied α -aryl acetic acid system using isothioureia catalysis could not be readily extended to the incorporation of the C(3)-imino group based upon these results.³² A simple epimerization study was carried out using isolated lactone product under basic conditions. Treatment of (\pm)-lactone product **145** (55:45 dr, *syn:anti*) with *i*-Pr₂NEt in CDCl₃ at rt gave a dr of 80:20 (*syn:anti*) after 5 h, suggesting that epimerization to favour the *syn*-diastereoisomer could occur at rt and this was favoured thermodynamically (Scheme 2.15). *In situ* epimerization may contribute to the varied results observed with this system.



Scheme 2.15: Epimerization study

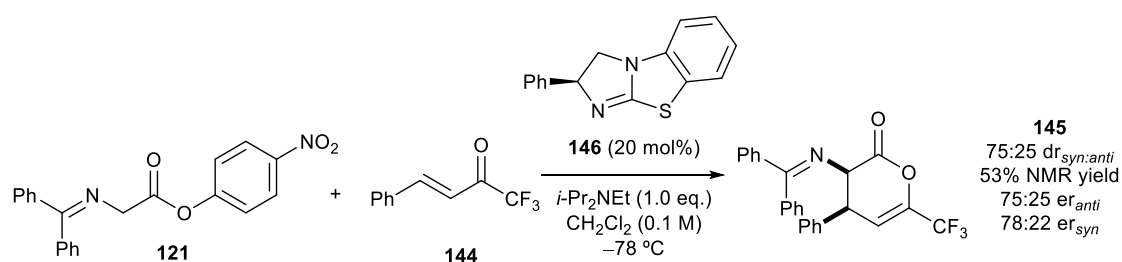
2.5. Conclusions

In this chapter, glycine derived Schiff base imines **121** and **122** were tested in isothiurea-catalyzed Michael addition-lactonization with typical electron deficient Michael acceptors. The use of either a α -keto- β,γ -unsaturated ester **132** or a β -ester- α,β -unsaturated enone **139** led to the isolation of the elimination products (**135** and **141**) in 60% and 36% yield respectively (Scheme 2.16).



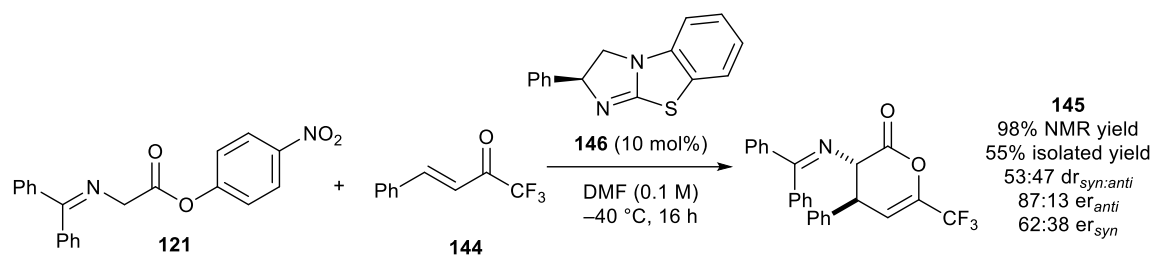
Scheme 2.16: Results with **132** and **139**

The elimination could be prevented by replacing the ester group in **132** with a trifluoromethyl group **144**. Initial screening on reaction conditions gave the lactone **145** in 75:25 dr (*syn:anti*), 53% NMR yield and 78:22 er (*syn-*) using 1 equivalent *i*-Pr₂NEt at -78 °C (Scheme 2.17).



Scheme 2.17: Result with base-mediated reaction

Additionally, a base-free protocol was developed in anhydrous DMF at -40 °C. Within 16 hours, the lactone **145** was isolated in a moderate 55% yield (98% NMR yield), 53:47 dr (*anti:syn*) and good enantioselectivity of 87:13 er for the *anti*-diastereoisomer (Scheme 2.18).

**Scheme 2.18: Base free enantioselective formal [4+2] cycloaddition**

One major drawback for this process was the difficulty associated with the isolation of the desired products and the inconsistent product *dr* and *er*. Therefore, the system has not been explored further. After proving the principle that amino esters could be α -functionalized using Lewis base catalysis, the attention was then turned into other stable nitrogen protection group of glycine esters.

2.6. References

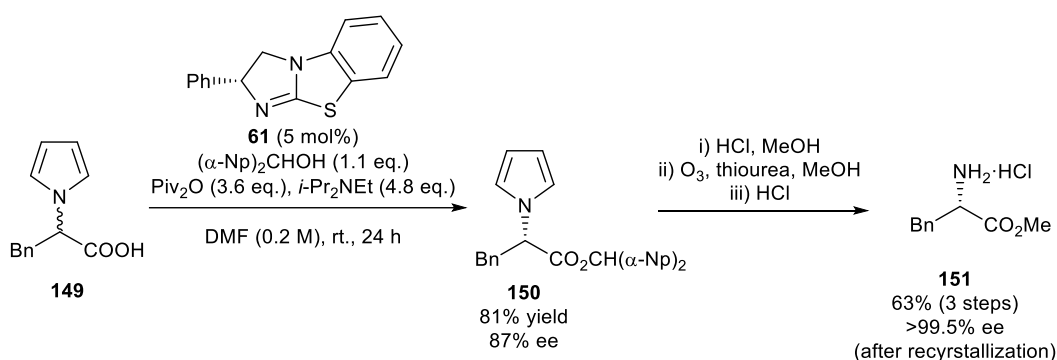
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Chapter 3: Formal [4+2] cycloadditions with trichloromethyl enones

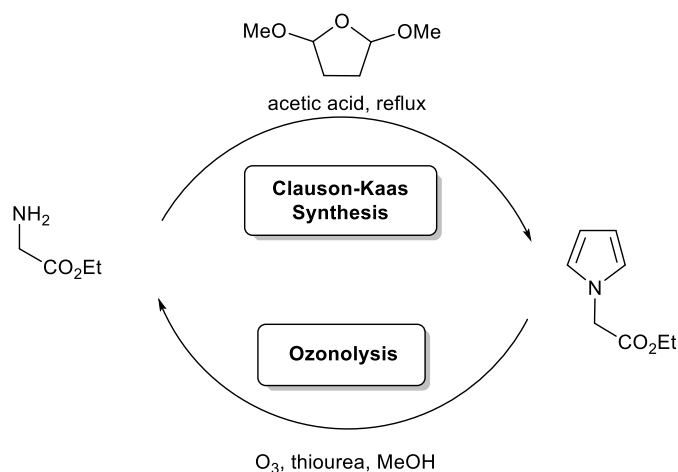
3.1. Overview

Following the investigation of α -functionalization of Schiff-base imine protected glycine esters with isothiurea catalysis in Chapter 2, attention was turned to the use of more stable N-substituents that could be incorporated into products. Recent work was published by Shiina using 2-(1H-pyrrol-1-yl)alkanoic acids **149** as α -amino acid equivalents in a BTM-catalysed dynamic kinetic resolution (DKR) to afford enantioenriched α -amino acid derivative **151** in good yield and with excellent enantioselectivity (Scheme 3.1).¹



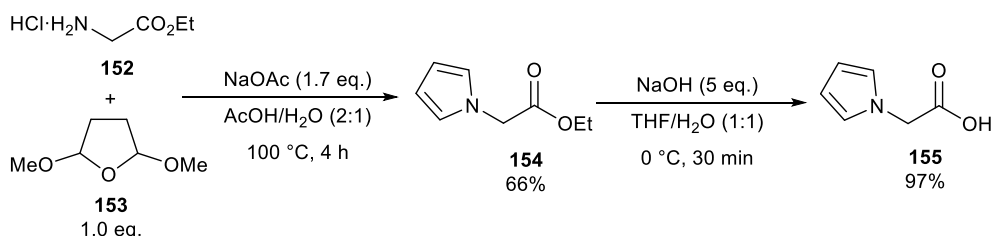
Scheme 3.1: Lewis base catalysed DKR of pyrrolyl acid 149

This N-bonded α -pyrrole substituent shares similar size and aromaticity with the corresponding α -aryl substituents that are well preceded in ammonium enolate chemistry promoted by isothiurea catalysis.² Based on the previous methodologies developed within the Smith group (Scheme 1.21), it was proposed that pyrrole-substituted glycine would be a suitable substrate to begin our study into developing a heteroatom-linked substrate for enantioselective α -functionalization with isothiurea catalysis. Facile pyrrole preparation via a Clauson-Kaas synthesis³ and chemoselective late-stage pyrrole degradation by ozonolysis^{4,5} make it an appealing protecting group (Scheme 3.2).

Scheme 3.2: Protection and deprotection of α -amino group

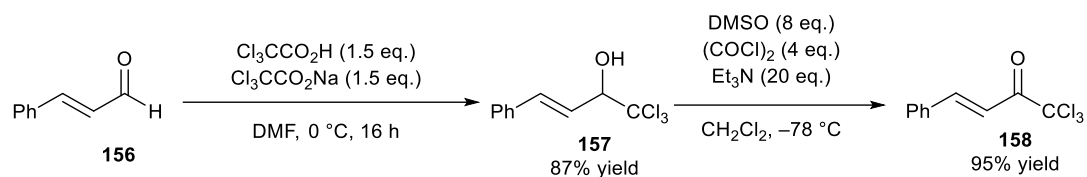
3.2. Substrates synthesis

Following a literature procedure by Taylor,⁶ a two-step synthesis of the model substrate **155** was performed. Condensation of glycine ethyl ester hydrochloride **152** and 2,5-dimethoxytetrahydrofuran **153** afforded ethyl 2-(1*H*-pyrrol-1-yl)acetate **154** in 66% good yield. Subsequent alkaline hydrolysis with NaOH in THF and water gave the target 2-(1*H*-pyrrol-1-yl)acetic acid **155** in 97% yield as a bench-stable white solid (Scheme 3.3).



Scheme 3.3: Synthesis of pyrrole acetic acid

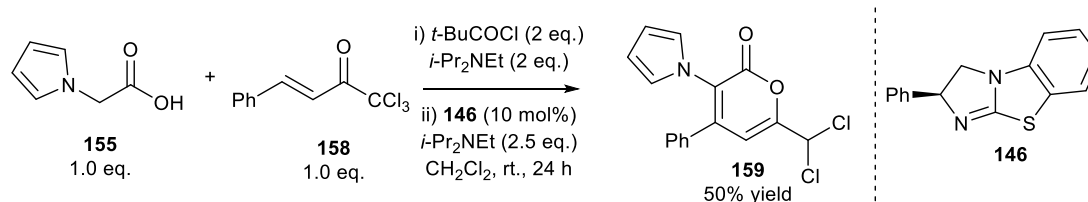
In order to evaluate the behaviour of this 2-(1*H*-pyrrol-1-yl)acetic acid **155** in a model Michael addition-lactonization, trichloromethyl enone **158** was initially used. An established two-step synthetic procedure towards the enone **158** was used as a starting point for the investigations.⁷ Beginning from cinnamyl aldehyde **156**, trichloromethyl carbinol **157** was synthesized using trichloroacetic acid and sodium trichloroacetate in DMF. Purification by column chromatography gave allylic alcohol **157** in 87% yield. Swern oxidation gave the corresponding enone **158** in 95% isolated yield as a bench-stable solid (Scheme 3.4).⁸

Scheme 3.4: Synthetic route towards trichloromethyl enone **158**

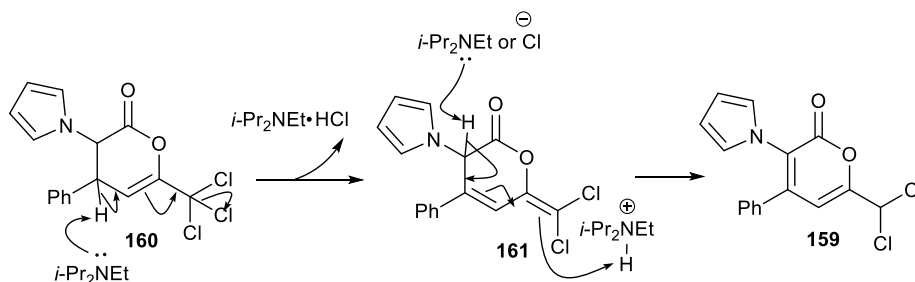
3.3. Evaluating the reactivity of 2-(1*H*-pyrrol-1-yl)acetic acid

3.3.1. Reaction conditions optimization

A mixed anhydride was generated in situ from 2-(1*H*-pyrrol-1-yl)acetic acid **155** and pivaloyl chloride, then BTM **146**, *i*-Pr₂NEt and Michael acceptor **158** were added. The reaction was stirred at room temperature in CH₂Cl₂ and monitored by TLC until complete consumption of the Michael acceptor was observed. Unfortunately, this reaction led to the exclusive formation of the pyranone **159**, which was isolated in 50% yield (Scheme 3.5).

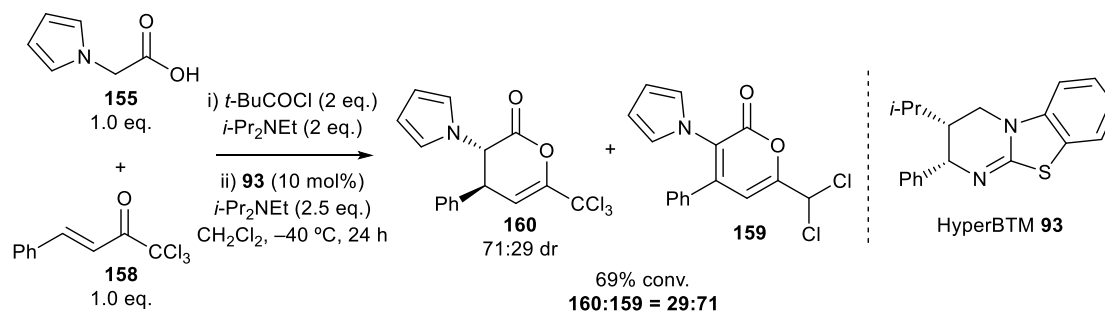
Scheme 3.5: Initial reactivity test with trichloromethyl enone **158**

The unexpected formation of pyranone **159** was proposed to be a consequence of excess base in the reaction. Assuming the formation of the desired lactone **160**, deprotonation at C(4), followed by loss of chloride generates intermediate **161**. Isomerization of **161** would lead to the observed pyranone **159** (Scheme 3.6). A similar elimination process, where phenylacetic acid was used as the enolate precursor, had previously been reported by the Smith group in 2014.⁷



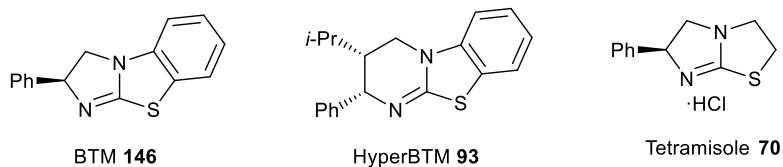
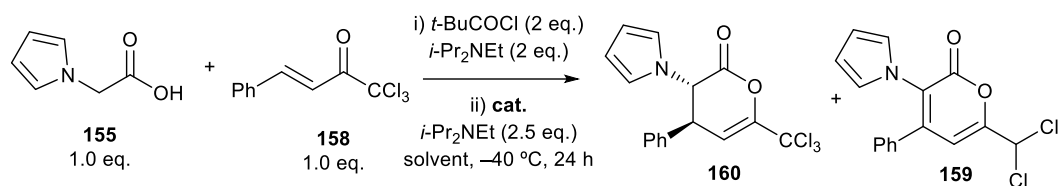
Scheme 3.6: Possible mechanistic explanation for pyranone formation

Using HyperBTM **93** as the isothioureia catalyst and performing the reaction at $-40\text{ }^{\circ}\text{C}$ allowed the first observation of the desired lactone **160** to be observed. ^1H NMR analysis of the crude reaction mixture revealed 69% conversion of the trichloromethyl enone **158**, along with a product distribution of 29:71 of lactone **160**:pyranone **159** (Scheme 3.7). The lactone **160** was formed in a moderate 71:29 dr.



Scheme 3.7: Observed formation of the desired lactone 160

Further screening of reaction conditions at $-40\text{ }^{\circ}\text{C}$ showed that the nature of solvent had a significant impact on the product distribution. Both toluene and DMF led to preferential formation of the desired lactone product **160** to pyranone **159** in product ratios of 70:30 and 85:15 respectively, but with much lower (37% and 40%) conversions of trichloromethyl enone **158** (Table 3.1, entry 1 and 2). Ethyl acetate resulted in an 80% conversion of trichloromethyl enone **158** into an approximately 88:12 mixture of **160**:**159** within 48 hours, with **160** being formed in a promising dr of 89:11 (entry 3). In acetonitrile, lactone **160** was observed as the only product, giving a good dr (90:10) and almost quantitative conversion of the trichloromethyl enone **158** (entry 4). Screening of other isothioureia catalysts **146** and **70** typically used in the Smith group resulted in lower reactivity of 30% and 49% conversion respectively. In both cases, lactone **160** was still observed as the only product, with high drs of 92:8 and 94:6 respectively (entry 5 and 6). Attempted reduction of catalyst loading from 10 mol% to 5 mol% showed minimal impact on the product distribution, but a slightly reduced conversion (95%) and diastereoselectivity (88:12) was observed (entry 7). A control reaction in the absence of the isothioureia catalyst did not lead to any conversion of **158** (entry 8). As a result, the conditions from entry 4 (10 mol% **93** in MeCN) were identified as the optimized conditions and used to explore the scope and limitations of this protocol.

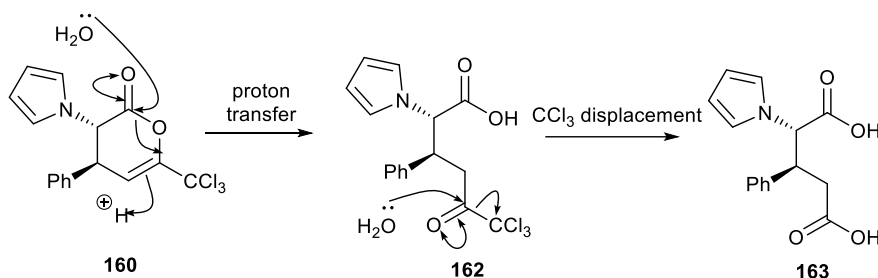


Entry	Cat. (mol%)	Solvent	Conv. ^a	160:159 ^a	160 dr ^a
1	93 (10)	PhMe	37%	70:30	80:20
2	93 (10)	DMF	40%	85:15	91:9
3 ^b	93 (10)	EtOAc	80%	88:12	89:11
4	93 (10)	MeCN	>99%	98:2	90:10
5	146 (10)	MeCN	30%	99:1	92:8
6	70 (10)	MeCN	49%	99:1	94:6
7	93 (5)	MeCN	95%	97:3	88:12
8	-	MeCN	0%	n/a	n/a

a. Determined by ¹H NMR analysis of crude reaction mixture. b. Reaction time of 48 h.

Table 3.1: Reaction optimization using pyrrolylacetic acid **155**

Attempts to isolate lactone **160** by column chromatography or recrystallization were unsuccessful. It is proposed that during the process of chromatographic purification, lactone **160** was ring-opened by water and subsequent CCl₃ displacement released the corresponding diacid derivative **163** which could not be isolated (Scheme 3.8).

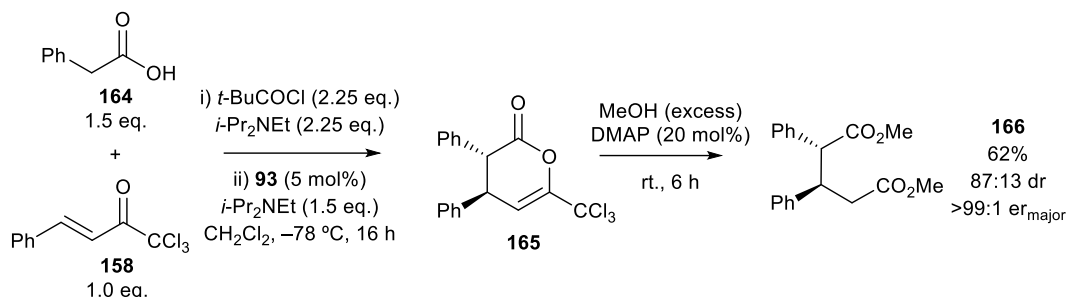


Scheme 3.8: Proposed decomposition of lactone to dicarboxylic acid derivative

3.3.2. In situ ring opening with nucleophiles

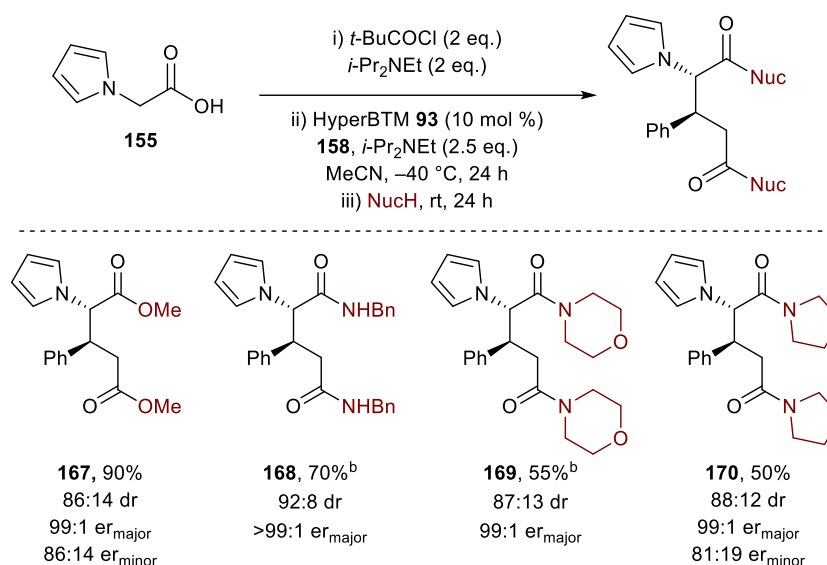
To facilitate the isolation and study of unstable lactone **160**, the crude Michael addition-lactonization product was treated directly with a nucleophile to generate a more stable

derivative resulting from ring opening and CCl_3 displacement. A similar procedure has previously been reported for the corresponding reaction from phenylacetic acid **164**, leading to the isolation of the diester derivative **166** (Scheme 3.9).⁷



Scheme 3.9: Previously established ring opening protocol

Based upon this precedent and protocol, a range of nucleophiles were tested. Pyrrolylacetic acid **155** and trichloromethyl enone **158** gave, after ring opening with MeOH and DMAP at room temperature, the diester **167** as a mixture of separable diastereoisomers with a ratio of 86:14 in 90% combined yield (Scheme 3.10). Chiral HPLC analysis showed that the major *anti*-(2*S*,3*S*) diastereoisomer was formed in excellent 99:1 e_r , while the minor *syn*-(2*R*,3*S*) diastereoisomer was isolated in a slightly reduced 86:14 e_r . Amines could also be used as nucleophiles in the ring opening protocol to afford diamide derivatives. Ring opening and aminolysis using an excess of benzylamine gave the diamide product **168** in 92:8 dr, 70% yield and excellent e_r of >99:1. Secondary amines such as morpholine and pyrrolidine were also compatible with this protocol, resulting in the isolation of **169** and **170** in slightly reduced yield (55% and 50% respectively) and dr (87:13), but still excellent enantioselectivity of 99:1 e_r for the major diastereoisomer in both cases. However, the enantioselectivity of the minor diastereoisomer for the pyrrolidine ring-opening derivative **170** was reduced to 81:19 e_r . Due to the high diastereoselectivity, small scale and the polar nature of the benzylamine ring-opening derivative **168**, the minor diastereoisomer of **168** could not be successfully isolated to enable the determination of its enantiomeric ratio.



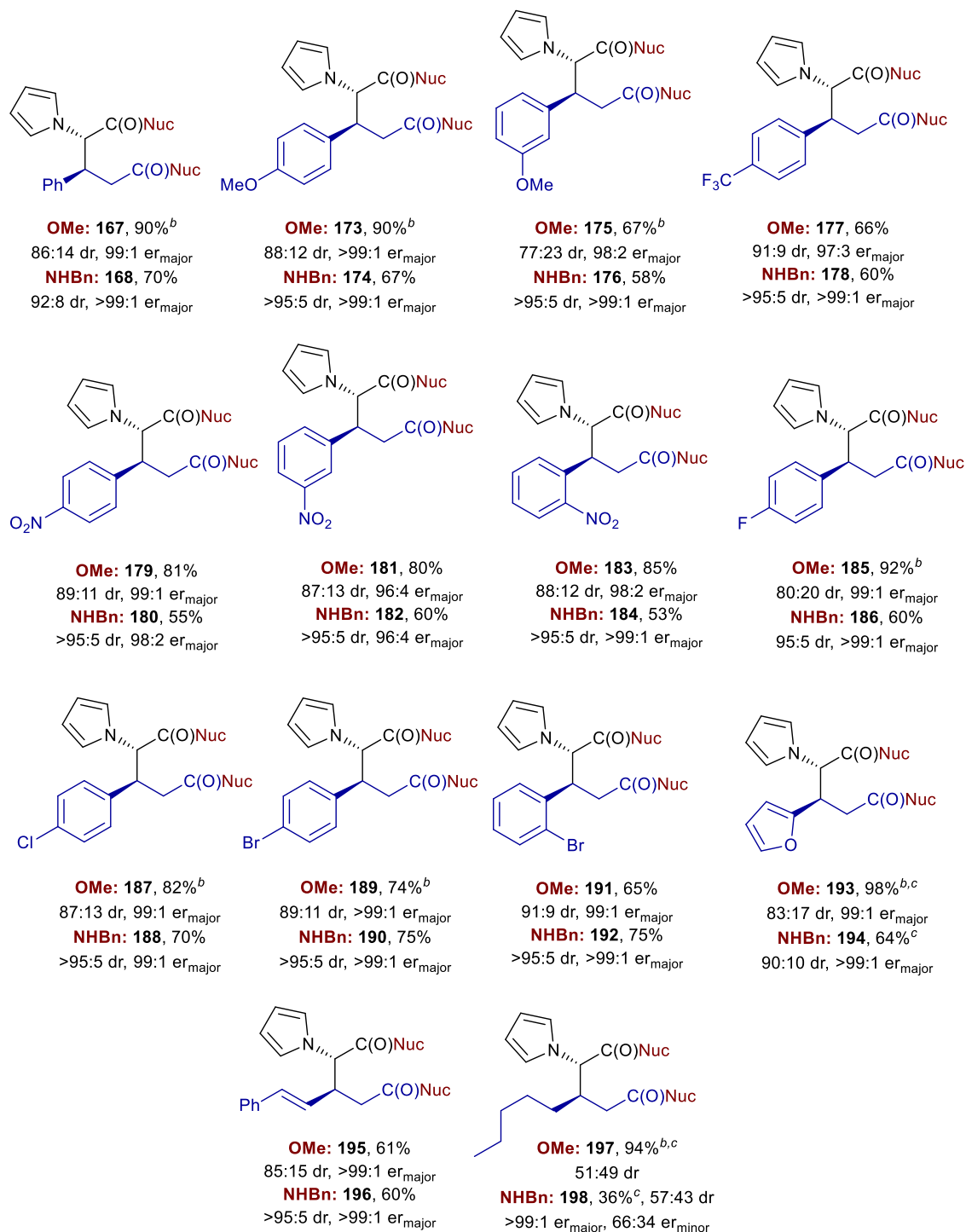
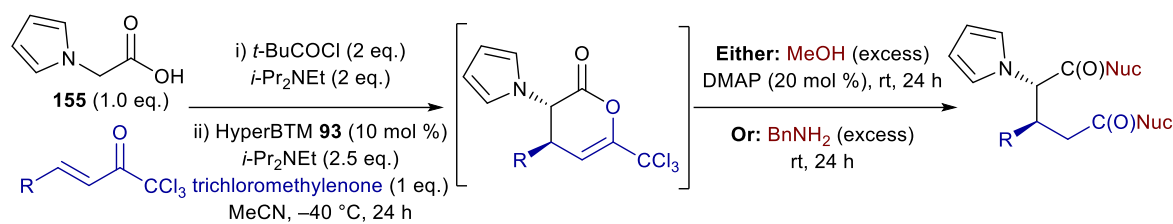
a. Yield referred to the combined isolated yield of separable mixture of diastereoisomers, unless otherwise stated. *dr* was determined from ¹H NMR analysis of crude reaction mixture. *er* was determined from chiral HPLC analysis. *b.* Isolated yield of the major diastereoisomer in >95:5 *dr*.

Scheme 3.10: Ring-opening and CCl₃ displacement^a

3.3.3. Scope and limitations

With reliable isolation of the derived products developed, the scope was explored by reacting pyrrolyl acetic acid **155** with a range of aryl, heteroaryl, alkenyl or alkyl substituted trichloromethyl enones (prepared from the reaction conditions outlined in Scheme **3.4**) to investigate the effect of both electronics and sterics of the β-substituents on the catalytic system. Under the optimized conditions, Michael addition-lactonization and subsequent *in-situ* nucleophilic ring opening and CCl₃ displacement via either methanolysis or aminolysis (with benzylamine) afforded the corresponding stable diester or diamide derivatives (Scheme **3.11**). The transformation was well tolerated for a range of aryl trichloromethyl enones. With electron-donating methoxy substituents on the aryl ring, both MeOH and benzylamine derivatives **173-176** were formed in good yields (58%-90%) with excellent enantioselectivity for the major diastereoisomer (>99:1 *er*). A selection of electron-withdrawing substituents, such as 4-trifluoromethyl and nitro group on each ring positions, were well tolerated under both ring-opening protocols, giving derivatives **177-184** in similar stereoselectivity (87:13 to >95:5 *dr* and up to >99:1 *er* for the major diastereoisomer) and yields (53%-85%) compared with electron-donating aryls. A range of halogen-substituted phenyl rings at either 4- or 2-position were also accommodated into the trichloromethylenone Michael acceptors, forming

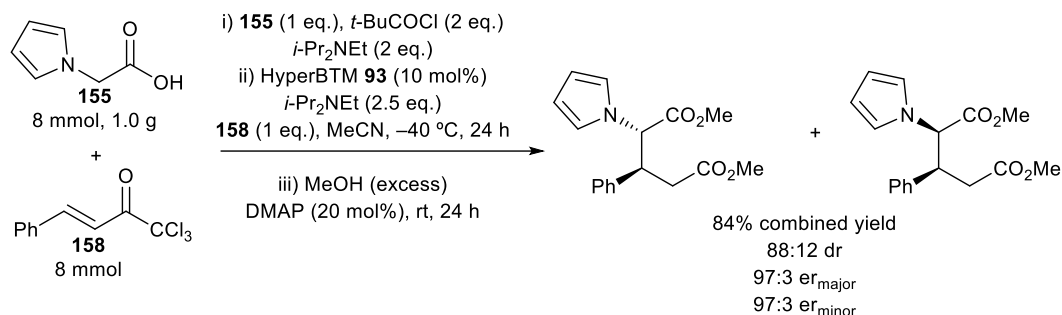
ring-opening derivatives **185-192** in excellent yields of up to 92% and 99:1 er for the major diastereoisomer in each case. An extension of the reaction time from 24 hours to 40 hours was necessary for complete conversion when using 2-furyl substituted trichloromethyl enone, giving the products **193** and **194** in good yields (98% and 64%) and excellent (99:1 er) enantioselectivity. An alkenyl substituted trichloromethyl enone was also tested, with both the diester **195** and diamide **196** formed in good yield (61 and 60% respectively) and excellent enantioselectivity (>99:1 er) for the major diastereoisomer. For both diester **197** and diamide **198**, low dr (51:49 and 57:43) was observed when an alkyl substituent replaced the normal aromatic rings. The diester **197** was isolated in 94% yield but the enantiomers could not be separated by HPLC. The corresponding diamide **198** was isolated in a slightly lower yield of 36%, albeit with excellent enantioselectivity (>99:1 er) for the major diastereoisomer and lower enantioselectivity (66:34 er) for the minor diastereoisomer. An interesting observation across all of these examples was that the BnNH₂ quenched diamides were consistently observed with higher dr (typically >95:5) when compared with the diesters from alcoholysis (typically *ca.* 85:15 dr). This will be discussed further in later sections.



a. Isolated yields of major diastereoisomer unless otherwise stated. dr was determined by ¹H NMR analysis of crude reaction mixture. er was determined by HPLC analysis. b. Combined isolated yield of separable mixture of diastereoisomers. c. Reaction at -40 °C for 40 h.

Scheme 3.11: Scope and limitations^a

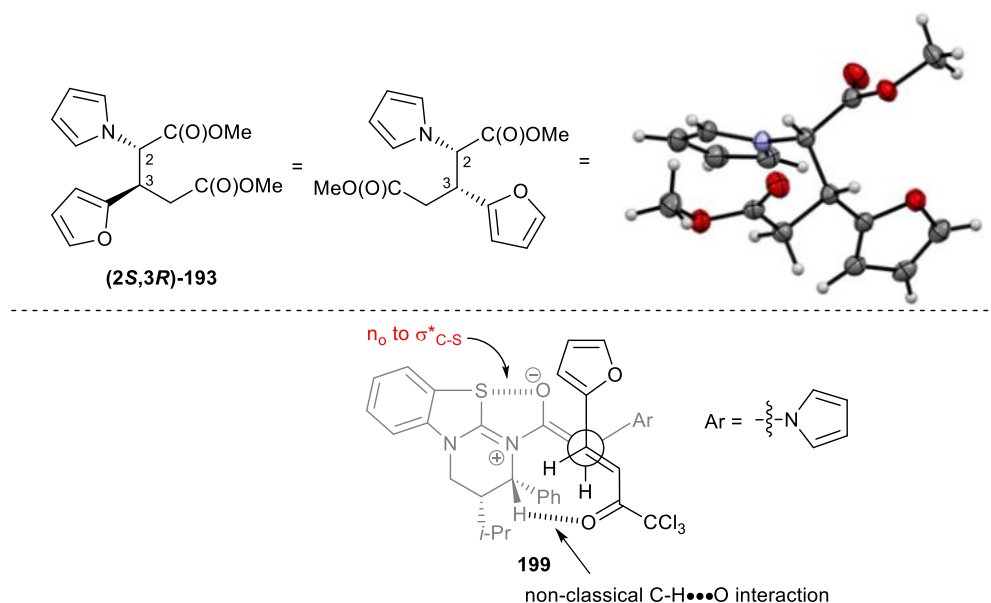
The protocol was also tolerated on gram scale (8 mmol **155**), exemplified by diester **162** being isolated in 84% combined yield, 88:12 dr and 97:3 er for both diastereoisomers (Scheme 3.12).



Scheme 3.12: Scale-up process

3.3.4. Stereochemistry determination

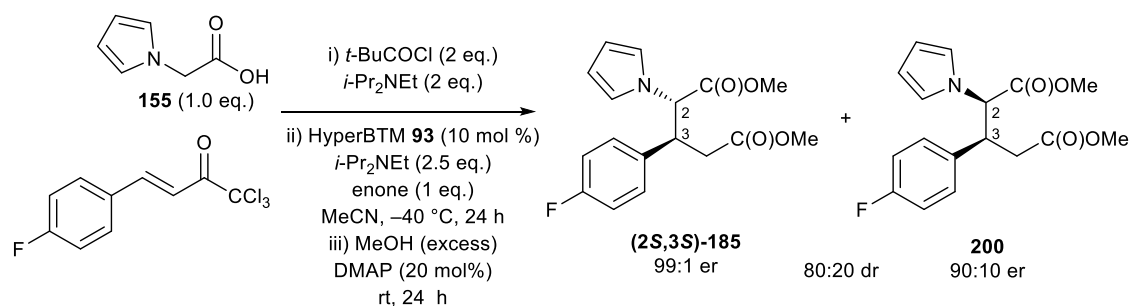
Single crystal x-ray analysis was performed on the major diastereoisomer of diester **193** (Scheme 3.13),⁹ allowing the relative and absolute configuration for the major diastereoisomer to be determined, with the stereochemistry of all other ring-opening products assigned by analogy. The (2*S*,3*R*)-configuration within the major diastereoisomer **193** is consistent with the stereochemical outcome previously observed using phenylacetic acid derived ammonium enolates in this process. This is consistent with the reaction of a (*Z*)-ammonium enolate and enone **199** via a pre-transition state assembly that places the two pro-stereogenic centres in a staggered array and orients the smallest C(3)-H substituent of the enone towards the catalyst, allowing for potential stabilization by non-classical C-H---O interaction between the acidic C-H of the catalyst and enone O.¹⁰



Scheme 3.13: Single crystal X-ray analysis and stereochemistry rationale

3.3.5. Epimerization studies

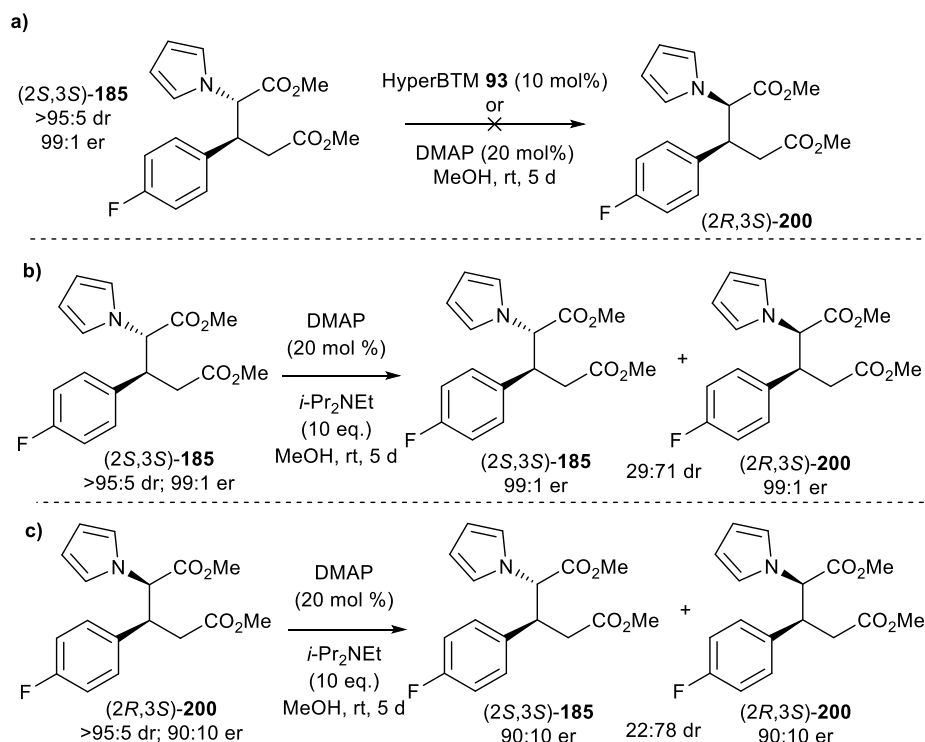
From analysing the scope, the BnNH_2 quenched diamide products were consistently observed with higher dr (typically >95:5) compared with the corresponding diesters from alcoholysis (typically 85:15 dr). Moreover, in the diester series, the minor diastereoisomer was generally isolated with lower er compared with the corresponding major diastereoisomer. For example, alcoholysis with MeOH resulted in an 80:20 (**185:200**) mixture of diastereoisomers, with the major (2S,3S)-diastereoisomer **185** having 99:1 er, while the minor diastereoisomer **200** had a 90:10 er (Scheme 3.14).



Scheme 3.14: Observed inconsistent stereoselectivity

To investigate the source of this inconsistency, a series of control experiments were performed, based on the hypothesis that the configuration at C(2) could be changed during methanolysis through epimerization. Isolated (2S,3S)-**185** (>95:5 dr, 99:1 er) was treated with either 10 mol% HyperBTM **93** or typical conditions used for methanolysis (MeOH, 20 mol% DMAP) and

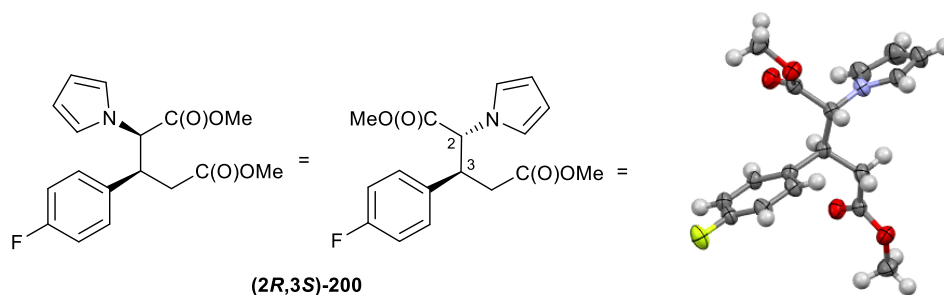
monitored using ^1H NMR spectroscopic analysis. No trace of minor diastereoisomer ($2R,3S$)-**200** was detected in either case (Scheme 3.15(a)). Treatment of ($2S,3S$)-**185** (>95:5 dr, 99:1 er) with DMAP (20 mol%) and *i*-Pr₂NEt (10 eq.) in MeOH for 5 days led to a 29:71 **185**:**200** ratio of diastereoisomers, both with er of 99:1 (Scheme 3.15(b)). Subjecting the isolated minor diastereoisomer ($2R,3S$)-**200** (>95:5 dr, 90:10 er) to the same conditions gave a similar 22:78 (**185**:**200**) ratio of diastereoisomers, both in the same 90:10 er (Scheme 3.15(c)).



dr was determined by ^1H NMR analysis of crude reaction mixture and *er* was determined by HPLC analysis.

Scheme 3.15: Epimerization of diester products

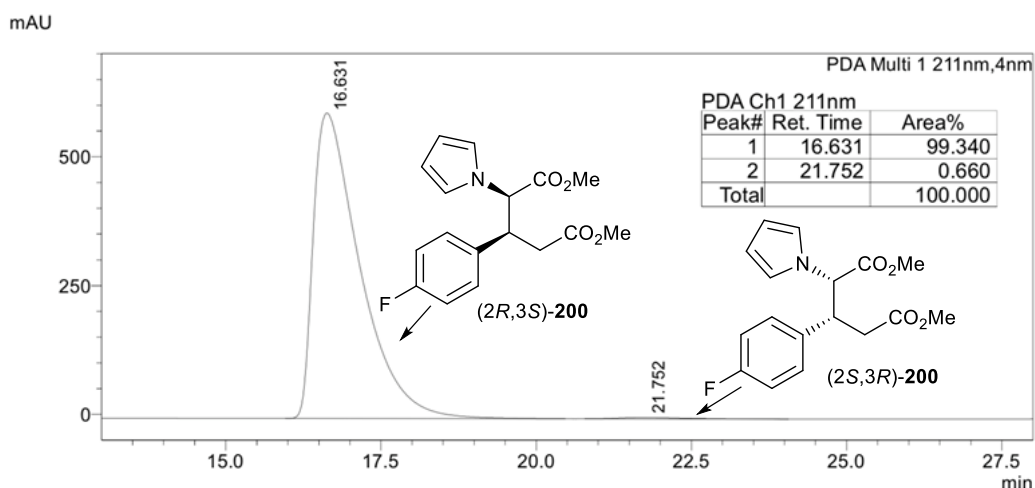
Single crystal X-ray analysis⁹ of the major product obtained from the epimerization of ($2S,3S$)-**185** (99:1 er) (Scheme 3.15(b)) enabled the relative and absolute configuration of **200** to be assigned unambiguously as ($2R,3S$)-**200** (Scheme 3.16).



Scheme 3.16: Single crystal X-ray analysis of **200**

Comparison of the HPLC trace of (2*R*,3*S*)-**200** used in single crystal X-ray analysis confirmed the (2*R*,3*S*) configuration of the minor diastereoisomer **200** from the catalytic reaction (Fig. 3.1). This suggested the presence of a base-mediated selective epimerization at either C(3) of the lactone or C(2) of the ring-opened intermediate/diester product.

HPLC traces for (2*R*,3*S*)-**200** (>95:5 d.r., 99:1 e.r.) isolated from epimerization study (Scheme 3.15(b)):



HPLC traces for **200** (>95:5 dr, 90:10 er) isolated from reaction mixture:

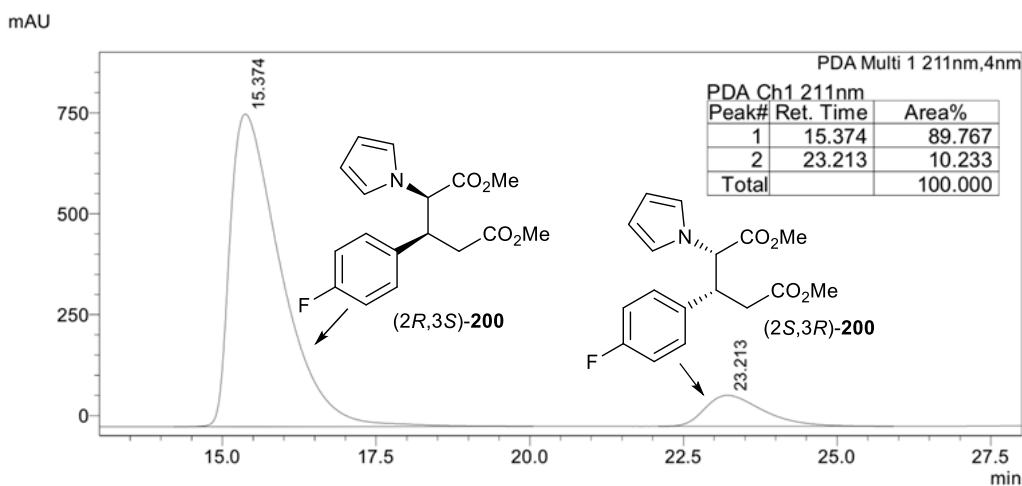
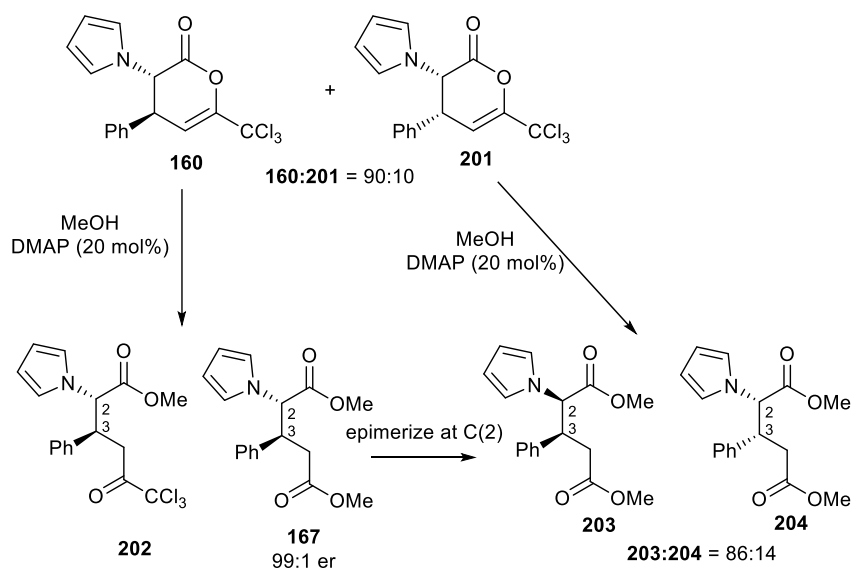


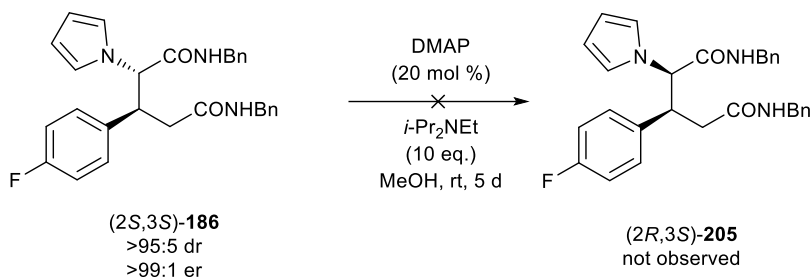
Fig. 3.1: Comparison in the HPLC traces

Assuming the catalyst has good control over the configuration at C(3) of the initially formed product **160**, lactone **201** was assumed as the minor diastereoisomer. MeOH ring opening would lead to the formation of the corresponding derivatives **167** and **202** (via the CCl_3 ketone) (Scheme 3.17). Epimerization of **167** or **202** at C(2) would give **203** which is enantiomeric to **204**, potentially leading to the observed lower er (**203:204**) for the minor diastereoisomer.



Scheme 3.17: Explaining the lower er for minor diastereoisomer

When treating the BnNH₂ ring-opening diamide **186** under similar conditions, no epimerization was observed, consistent with the observed high dr for this series of products (Scheme 3.18).

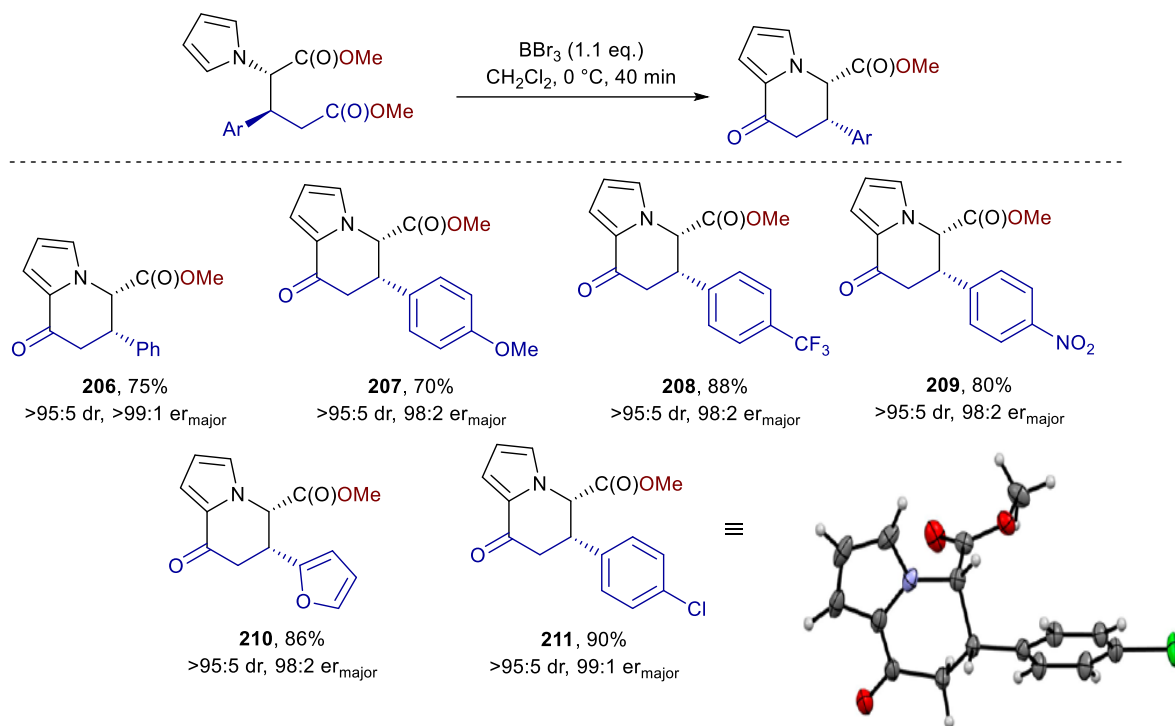


Scheme 3.18: Epimerization of diamide product

3.3.6. Product derivatization

The electron-rich nature of pyrrole was exploited in an intramolecular Friedel-Crafts acylation (Scheme 3.19).¹¹ Treatment of isolated enantiopure **187** (>95:5 dr) with Lewis acid boron tribromide rapidly led to the formation of the corresponding acylation product dihydroindolizinone **206**, which was isolated in 75% yield without erosion in either diastereoselectivity or enantioselectivity (>95:5 dr, 99:1 er). This Friedel-Crafts acylation protocol was compatible with diester substrates bearing aryl substituents with either electron-donating (4-OMe) or electron-withdrawing (4-CF₃ and 4-NO₂) groups, and the products **207-209** were isolated in high yield (70% to 88%), each as a single stereoisomer. Selective acylation of pyrrole was achieved in the presence of a 2-furyl substituent, with product **210** being

isolated in 86% yield as a single stereoisomer. A 4-Cl-aryl substituent was also well tolerated in the system, forming **211** in 90% yield as a single stereoisomer. Single crystal X-ray analysis⁹ confirmed the relative and absolute configuration of the dihydroindolizinone **211**, allowing the configuration of all other examples to be assigned by analogy.

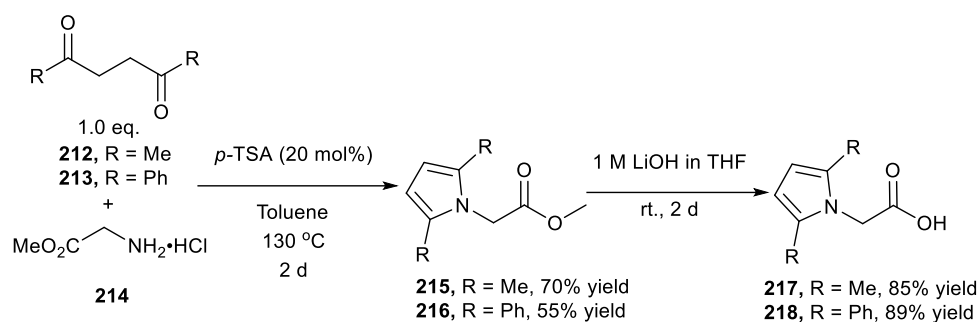


Yields referred to isolated yields. *dr* was determined by ^1H NMR analysis of crude reaction mixture. *er* was determined by chiral HPLC analysis.

Scheme 3.19: Synthesis of dihydroindolizinones

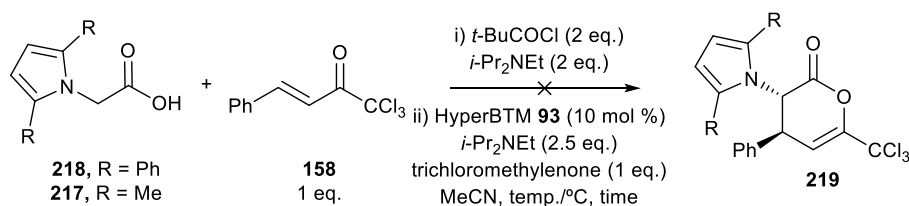
3.4. Substituted pyrrole acetic acids

Aiming to expand the scope of the Michael addition-lactonization protocol, 2,5-disubstituted pyrrole acetic acids were synthesized as potential precursors. Acid-catalyzed condensation of 1,4-diketones **212** and **213** with glycine methyl ester in refluxing toluene in a sealed tube gave 2,5-disubstituted pyrrole ester **215** and **216** in 70% and 55% yield respectively. Hydrolysis with LiOH in THF gave the corresponding diphenyl- and dimethyl substituted pyrrole acetic acid **218** and **217** in 89% and 85% yield, respectively (Scheme 3.20).¹²



Scheme 3.20: Synthesis towards 2,5-disubstituted pyrrole acetic acid

When **217** and **218** were subjected to the previously developed reaction conditions, >95% starting material was recovered in both cases even after long reaction time of 4 days (Table 3.2, entry 1-2). Performing the reaction with **218** at room temperature did not provide any improvements in the conversion, with more than 90% starting material being recovered after 48 h (entry 3). The general lack of conversion for this series of substrates was presumably due to increased steric bulk caused by the pyrrole *ortho*-substituents.



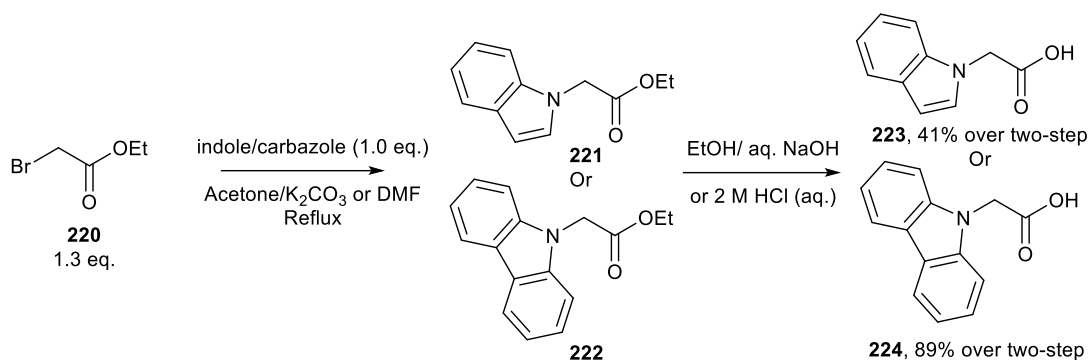
Entry	Acid	Temp.	Time	Comments
1	217	-40 °C	4 d	>95% 158 recovered ^a
2	218	-40 °C	4 d	>95% 158 recovered ^a
3	218	rt.	48 h	90% 158 recovered ^a

a. Based upon the **158** recovered after chromatographic purification.

Table 3.2: Test reactions with 2,5-disubstituted pyrrole acetic acid

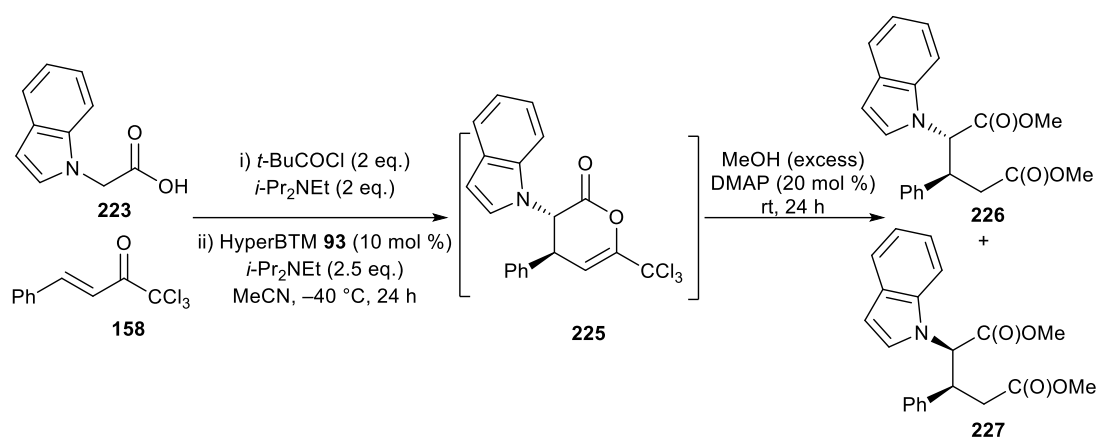
3.5. *N*-Heteroaryl acetic acids as enolate precursors

With the substituted pyrrolyl acetic acids showing no conversion in Michael addition-lactonization, attention turned to exploring the reactivity of other nitrogen linked α -heteroaryl acetic acids. Following procedures from the recent literature, both 2-indole acetic acid **223** and 2-carbazole acetic acid **224** were synthesized by nucleophilic substitution of ethyl bromoacetate **220** with the requisite heteroaryl followed by hydrolysis (Scheme 3.21).^{13,14}

Scheme 3.21: Preparation of *N*-heteroaryl acetic acids

3.5.1. Reactivity with trichloromethyl enone

Both isolated 2-indolyl and 2-carbazolyl acetic acids **223** and **224** were subjected to the previously developed reaction conditions with trichloromethyl enone. After 24 h, no conversion of the Michael acceptor was observed for **224** although in the case of 2-indolyl acetic acid **223**, the desired lactone **225** was observed in a promising 90:10 dr via 1H NMR analysis of crude reaction mixture. Subsequent ring opening methanolysis afforded the diester products **226** and **227** in 63% combined yield, 80:20 dr and high er (95:5) for the major diastereoisomer **226** and 75:25 er for the minor (Table 3.3, entry 1). Increasing the trichloromethyl enone **158** stoichiometry to 1.2 and 1.5 equivalents gave the diesters **226** and **227** in slightly increased combined yield of 83% and 87% respectively (entry 2-3), while both dr (80:20) and er (95:5 for **226** and 74:26 for **227**) were consistent with before. Thus, the conditions from entry 2 were chosen as a basis for further study.

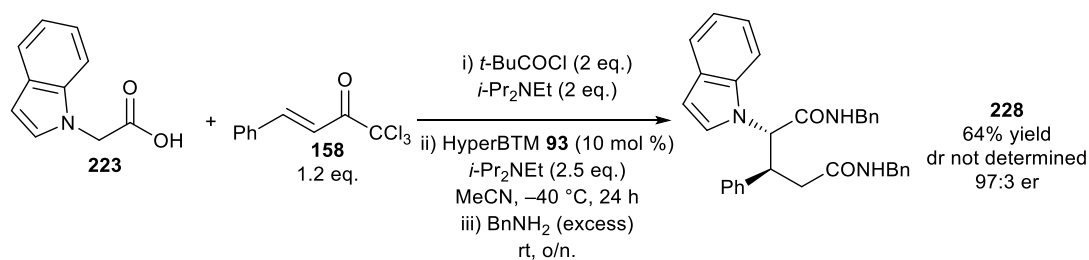


Entry	eq. of 158	dr of 225 ^a	dr (226:227) ^a	226 er ^b	227 er ^b	Yield ^c
1	1.0	90:10	80:20	95:5	75:25	63%
2	1.2	91:9	80:20	95:5	74:26	83%
3	1.5	91:9	80:20	95:5	74:26	87%

a. dr determined from ¹H NMR analysis of crude reaction mixture. b. er determined from chiral HPLC analysis of isolated diastereoisomer (>95:5 dr). c. Combined isolated yield of separable mixture of diastereoisomers.

Table 3.3: Optimization using 2-indolyl acetic acid

Ring opening process with benzylamine gave diamide **228** in 64% yield and 97:3 er (Scheme 3.22). This was slightly lower than the er observed using pyrrolyl acetic acid after aminolysis (>99:1 er). Unfortunately, the dr could not be clearly determined from the crude reaction mixture although **228** was isolated as a single diastereoisomer (>95:5 dr).

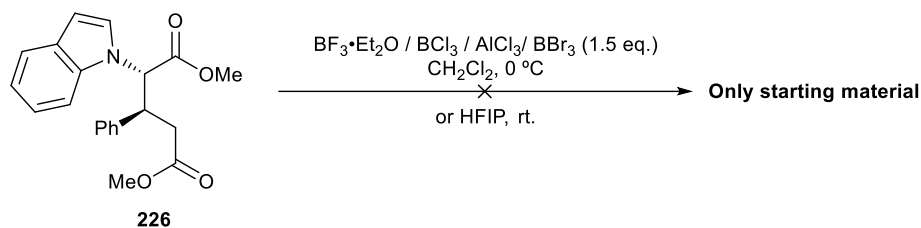


Scheme 3.22: Aminolysis with 2-indolyl acetic acid substrate

3.5.2. Exploring the synthetic utility of alcoholysis derivative

By analogy to the pyrrole substituted diesters, intramolecular Friedel-Crafts acylation of indole ester **226** was proposed. A series of conditions were tested, including BBr₃, BF₃, BCl₃ and AlCl₃ in CH₂Cl₂ or HFIP (Scheme 3.23).^{15–20} Unfortunately, under all the conditions tested, no cyclization was detected. Either the starting material was recovered, or a complex mixture was observed. A possible explanation was that the methyl ester is not a reactive enough acylating

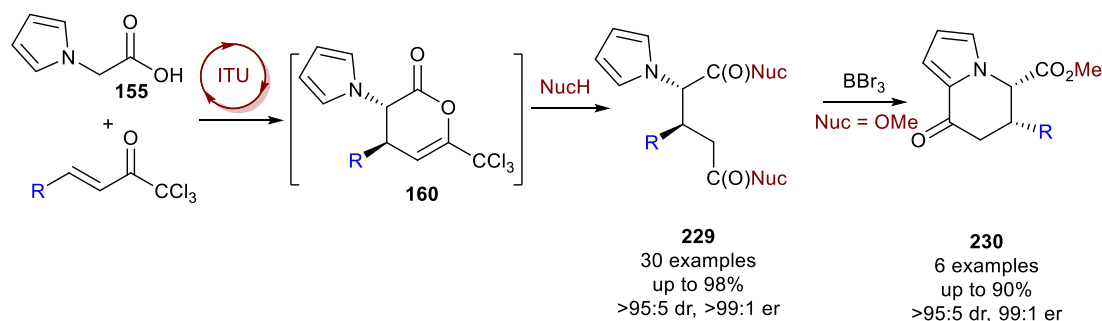
group, particularly with indole substrates where typically an acyl halide, a carboxylic acid or a mixed anhydride was used as the acylating group.^{15–20} So this was not investigated further.



Scheme 3.23: Attempted Friedel-Crafts acylation on indole

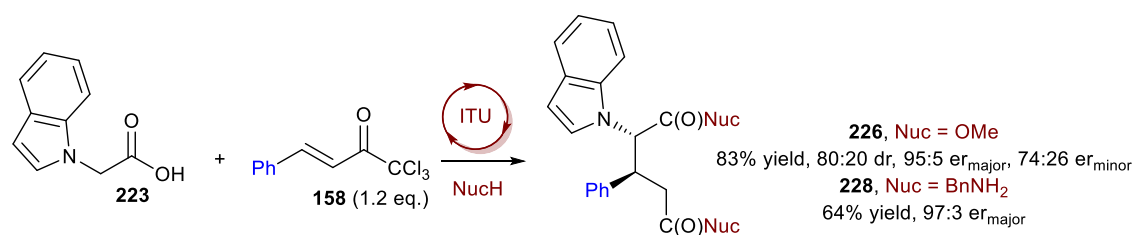
3.6. Conclusions

In this chapter, the successful application of 2-pyrrolyl acetic acid as a C1-ammonium enolate precursor in isothiurea catalyzed Michael addition-lactonization with a wide variety of α,β -unsaturated trichloromethyl enones was demonstrated. The intermediate δ -lactone **160** could be readily ring opened by either alcoholysis or aminolysis to afford substituted pyrrole derivatives **229** with excellent diastereo- and enantioselectivity. These products could be further derivatized into substituted dihydroindolizinones **230** through intramolecular Friedel-Crafts acylation (Scheme **3.24**).



Scheme 3.24: Michael addition-lactonization and derivatization

2-Pyrrolyl acetic acids with *o*-substituents did not show any reactivity although 2-indolyl acetic acid **223** participated in the lactone formation, with ring-opening leading to diester **226** and diamide **228**. Friedel-Crafts derivatization was unsuccessful (Scheme **3.25**).



Scheme 3.25: Results with 2-indolyl acetic acid 223

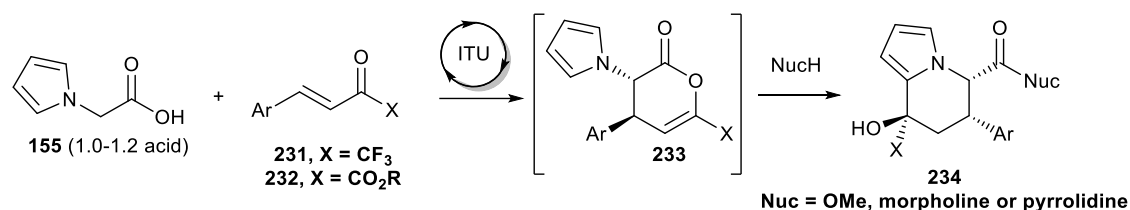
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Chapter 4: One-pot synthesis of tetrahydroindolizine derivatives

In this chapter, isothiurea-catalyzed Michael addition-lactonization using 2-pyrrolyl acetic acid **155** with trifluoromethyl enones **231** and α -keto- β,γ -unsaturated esters **232** was exploited as part of a one-pot process for the synthesis of 5,6,7,8-tetrahydroindolizine derivatives **234** in high dr and er by ring-opening with a nucleophile (MeOH, morpholine or pyrrolidine, Scheme 4.1).



Scheme 4.1: One-pot synthesis of 5,6,7,8-tetrahydroindolizines

4.1. Overview

The 5,6,7,8-tetrahydroindolizine structure is a commonly found core motif in many drug molecules.¹ As a consequence the construction of this building block has attracted the attention of synthetic chemists. For example, tetrahydroindolizines are found as the core structure in the anticancer natural alkaloid Rhazinicine² **235** and the antimicrobial agent Polygonatine A **236**³ (Fig. 4.1). CMV423 **237**, a tetrahydroindolizine derivative, was also developed as a treatment of human cytomegalovirus infections.⁴

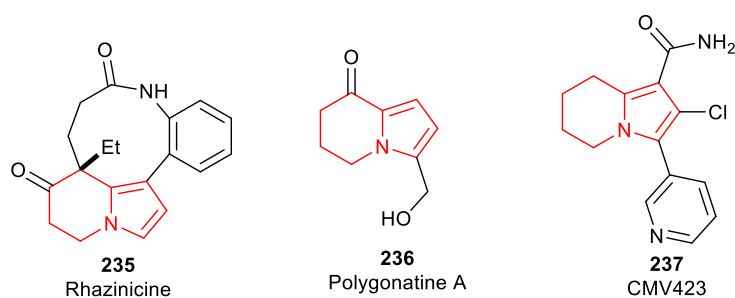
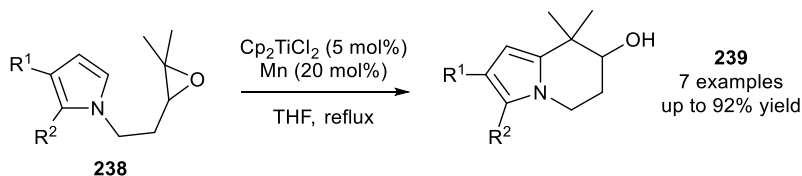


Fig. 4.1: Tetrahydroindolizines found in biologically important molecules

5,6,7,8-Tetrahydroindolizine derivatives are usually synthesized from Brønsted acid or Lewis acid mediated Friedel-Crafts alkylation/acylation with pyrroles.⁵ However, this process is typically limited by the use of stoichiometric moisture sensitive Lewis acids. To overcome the problem of using a stoichiometric amount of reagent, several catalytic methods towards

tetrahydroindolizine have been developed.^{6–8} For example, a transition-metal catalyzed radical cyclization with pyrrole derivatives **238** containing epoxides to afford tetrahydroindolizines **239** in good yields has been developed (Scheme 4.2).⁹

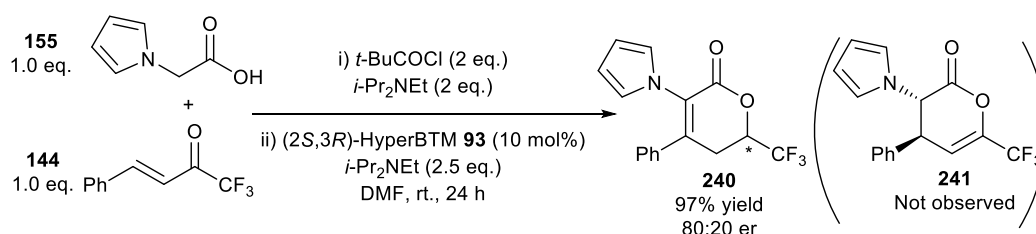


Scheme 4.2: Ti-catalyzed synthesis of tetrahydroindolizines

Following on from the stepwise Michael addition-lactonization and intramolecular Friedel-Crafts acylation with trichloromethyl enone Michael acceptors and 2-pyrrolyl acetic acid **155** detailed in Chapter 3, it was initially assumed that the same protocol could also be applied with trifluoromethyl enone Michael acceptor substrates to access tetrahydroindolizines, via ring-opening and subsequent intramolecular cyclization in a one-pot process.

4.2. Proof of concept study

Initial proof of concept studies began with the *in situ* activation of 2-pyrrolyl acetic acid **155** using *t*-BuCOCl, followed by HyperBTM **93** catalyzed Michael addition-lactonization with trifluoromethyl enone Michael acceptor **144** in DMF. At room temperature, the reaction was monitored by TLC analysis, with full consumption of the starting material observed within 24 hours. ¹H NMR analysis of the crude material revealed the exclusive formation of the unexpected isomerized 5,6-dihydropyranone **240**, rather than the expected product of catalysis, 3,4-dihydropyranone **241** (Scheme 4.3). Chromatographic purification allowed **240** to be isolated in 97% yield with moderate enantioselectivity (80:20 er).



Scheme 4.3: Unexpected formation of the isomerized product

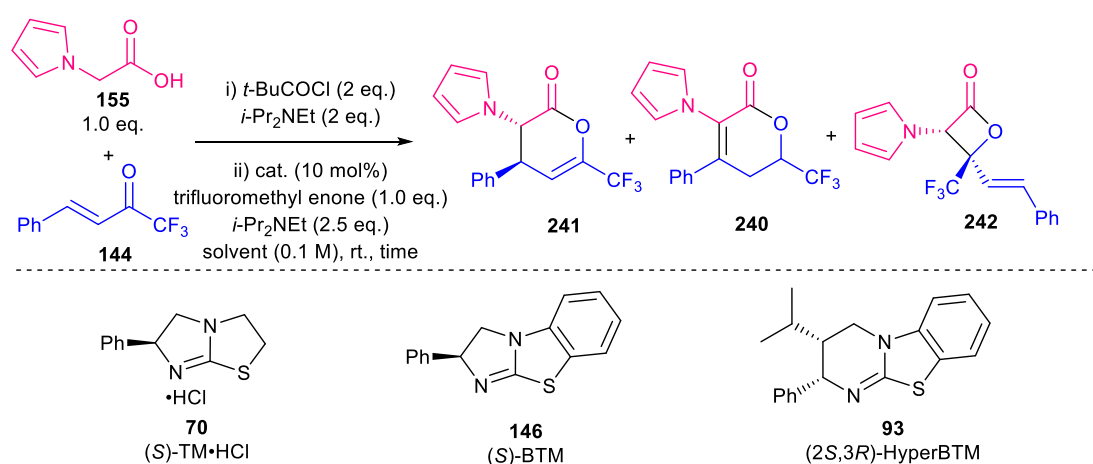
The formation of this enantioenriched isomerized product 5,6-dihydropyranone **240** had not been observed previously when aryl acetic acid derivatives had been used as the C1-ammonium enolate precursor in this transformation.¹⁰ At this stage it was simply assumed that

240 was produced from the catalytically-generated 3,4-dihydropyranone **241** under the reaction conditions by isomerization. Attention subsequently focused on reaction optimization to favour formation of 3,4-dihydropyranone **241** and minimize the isomerization of **241** to **240**.

4.2.1. Reaction optimization

Screening started by using different solvent/catalyst combinations at room temperature (Table 4.1). In amide solvents (DMF and *N,N*-dimethylacetamide (DMA)), exclusive formation of the isomerization product **240** was found within 24 hours with all three isothiourea catalysts **70**, **146** and **93**. Quantitative conversion of the starting Michael acceptor **144** was observed for each case, with **240** being isolated in excellent yields (95-97%) and good enantioselectivity (75:25 to 80:20 er) (entry 1-4). Another polar solvent, cyclohexanone, could also be used in the catalytic process, with full conversion of the Michael acceptor **144** into the isomerized product **240** using HyperBTM **93** (entry 5). When switching the solvent to 1,2-dichloroethane (DCE), the 5,6-dihydropyranone **240** was still the major product, however the desired catalytic product 3,4-dihydropyranone **241** and the β -lactone **242** were detected by ^1H NMR analysis in a product distribution of 3:94:3 (**241:240:242**) (entry 6). For simplicity these product distributions take into account a mixture of diastereoisomers for both **241** (typically *ca.* 80:20) and **242** (typically >95:5). The use of MeCN as solvent resulted in full conversion of enone **144** within 4 hours to give a 20:65:15 mixture of **241:240:242**, with the 5,6-dihydropyranone **240** still being formed as the major product (entry 7). Due to the difficulties associated with the isolation of the desired catalytic product 3,4-dihydropyranone **241** by chromatography, product ratios of the crude mixture, as well as conversion of starting material, were used to expedite optimization. The use of CH_2Cl_2 , a common solvent used in Michael addition-lactonization procedures, gave a product distribution of 20:30:50 (**241:240:242**) with the β -lactone **242** obtained as the major product (entry 8). Other chlorinated solvents, such as CHCl_3 and CCl_4 , were also tested. Less than 5% conversion was found with CHCl_3 (entry 9), while CCl_4 gave a good conversion of 95% into a product distribution of 57:26:17 (**241:240:242**) (entry 10). Uncommon solvents dimethyl carbonate (DMC) and 2-methyl THF both gave 85% conversion of trifluoromethyl enone **144**, with the 3,4-dihydropyranone **241** being observed as the major product in each case (65% and 69% product selectivity respectively) (entry 11

and **12**). A similar product selectivity for **241** was observed when the reaction was conducted in *tert*-butylmethyl ether (MTBE), but a lower conversion of 63% was found (entry **13**). A much improved product selectivity with more than 70% 3,4-dihydropyranone **241** was obtained with solvents toluene, 1,4-dioxane, Et₂O, THF and EtOAc, with all solvents also providing good conversions (83-92%) (entry **14-18**). The formation of the isomerized product 5,6-dihydropyranone **240** could be completely suppressed when *tert*-amyl alcohol was used as the solvent, with 88% conversion of the Michael acceptor **144** to give a product ratio of 84:16 (**241:242**) (entry **19**). Finally, an excellent conversion of 98% was obtained using either cyclopentylmethyl ether (CPME) or isopropyl acetate (*i*-PrOAc) as the solvent, giving 85% and 88% selectivity for 3,4-dihydropyranone **241** respectively, with only a trace (<5%) of isomerized product **240** detected by ¹H NMR analysis of the crude reaction material (entry **20-21**).



Entry	Cat.	Solvent	Time/ h	Conv. ^a	Product ratio 241:240:242 ^{a,b}
1	70	DMF	24	100%	0:100 (95%, 20:80 er):0
2	146	DMF	24	100%	0:100 (96%, 25:75 er):0
3	93	DMF	24	100%	0:100 (97%, 80:20 er):0
4	93	DMA	18	100%	0:100:0
5	93	cyclohexanone	18	100%	0:100:0
6	93	DCE	18	95%	3:94:3
7	93	MeCN	4	100%	20:65:15
8	93	CH ₂ Cl ₂	18	100%	20:30:50
9	93	CHCl ₃	18	<5%	n/d.
10^c	93	CCl ₄	18	95%	57:26:17
11	93	DMC	18	85%	65:10:24
12	93	2-MeTHF	18	85%	69:16:15

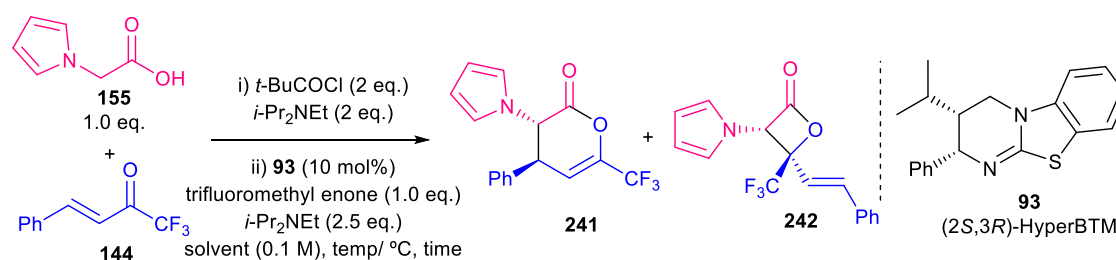
13	93	MTBE	18	63%	65:5:30
14	93	Toluene	18	92%	72:13:15
15	93	1,4-dioxane	18	83%	77:3:20
16	93	Et ₂ O	18	90%	75:8:17
17	93	THF	18	86%	76:11:14
18	93	EtOAc	18	90%	75:18:7
19	93	<i>tert</i> -Amyl alcohol	18	88%	84:0:16
20^c	93	CPME	18	97%	85:0:15
21^c	93	<i>i</i> -PrOAc	18	98%	88:5:7

a. Determined by ¹H NMR analysis of crude reaction mixture. b. Isolated yield and *er* for individual product in parenthesis. c. With 1.2 eq. acid **155**.

Table 4.1: Solvent optimization at room temperature

During the optimization process some solvents, such as DMSO, 1,2-dimethoxyethane, HFIP and MeNO₂, either show no conversion of the CF₃ enone **144**, or gave a complex mixture where no dihydropyranone **241** was detected by ¹H NMR analysis of the crude material.

Using a small solvent selection, the reaction was performed at a lower temperature in an attempt to improve product selectivity for **241**, whilst maintaining high conversion (Table 4.2). In general, using HyperBTM as catalyst, at lower temperatures no isomerized product 5,6-dihydropyranone **240** was detected by ¹H NMR analysis, but formation of β-lactone **242** was still observed. In DMF at –60 °C, reduced conversion of 70% was observed, giving a product distribution of 86:14 (**241:242**), with no isomerized product **240** detected (entry 1). Inspired by this result, the reaction was performed at –60 °C and –78 °C in CH₂Cl₂, but unfortunately both conditions gave an approximate 50:50 ratio of **241:242** (entry 2 and 3). A promising product distribution of 85:15 (**241:242**), as well as quantitative conversion of the Michael acceptor **144** was observed with the reaction conducted in MeCN at –40 °C (entry 4). When either CPME or isopropyl acetate was used as solvent at –40 °C, quantitative conversion was observed, giving a product distribution of 84:16 and 90:10 (**241:242**) respectively (entry 5 and 6).



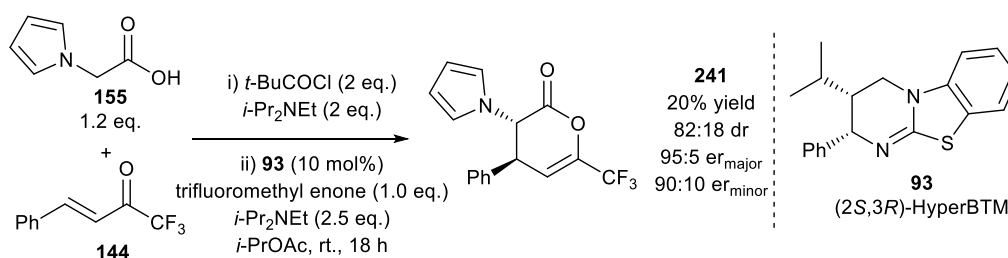
Entry	Solvent	Temp./ °C	Time/ h	Conv. ^a	Product ratio 241:242 ^a
1	DMF	-60	18	70%	86:14
2	CH ₂ Cl ₂	-60	15	95%	52:48
3	CH ₂ Cl ₂	-78	24	85%	56:44
4 ^b	MeCN	-40	20	99%	85:15
5 ^b	CPME	-40	20	97%	84:16
6 ^b	Isopropyl acetate	-40	20	98%	90:10

a. Determined by ¹H NMR analysis of crude reaction mixture. b. With 1.2 eq. acid **155**.

Table 4.2: Screening of solvents at low temperatures

4.2.2. Exploring the isomerization process

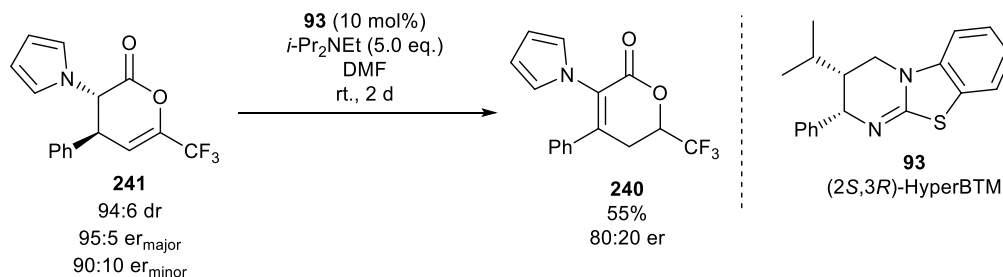
To provide further insight into the proposed isomerization of 3,4-dihydropyranone **241** to 5,6-dihydropyranone **240**, and to probe the origin of the enantioenrichment of 5,6-dihydropyranone **240**, control reactions were conducted. Performing the Michael addition-lactonization process at room temperature in isopropyl acetate allowed isolation of 3,4-dihydropyranone **241** in 82:18 dr and a low isolated yield of 20% due to instability towards purification by column chromatography. Despite the low yield, the enantioenrichment of both the major and minor diastereoisomers could be determined as 95:5 er and 90:10 er, respectively (Scheme 4.4).



Scheme 4.4: Isolation of 3,4-dihydropyranone **241**

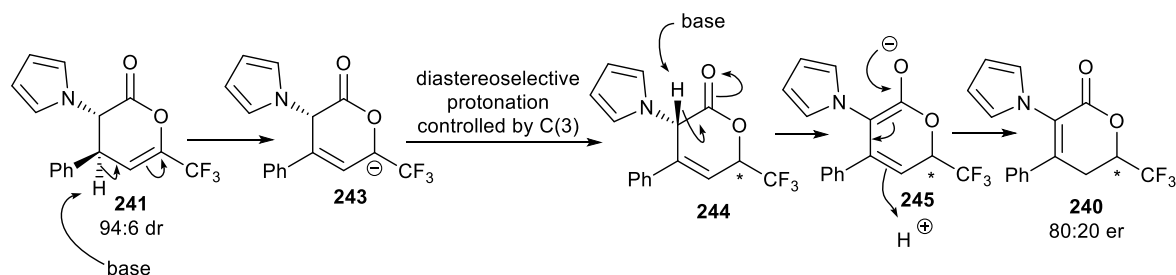
A sample of the isolated 3,4-dihydropyranone **241** (94:6 dr, 95:5 er_{major}, 90:10 er_{minor}) was dissolved in DMF at room temperature, however no isomerization to 5,6-dihydropyranone **240** was detected by TLC analysis after overnight stirring. Next, (2*S*,3*R*)-HyperBTM **93** (10 mol%)

and 5 eq. *i*-Pr₂NEt were added, with formation of 5,6-dihydropyranone **240** in 55% isolated yield after 2 d (Scheme 4.5). HPLC analysis of **240** revealed an enantioselectivity of 80:20 er.



Scheme 4.5: Isomerization of isolated xx in DMF

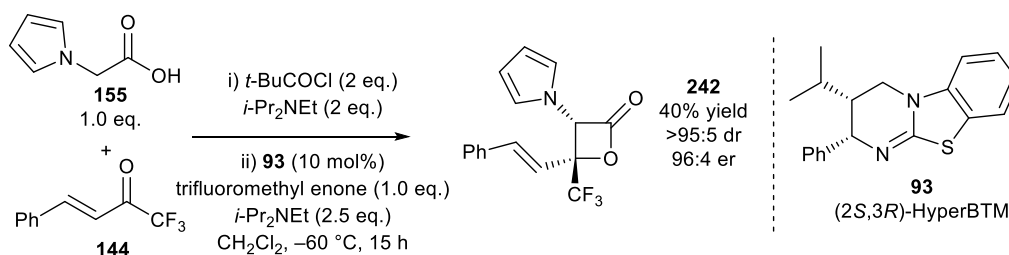
The absolute configuration of the 5,6-dihydropyranone **240** has not been confirmed to date, as a suitable single crystal could not be obtained for X-ray analysis. However a tentative mechanism can be proposed to explain how this enantioenriched product may be obtained. Isomerization through initial deprotonation at C(4), followed by protonation at C(6) must be diastereoselective and controlled by the C(3)-stereocentre. Deprotonation at C(3) generates the conjugated system **245**, followed by further protonation at C(5) to give the desired product (Scheme 4.6).



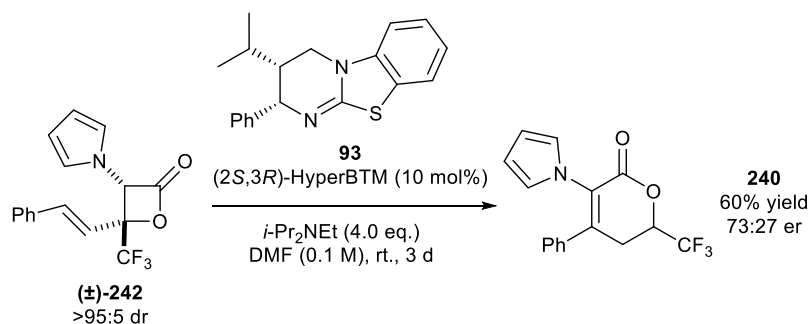
Scheme 4.6: Proposed mechanism for isomerization and the origin of enantioselectivity

4.2.3. β -lactone from [2+2] cycloaddition

One of the interesting observations in this catalytic system was the observation of the β -lactone which was presumably generated from a competing [2+2] cycloaddition. β -Lactone **242** was isolated from the reaction performed in CH₂Cl₂ at -60 °C, in 40% yield as a single diastereoisomer (>95:5 dr, based on ¹H and ¹⁹F NMR analysis) (Scheme 4.7). HPLC analysis revealed an excellent enantioselectivity of 96:4 er. The absolute and relative configuration of this β -lactone **242** was not unambiguously confirmed but assigned as (3*S*,4*R*) by analogy to the configuration of perfluoroalkyl substituted β -lactones formed through a related HyperBTM-catalyzed process.¹¹

Scheme 4.7: Isolation of β -lactone **242**

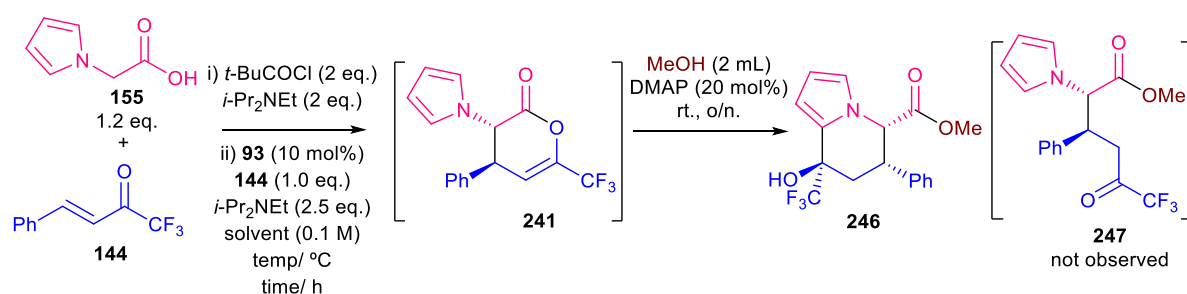
As the β -lactone was only obtained during reaction optimization when certain solvents or low reaction temperatures were employed, it was hypothesized that the β -lactone may be either unstable, or further transformed under the reaction conditions. To investigate this possibility, an isolated sample of racemic β -lactone **242** was subjected to 4 eq. *i*-Pr₂NEt and (2*S*,3*R*)-HyperBTM (10 mol%) in DMF. Interestingly, transformation of the racemic β -lactone **242** into 5,6-dihydropyranone **240** was observed within 3 days, with **240** isolated in 60% yield and with an enantioenrichment of 73:27 er (Scheme 4.8). This result could be explained by an isothioureia-mediated retro-formal [2+2] cycloaddition to reform the C(1)-ammonium enolate and CF₃ enone Michael acceptor, which may then engage in a subsequent enantioselective Michael addition-lactonization to give 3,4-dihydropyranone, which following the isomerization described in the previous section, gives the enantioenriched 5,6-dihydropyranone **240**.

Scheme 4.8: Formation of the isomerized product from β -lactone

4.2.4. Ring opening with nucleophiles

With 3,4-dihydropyranone **241** being observed as the major product (>80% product selectivity) by ¹H NMR analysis under several reaction conditions, *in situ* ring opening with a suitable nucleophile was investigated to facilitate the isolation of stable derivatives of the Michael addition-lactonization product 3,4-dihydropyranone **241**. Only small quantities (typically <5%) of the β -lactone **242** could be isolated upon ring-opening and could not be fully characterised.

Ring-opening was initially explored by methanolysis with an excess of methanol and 20 mol% DMAP (Table 4.3). For the reactions conducted at room temperature in CPME, the initial 3,4-dihydropyranone product **241** was formed in 81:19 dr. After *in situ* ring-opening with MeOH, the tetrahydroindolizine **246** was obtained in 88% yield, 75:25 dr, 93:7 er for the major diastereoisomer and 81:19 er for the minor diastereoisomer rather than the expected simple ring-opening product **247** (entry 1). Presumably, the ring-opening product **247** was initially formed, but underwent spontaneous cyclization to give the tetrahydroindolizine **246**. A new stereocentre was generated at C(8) during the cyclization, but only two diastereoisomers were identified from both ^1H and ^{19}F NMR analysis. Switching the solvent to *tert*-amyl alcohol led to the formation of **241** in improved dr (87:13), however following addition of methanol a lower isolated yield (47%) of tetrahydroindolizine **246** was obtained, with reduced product er for both diastereoisomers to 60:40 (entry 2). In isopropyl acetate at room temperature, 3,4-dihydropyranone **241** was formed in a dr of 82:18, with ring-opening with MeOH giving tetrahydroindolizine **246** in 88:12 dr, 71% yield, excellent er (97:3) for the major diastereoisomer, but lower er (68:32) for the minor diastereoisomer (entry 3). In MeCN at -40 °C, **241** was prepared in a good dr (87:13), giving tetrahydroindolizine **246** after ring-opening in a moderate 60% yield, 81:19 dr but excellent er (98:2 and 97:3 for each diastereoisomer) (entry 4). Using CPME at -40 °C provided **241** (81:19 dr), which subsequently gave tetrahydroindolizine **246** in high dr (88:12), 76% isolated yield and good er (94:6) for the major diastereoisomer (entry 5). The optimal conditions for the ring-opening process was found using isopropyl acetate as solvent at -40 °C, with tetrahydroindolizine **246** obtained in high dr (91:9) and yield (83%), and consistently excellent er for both major and minor diastereoisomer (98:2 and 96:4) (entry 6).

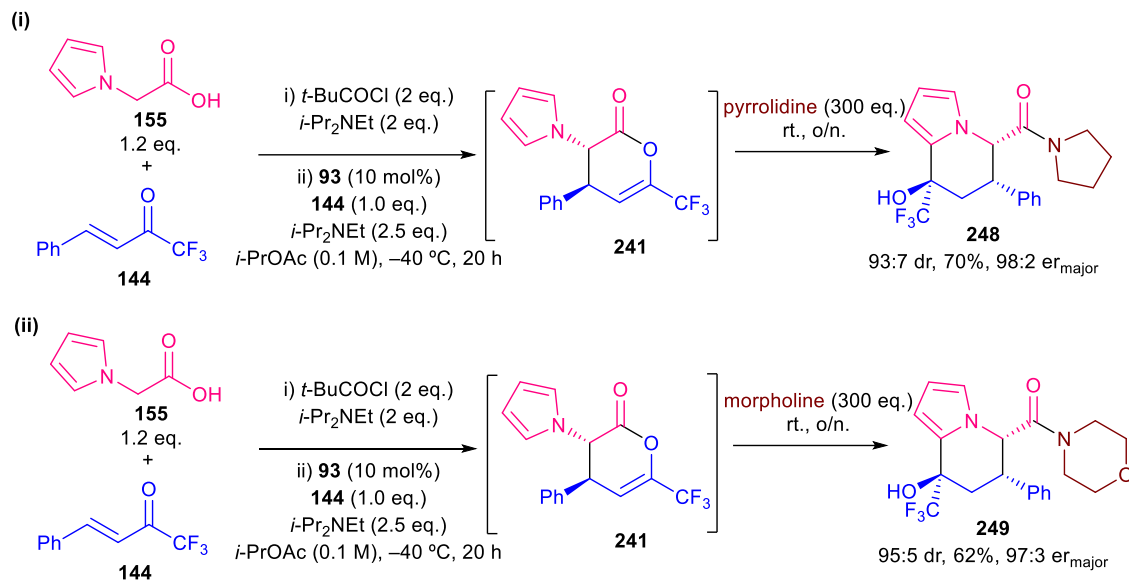


Entry	Solvent	Temp.	Time/ h	dr of 241 ^a	Yield ^b	dr of 246 ^a	er of 246 ^c
1	CPME	rt	18	81:19	88%	75:25	93:7 (major) 81:19 (minor)
2 ^d	<i>tert</i> -Amyl alcohol	rt	18	87:13	47%	70:30	62:38 (major) 60:40 (minor)
3	Isopropyl acetate	rt	18	82:18	71%	88:12	97:3 (major) 68:32 (minor)
4	MeCN	-40 °C	20	87:13	60%	81:19	98:2 (major) 97:3 (minor)
5	CPME	-40 °C	20	81:19	76%	88:12	94:6 (major) 92:8 (minor)
6	Isopropyl acetate	-40 °C	20	82:18	83%	91:9	98:2 (major) 96:4 (minor)

a. Determined by ¹H and ¹⁹F NMR analysis of crude reaction mixture. *b.* Combined isolated yield of **246** as a mixture of diastereoisomers. *c.* Determined by chiral HPLC analysis of isolated product. *d.* With 1.0 eq. **155**.

Table 4.3: Optimization for ring-opening with MeOH

In addition to methanolysis, secondary amines could also be applied as nucleophiles to provide tetrahydroindolizine products. After treating the reaction mixture at -40 °C in isopropyl acetate with an excess (300 eq.) of pyrrolidine, the cyclization product **248** was obtained in 93:7 dr, 70% isolated yield and an excellent er (98:2) for the major diastereoisomer (Scheme **4.9(i)**). If less pyrrolidine (5 eq.) was used, a reduced isolated yield of **248** (50%) was observed due to the formation of unidentified side products. Morpholine was also successfully applied to give the cyclization product in 95:5 dr, 62% isolated yield and 97:3 er (Scheme **4.9(ii)**). Compared to MeOH (£3 per 100 mL, Sigma-Aldrich), the secondary amines are significantly more expensive (£17.3 per 100 mL for morpholine and £33.5 per 100 mL for pyrrolidine, Sigma-Aldrich). Due to this price difference and the lower boiling point of MeOH, to simplify product isolation, subsequent studies on the scope of this transformation used methanol for the ring-opening step.



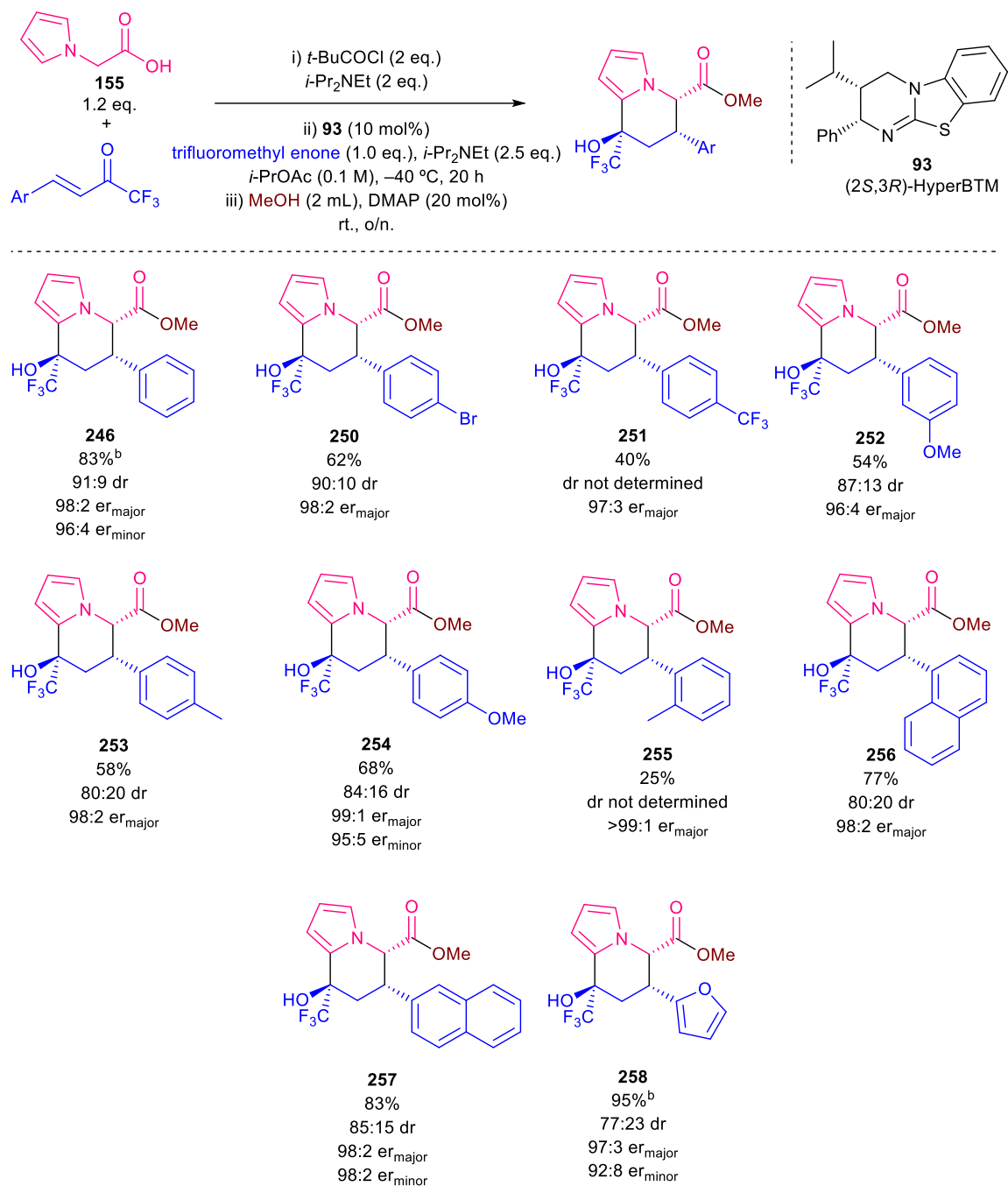
dr determined by ^1H and ^{19}F NMR analysis of crude reaction mixture, yield refers to the isolated yield in >95:5 *dr*, *er* was determined by chiral HPLC analysis.

Scheme 4.9: Ring opening with 2° amines

4.2.5. Reaction scope

The scope of this transformation was studied with different aryl/heteroaryl substituted trifluoromethyl enones, followed by methanolysis, to give a range of enantioenriched tetrahydroindolizine derivatives (Scheme 4.10). Incorporation of formally-electron withdrawing groups at the 4-position and 3-position of the β -aryl ring of the CF_3 enone Michael acceptor,¹² tetrahydroindolizines **250**, **251** and **252** were formed in good *dr* (87:13 to 90:10) and excellent *er* (96:4 to 98:2), however **251** was only obtained in low 40% yield. Trifluoromethyl enones bearing electron rich β -aryl rings (4-MeC₆H₄ or 4-OMeC₆H₄) were also tolerated, forming cyclization products **253** and **254** in 58% and 68% yield, moderate *dr* (80:20 and 84:16) and excellent *er* for the major diastereoisomer in each case (98:2 and 99:1). With the incorporation of a 2-Me substituent on the β -aryl ring of the CF_3 enone, a significantly lower isolated yield of tetrahydroindolizine **255** (25%) was found, however excellent enantioselectivity for the major diastereoisomer (>99:1 *er*) was still observed. Electron neutral 1-naphthyl and 2-naphthyl substituted CF_3 enones were also tolerated, giving products **256** and **257** in good yield (77% and 83%), good *dr* (80:20 and 85:15) and excellent *er* for the major diastereoisomer (both 98:2 *er*). Incorporation of a 2-furyl group at the β -position of the CF_3 Michael acceptor was also tolerated, giving cyclization product **258** in high 95% yield, good *dr*

of 77:23, high er for the major diastereoisomer (97:3) and slightly reduced er for the minor diastereoisomer (92:8).

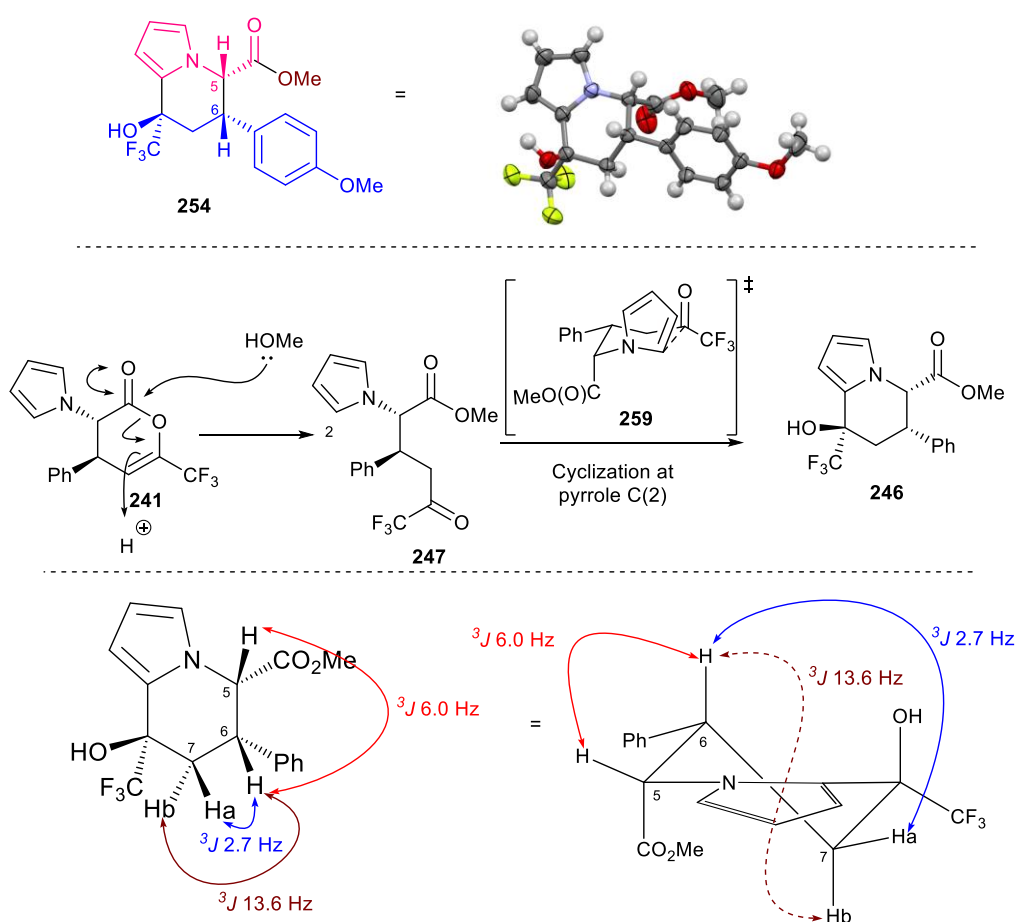


a. Yield refers to isolated yield of major diastereoisomer (>95:5 dr) unless otherwise stated. dr determined by ^1H and ^{19}F NMR analysis of crude reaction mixture following ring-opening, e_r determined by chiral HPLC analysis. b. Combined isolated yield as a mixture of diastereoisomers.

Scheme 4.10: Scope using different trifluoromethyl enones^a

The crystal structure of the enantioenriched major diastereoisomer of **254** was obtained by single crystal X-ray analysis,¹³ allowing determination of its absolute and relative configuration, with the configuration of the major diastereoisomer for all other cyclization products and 3,4-

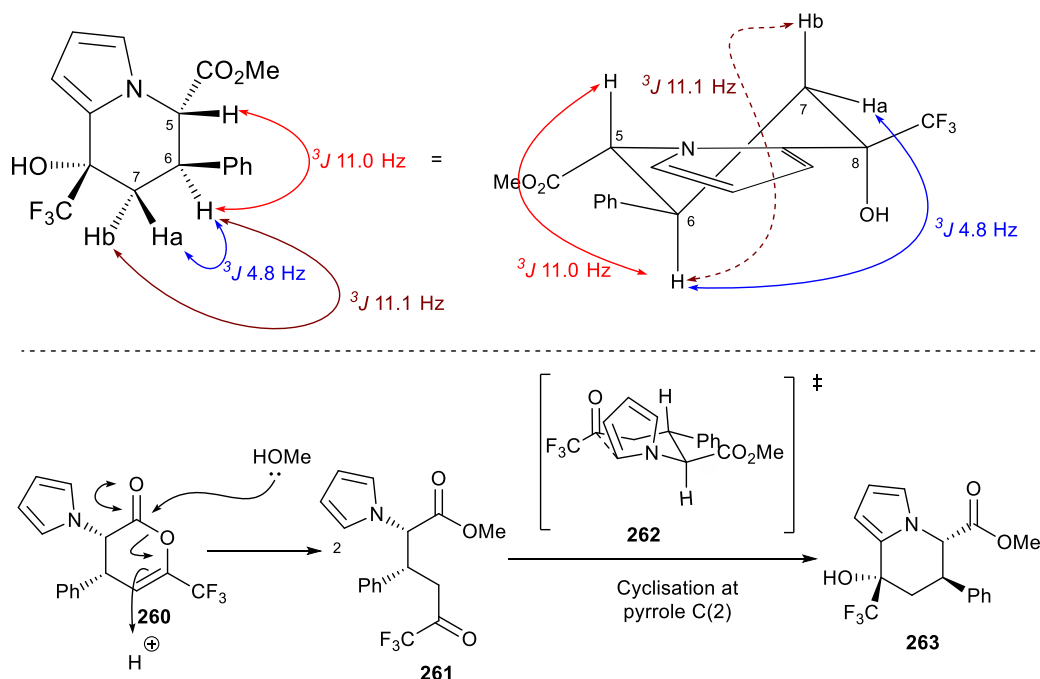
dihydropyranone **241** being assigned by analogy (Scheme 4.11). The configuration of the stereocentre at C(8), formed during the cyclization process, may be rationalised using a chair-like Zimmerman–Traxler type transition state¹⁴ **259** with the CF₃ group in a pseudo-equatorial position. In solution, coupling constants analysis for the major diastereoisomer **246** showed: (i) C(5)H and C(6)H of 6.0 Hz (axial-equatorial coupling); (ii) C(6)H and C(7)Ha of 2.7 Hz (axial-equatorial coupling); (iii) C(6)H and C(7)Hb of 13.6 Hz (trans-diaxial coupling). Based upon Karplus equation, the observed coupling constants are consistent with the half-chair structure determined by the X-ray single crystal analysis in the solid state.¹⁵



Scheme 4.11: Determination of absolute configuration of **254, and proposed cyclization transition state**

Due to isolation difficulties, an enantioenriched sample of the minor diastereoisomer could not be isolated and crystallized to enable determination of its absolute or relative configuration. However analysis of the coupling constants for the minor diastereoisomer showed the coupling constant between C(5)H and C(6)H was 11.0 Hz, which can be assigned,

according to Karplus equation,¹⁵ as a trans-diaxial coupling. This is consistent with a change in the relative configuration between C(5) and C(6) for the two diastereoisomers. Assuming the configuration at C(5) is consistent with that observed within the major diastereoisomer, the configuration at C(6) is assigned as (*R*). No information on the relative configuration of C(8) was obtained from ¹H NMR analysis of the minor diastereoisomer but it is assigned as (*S*)- assuming a similar cyclisation transition state **262** (Scheme 4.12)



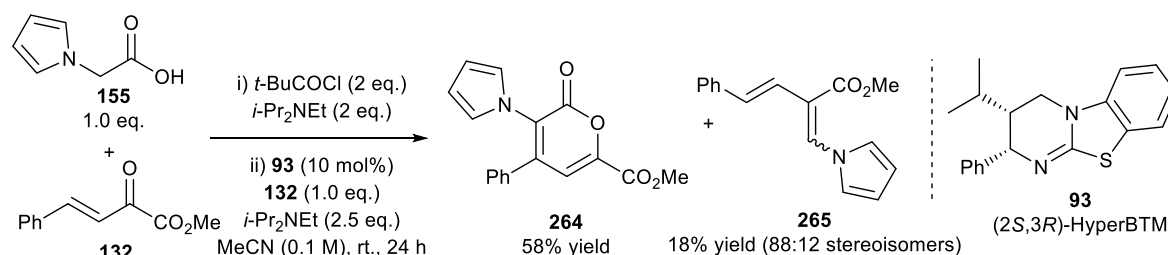
Scheme 4.12: Coupling constant analysis and proposed transition state for the minor diastereoisomer

4.3. The use of α -keto- β,γ -unsaturated esters in the synthesis of tetrahydroindolizine derivatives

After the successful synthesis of tetrahydroindolizine derivatives using trifluoromethyl enone Michael acceptors, attention was turned to the use of an alternative electron-deficient Michael acceptor, α -keto- β,γ -unsaturated esters (Chapter 2). It was assumed that the α -keto ester group may also allow the one-pot synthesis of alternatively-functionalized tetrahydroindolizine derivatives.

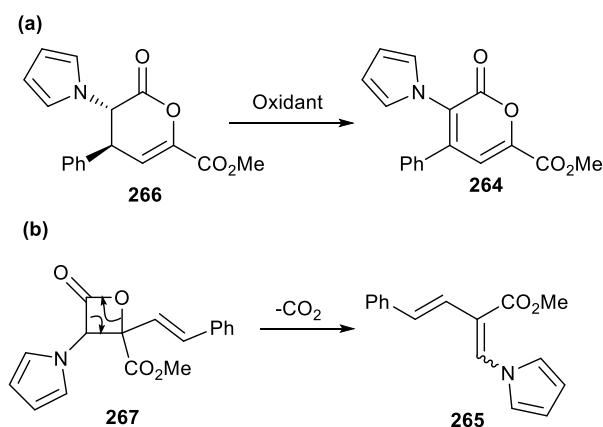
4.3.1. Reaction conditions screening

Initial studies were carried out in MeCN at room temperature using 10 mol% HyperBTM **93** (Scheme 4.13). In contrast to the work using CF₃ enones, no 3,4-dihydropyranone, 5,6-dihydropyranone or β -lactone products were observed. Instead, a mixture of pyranone **264** and diene **265** were identified by ¹H NMR analysis of the crude material. Chromatographic purification allowed the isolation of the major pyranone **264** in 58% yield, while diene **265** was isolated in 18% yield as a mixture of stereoisomers in 88:12 ratio (not assigned by ¹H NMR).



Scheme 4.13: Observation of a mixture of two products at room temperature

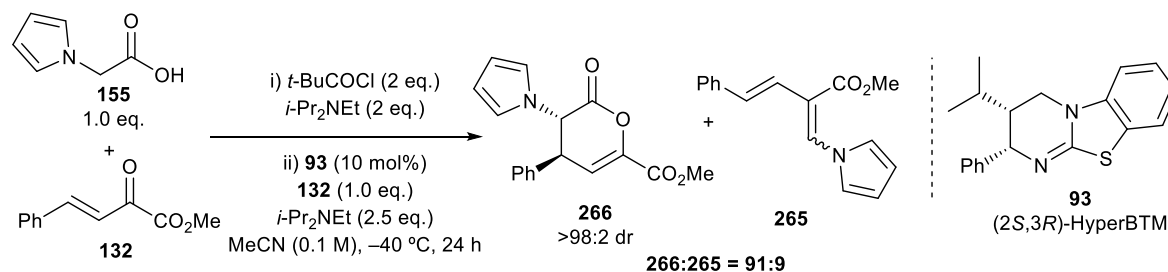
Although these products were unexpected, the origin of their generation can be proposed (Scheme 4.14). Assuming initial formation of Michael addition-lactonization product 3,4-dihydropyranone **266**, an oxidant, for example trace of oxygen dissolved in commercially available dry MeCN, may be responsible for oxidizing **266** into pyranone **264** (Scheme 4.14(a)). Formation of diene **265** is most likely to form following initial formation of a β -lactone **267**, followed by entropy-driven elimination of CO₂ (Scheme 4.14(b)).



Scheme 4.14: Proposed formation of unexpected products 264 and 265

To circumvent formation of these unwanted products, the reaction was performed at -40 °C in MeCN. At this temperature, pyranone **264** was not observed by ¹H NMR analysis of the

crude mixture, and full consumption (within 24 hours) of **132** into a 91:9 mixture of the desired 3,4-dihydropyranone **266** and diene **265** was found, with the 3,4-dihydropyranone **266** formed as a single diastereoisomer in >98:2 dr (Scheme 4.15). Other solvents were tested (CH₂Cl₂ and *i*-PrOAc), but neither of them provided any improvement compared to MeCN.

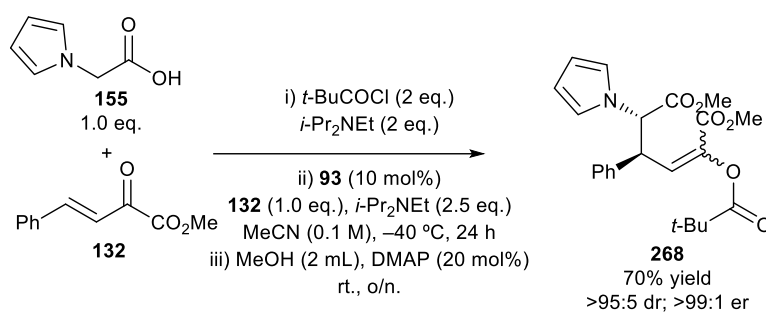


Scheme 4.15: Reaction performed at -40 °C in MeCN

Unfortunately, all attempts, including chromatography and recrystallization, to isolate the 3,4-dihydropyranone **266** resulted in full decomposition. The unstable nature of this product suggested that a ring-opening procedure should be carried out to facilitate the isolation of a stable ring-opening derivative.

4.3.2. Ring opening with MeOH

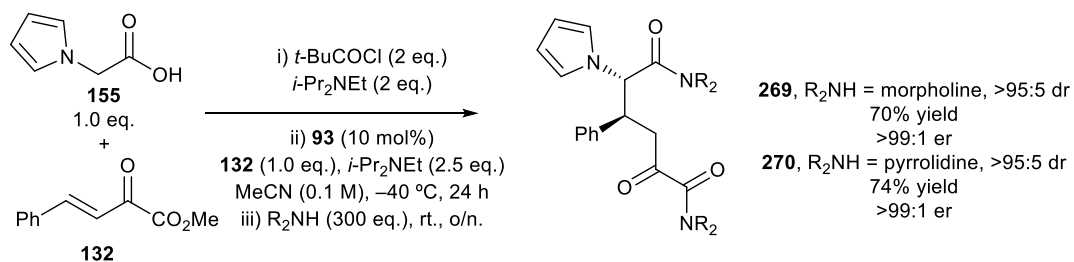
As a starting point for the ring opening study, MeOH was selected as a nucleophile due to its readily accessibility and low boiling point. After treating the reaction mixture at -40 °C in MeCN with MeOH (2 mL) and DMAP (20 mol%), a mixture of several products was identified by ¹H NMR analysis of the crude material (Scheme 4.16). Chromatographic purification allowed the isolation of the MeOH ring-opening derivative **268** from 3,4-dihydropyranone **266** (70% yield, >95:5 dr and >99:1 er) as the major product. The high dr and excellent er observed for the major ring-opened product **268** suggested that the initial 3,4-dihydropyranone **266** product was synthesized with an excellent level of both enantio- and diastereoselectivity. Inspired by this excellent degree of enantioselectivity, the use of secondary amines as ring-opening nucleophiles was tested next.



Scheme 4.16: Exploring the ring opening with MeOH

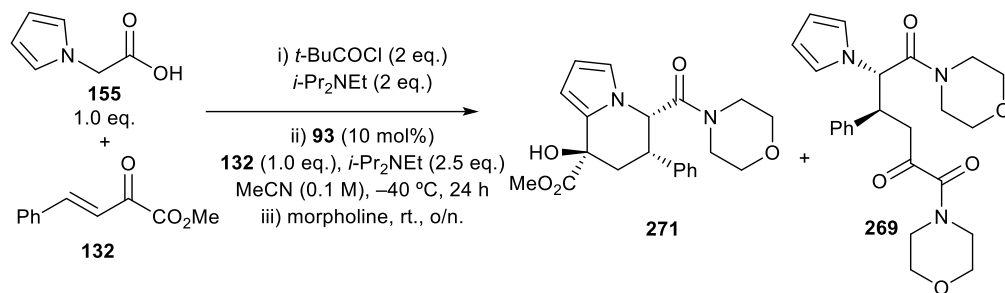
4.3.3. Ring-opening process with amines

When employing an excess (300 eq.) of secondary amines morpholine or pyrrolidine for the ring-opening process, diamide products **269** and **270** were obtained in 70% and 74% isolated yield, and with excellent diastereoselectivity (>95:5 dr) and enantioselectivity (>99:1 er) (Scheme 4.17). Formation of these products can be explained through a sequential ring-opening/amidation process. The absence of any tetrahydroindolizine products suggests that nucleophilic attack of the secondary amine on the α -ketoester to form the amide was much faster than the competing intramolecular cyclization process with pyrrole. In order to slow down this amide formation and provide an opportunity for cyclization to give the desired tetrahydroindolizine product, the use of fewer equivalents of amine was investigated for the ring opening process.



Scheme 4.17: Formation of diamides with an excess of amines

Reducing the equivalents of morpholine to 10 provided tetrahydroindolizine **271** in addition to diamide **269**, with a product distribution of 62:38 (**271**:**269**) (Table 4.4, entry 1). The use of 5 equivalents of morpholine provided improved selectivity for tetrahydroindolizine (86:14, **271**:**269**) and a slightly increased isolated yield of 64% (entry 2). The best results were obtained when 2 equivalents of morpholine were employed, giving exclusively the tetrahydroindolizine **271** in 75% isolated yield, >95:5 dr and >99:1 er (entry 3).

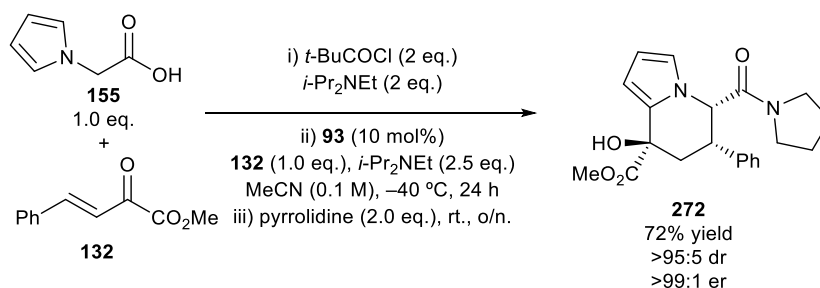


Entry	Morpholine eq.	271:269 ^a	Isolated yield of 271 ^b	dr of 271 ^a	er of 271 ^c
1	10	62:38	42%	>95:5	>99:1
2	5	86:14	64%	>95:5	>99:1
3	2	100:0	75%	>95:5	>99:1

a. Determined by ¹H NMR analysis of the crude reaction mixture. b. Isolated yield of **271** as a single diastereoisomer (>95:5 dr). c. Determined by chiral HPLC analysis.

Table 4.4: Optimization for the formation of tetrahydroindolizine product

Using these optimal conditions, the same reaction was repeated and quenched with 2 equivalents of pyrrolidine (Scheme 4.18). Tetrahydroindolizine **272** was formed exclusively in a similar isolated yield of 72%, and equally excellent >95:5 dr and >99:1 er.

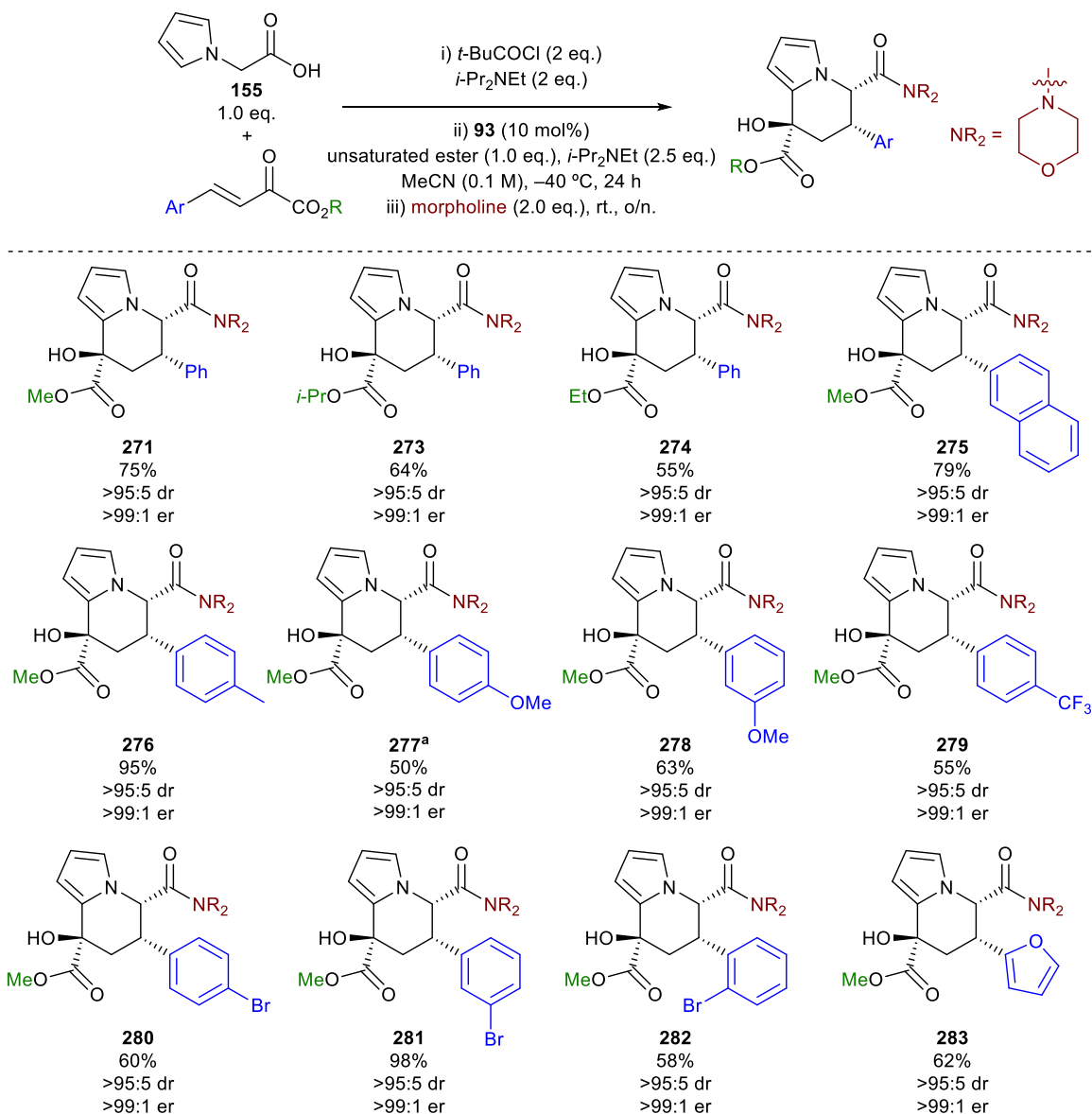


Scheme 4.18: Tetrahydroindolizine product formation with 2 eq. pyrrolidine

4.3.4. Exploring the scope of α -keto- β,γ -unsaturated esters

With the optimized conditions giving the desired tetrahydroindolizine product, the scope was further studied with different α -keto- β,γ -unsaturated esters, and employing morpholine (2 equiv.) as the nucleophile in the ring-opening process (Scheme 4.19). In all cases the tetrahydroindolizine products were obtained with consistently excellent diastereo- and enantioselectivity (>95:5 dr and >99:1 er in each case). Both *i*-Pr ester and ethyl esters were tolerated, giving products **273** and **274** in good yield (64% and 55%). The use of electron-

neutral 2-naphthyl substituted unsaturated keto ester gave tetrahydroindolizine **275** in a good yield of 79%, whilst incorporation of an electron-donating 4-Me substituent on phenyl ring of the unsaturated keto ester afforded tetrahydroindolizine **276** in an excellent yield of 95%. Due to the low solubility of 4-methoxyphenyl substituted keto ester in MeCN, the reaction was conducted in CH₂Cl₂, with the cyclization product **277** isolated in a slightly lower yield of 50%. Incorporation of formally electron-withdrawing 3-OMe or 4-CF₃ substituent on the phenyl ring of unsaturated keto esters was also tolerated,¹² giving the corresponding tetrahydroindolizine **278** and **279** in 63% and 55% yield respectively. A range of keto ester Michael acceptors with a 2-, 3- or 4-Br substituent on the phenyl ring of the α -keto- β,γ -unsaturated esters gave products **280-282** in 58% to 98% isolated yield and excellent er. Finally, 2-furyl derived unsaturated keto ester afforded the cyclization product **283** in comparable 62% isolated yield. Attempts to obtain a crystal structure for the isolated tetrahydroindolizines were unsuccessful and so the relative configuration was assigned based upon the observed average coupling constant of 6.1 Hz between C(5)-H and C(6)-H for the major diastereoisomer **271** (compared with the observed coupling constants of 11.0 Hz for the minor diastereoisomer within CF₃ containing tetrahydroindolizine) and the absolute configuration of all the isolated tetrahydroindolizines were assigned by analogy to the crystal structure obtained earlier when using CF₃ enone Michael acceptors (Scheme **4.11**).

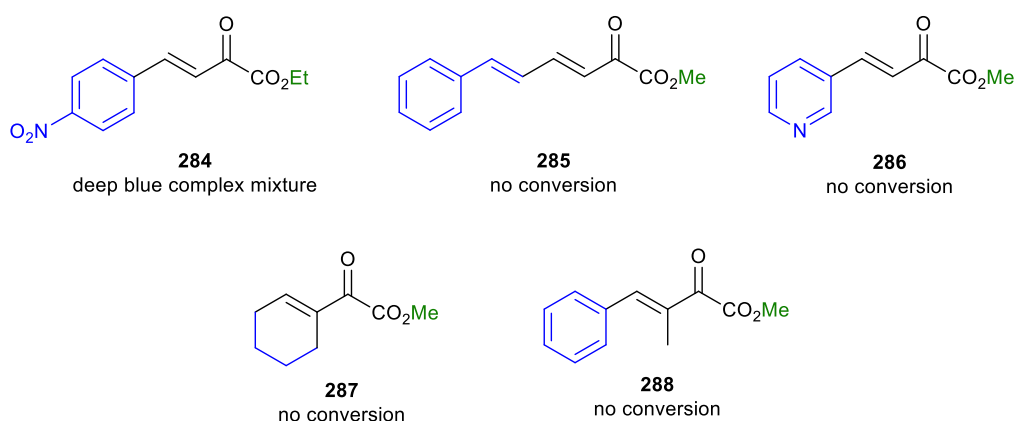


a. Reaction in CH_2Cl_2 . b. Yield refers to isolated yield as a single diastereoisomer of >95:5 dr, dr determined by ^1H NMR analysis of the crude ring-opening mixture, er determined by chiral HPLC analysis.

Scheme 4.19: Scope with α -keto- β,γ -unsaturated esters^b

During investigation of the substrate scope of this process, some limitations with respect to the α -keto- β,γ -unsaturated ester substrate were recognized (Scheme 4.20). With 4-NO₂ substituted substrate **284**, full consumption of **284** into an unidentified complex mixture, which was deep blue in colour, was observed. Incorporation of an alkenyl substituent, or a 3-pyridyl group at the γ -position of the α -keto- β,γ -unsaturated ester provided no formation of the desired dihydropyranone, which was attributed to the substrate's low solubility in both CH_2Cl_2 and MeCN at -40°C . Introduction of an extra substituent at the β -position of the

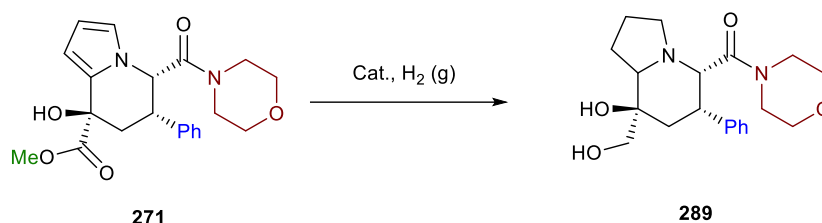
Michael acceptor was also investigated, however application of α -ketoesters resulted in the no product formation and only the return of starting materials. These final results are consistent with previous enantioselective isothiurea-catalyzed Michael addition-cyclization methodologies,¹⁶ in which, to date, the use of Michael acceptors bearing a substituent adjacent to the ketone/imine moiety have not been successfully applied.



Scheme 4.20: Unsuccessful Michael acceptors

4.3.5. Exploring the synthetic utility

The synthetic utility of this cyclization product was explored next. Based on a number of literature precedents on related systems,¹⁷⁻¹⁹ the selective hydrogenation of tetrahydroindolizine **271** was tested. Unfortunately, under all the catalytic conditions tested so far using either PtO₂ or Rh (entry **1-3**), full consumption of starting material **271** was observed after overnight stirring to afford a complex mixture of unidentified products. A shorter reaction time, as well as lower pressure of hydrogen did not show any improvements. Purification by column chromatography was not successful for the isolation of any hydrogenation products (Table **4.5**).

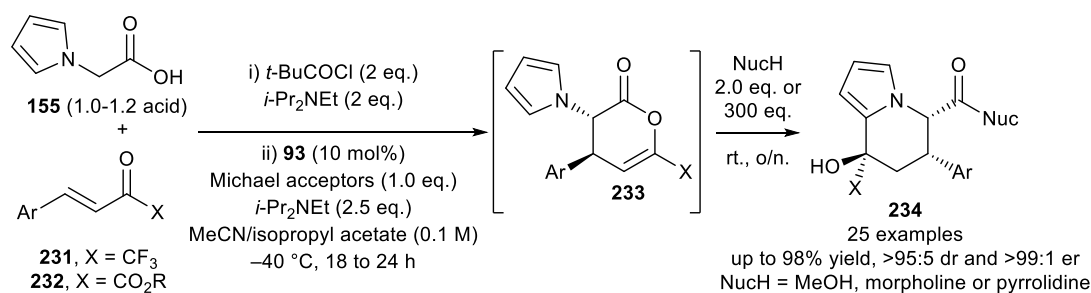


Entry	Conditions	Results
1	PtO ₂ (25 mol%), AcOH, H ₂ balloon, rt., o/n.	Complex mixture
2	5% Rh on Al ₂ O ₃ (5 w/w%), MeOH, rt., 5 atm H ₂ , o/n.	Complex mixture
3	5% Rh on Al ₂ O ₃ (5 w/w%), HFIP, rt., 5 atm H ₂ , o/n.	Complex mixture

Table 4.5: Attempts on hydrogenation of tetrahydroindolizine 271

4.4. Conclusions

In conclusion, a one-pot isothiourea-catalyzed Michael addition/lactonization followed by *in situ* ring-opening with a nucleophile (MeOH or secondary amine) afforded highly enantioenriched tetrahydroindolizine products **234** bearing 3 stereogenic centres in up to 98%, >95:5 dr and >99:1 er (Scheme 4.21). 25 Examples, with the incorporation of both electron-withdrawing and donating aryl ring, as well as heterocycles, were successfully synthesized. The absolute configuration of products in the CF₃ enone series were confirmed by single crystal X-ray analysis. Unfortunately further derivatization through transition-metal catalyzed hydrogenation was not unsuccessful.



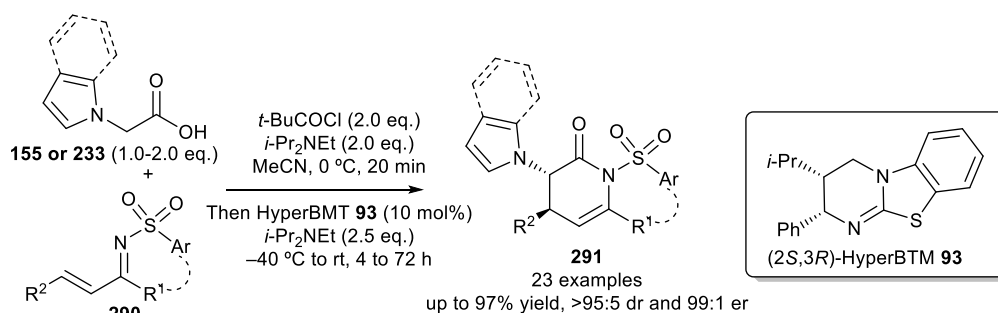
Scheme 4.21: One-pot synthesis of tetrahydroindolizine

4.5. References

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Chapter 5: Enantioselective synthesis of C(3)-pyrrolyl/C(8)-indolyl dihydropyridinones

Having demonstrated the application of 2-pyrrolyl acetic acid **155** in Michael addition-lactonization (Chapter **3** and **4**), this chapter describes further organocatalytic formal [4+2] cycloadditions with 2-pyrrolyl and 2-indolyl acetic acids **233** as C1-ammonium enolate precursors. Interest will focus on the use of both acyclic α,β -unsaturated ketimines and cyclic sulfonamide derived α,β -unsaturated ketimines in isothiurea catalyzed Michael addition-lactamization processes to access chromatographically stable dihydropyridinones **291** (Scheme **5.1**).



Scheme 5.1: Isothiurea catalyzed synthesis of dihydropyridinones

5.1. Introduction

In the area of natural products and bioactive small molecules, the dihydropyridinone motif is recognized as an important heterocyclic molecule containing a six membered ring with a cyclic amide.^{1,2} For example, the tetracyclic dihydropyridinone Finasteride **292** was used in the treatment of human hair loss,³ meanwhile the spiro-cyclic dihydropyridinone **293** showed its bioactivity in the antiproliferation of leukemia cell (Fig. **5.1**).⁴

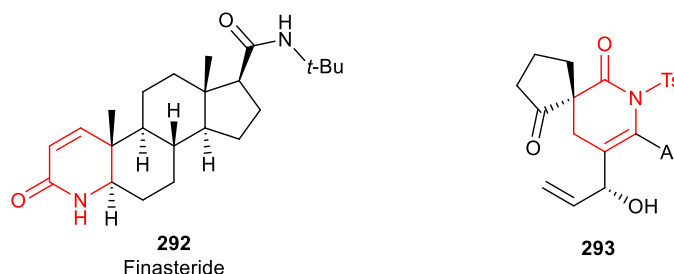
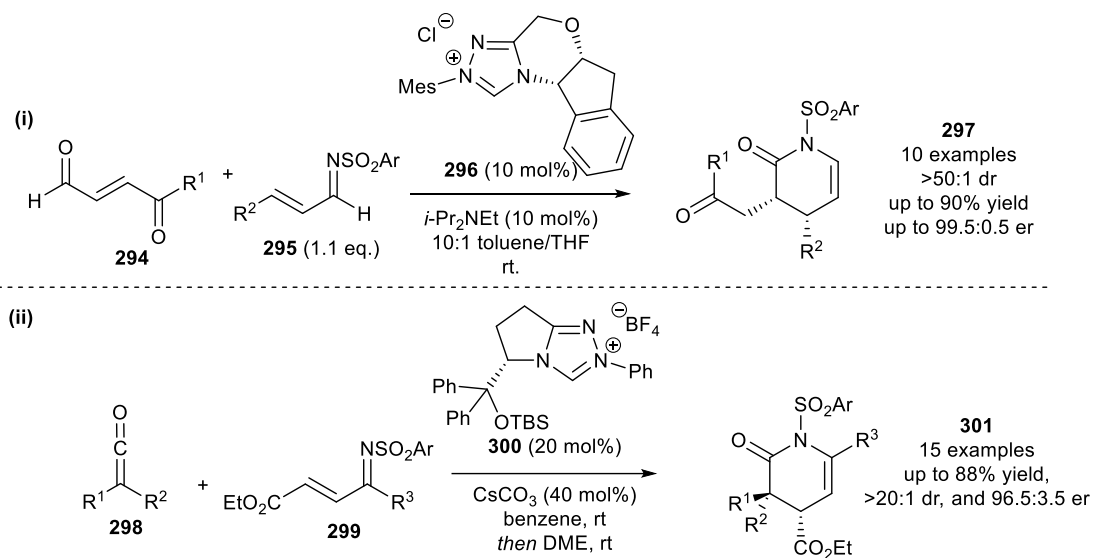


Fig. 5.1: Commonly found bioactive small molecules containing dihydropyridinone

Historically, one major synthetic approach towards these dihydropyridinone derivatives via [4+2] cycloaddition was the aza-Diels-Alder reaction through either a normal-electron demand

(involving nitrogen containing electron rich dienes and electron poor dienophiles) or an inverse-electron demand (involving nitrogen containing electron deficient dienes and electron rich dienophiles) pathway.^{5,6} Due to the high demand to access these dihydropyridinone derivatives in their enantioenriched form, approaches featuring the use of a compatible Lewis acid with chiral ligands have been developed.⁶⁻⁹ In addition, since the wide application of organocatalysis, several organocatalytic aza-Diels-Alder reaction have been developed,¹⁰⁻¹³ with the most state-of-the-art NHC-catalyzed aza-Diels-Alder reaction being developed by Bode¹⁴ and Ye.¹⁵ In Bode's procedure (Scheme 5.2(i)), enals **294** and α,β -unsaturated aldimines **295** were reacted using NHC pre-catalyst **296** to form **297** in high yield and excellent stereoselectivity,¹⁴ while ketenes **298** and α,β -unsaturated ketimines **299** were employed in Ye's work to obtain **301** in comparable yield and enantioselectivity (Scheme 5.2(ii)).¹⁵



Scheme 5.2: NHC-catalysed enantioselective synthesis of dihydropyridinones

In addition to acyclic α,β -unsaturated ketimines, cyclic sulfonamide core structures, commonly derived from the corresponding artificial sweetener saccharin **302**, have been used by synthetic chemists to access dihydropyridinones and their derivatives.^{16,17} It is widely found in many biologically active drug molecules, such as Ampiroxicam **303**,¹⁸ an example of anti-inflammatory agent (Fig. 5.2). Another biologically active drug molecule Ipsapirone **304**,¹⁹ recognized for its application as a neuroprotectants, also consists of the core cyclic sulfonamide structure.

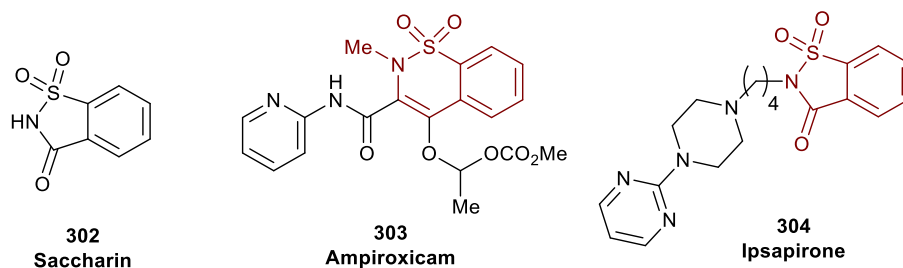
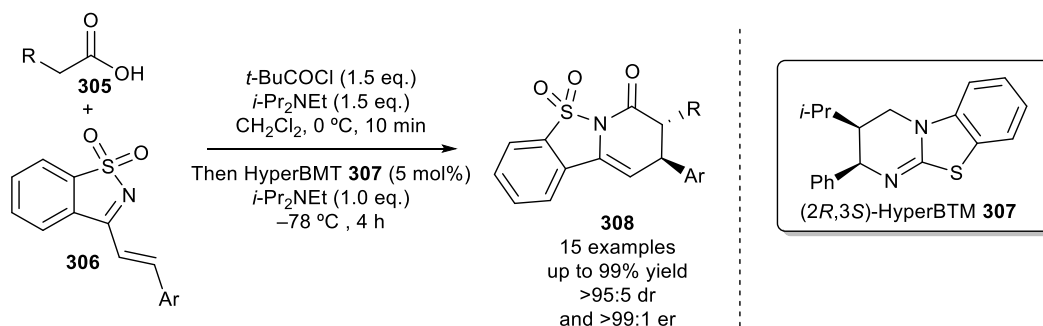


Fig. 5.2: Saccharin and its derivatives

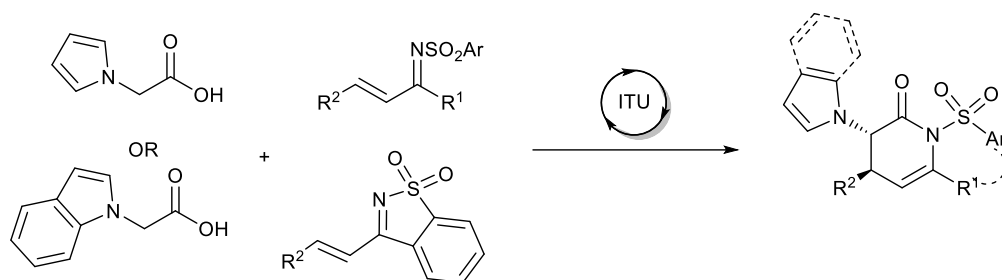
5.2. Previous work in the Smith Group

Along with N-heterocyclic carbene catalysis, the use of C1-ammonium enolates have been demonstrated for the enantioselective Michael addition/lactamization to access of dihydropyridinones with α,β -unsaturated ketimines **306** as Michael acceptors (Scheme 1.20).²⁰ The same Michael addition-lactamization strategy with isothiurea catalysis could also be applied in the synthesis of polycyclic dihydropyridinones. Starting with saccharin-derived α,β -unsaturated ketimines **306** and aryl/heteroaryl acetic acids **305**, after *in situ* activation with pivaloyl chloride and *i*-Pr₂NEt, cyclic dihydropyridinones **308** could be obtained in high dr (>95:5 dr), good yield (up to 99%) and excellent enantioselectivity (>99:1 er) (Scheme 5.3).²¹



Scheme 5.3: Isothiurea catalyzed enantioselective synthesis of tricyclic dihydropyridinones

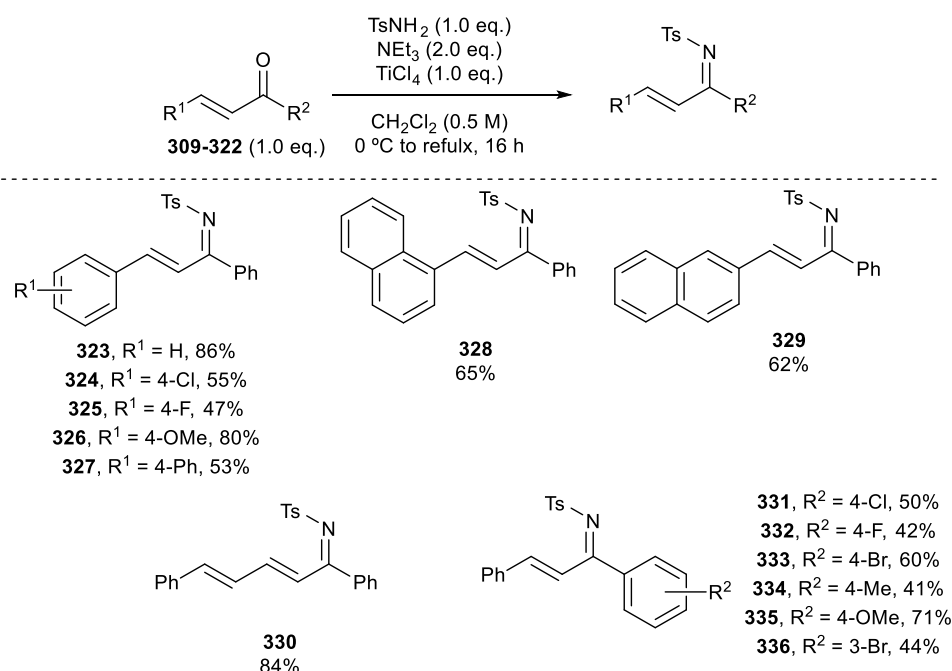
Following these strategies, this chapter describes the use of acyclic α,β -unsaturated ketimines and saccharin-derived α,β -unsaturated ketimines in Michael addition-lactamization with pyrrolyl **155** or indolyl acetic acid **223** (Scheme 5.4).



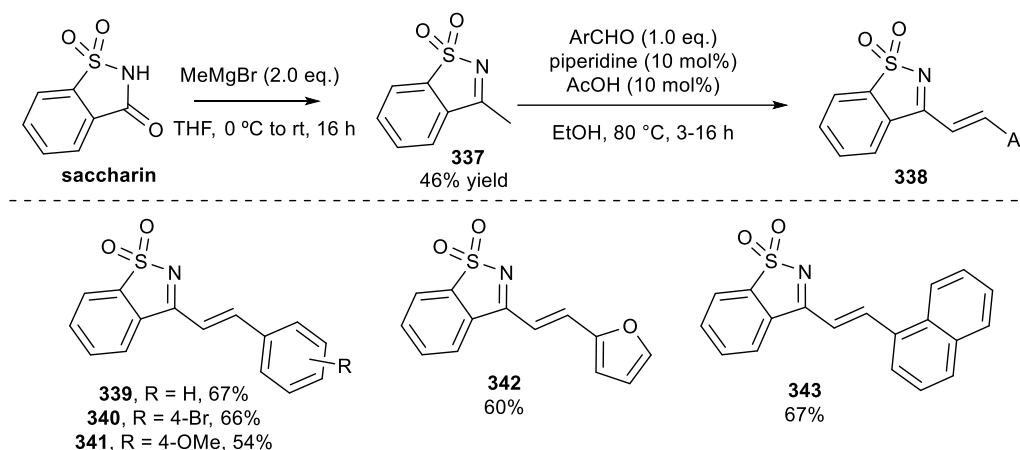
Scheme 5.4: Proposed isothiurea-catalyzed Michael addition-lactamization

5.3. Substrate preparations

α,β -Unsaturated ketimines **323-336** were prepared from the corresponding substituted chalcones **309-322** via condensation with *p*-toluenesulfonamide in the presence titanium tetrachloride (1 equiv.) and triethylamine (2 equiv.) (Scheme 5.5).²⁰ Following chromatographic purification, ketimines were obtained in a range of yields between 41% to 86% as bench stable solids. ¹H NMR analysis of the isolated ketimine **323** indicated the presence of a single ketimine (*E*)-isomer, with proton chemical shifts showing a good correlation with the literature values.²⁰ Considering the large C=N bond isomerization barrier of *ca.* 109 kJ/mol, the isomerization to another imine configuration was unlikely at room temperature.²²

Scheme 5.5: Preparation of α,β -unsaturated ketimines

Saccharin-derived Michael acceptors **339-343** were synthesized from saccharin via a two-step literature procedure,²¹ and was carried out by summer placement student Lucas Bacheley. Grignard addition between saccharin and MeMgBr afforded the intermediate imine **337** in 46% isolated yield. Subsequent aldol condensation between imine **337** and benzaldehyde derivatives gave the corresponding α,β -unsaturated ketimines **339-343** in good yield (up to 67%) (Scheme 5.6).



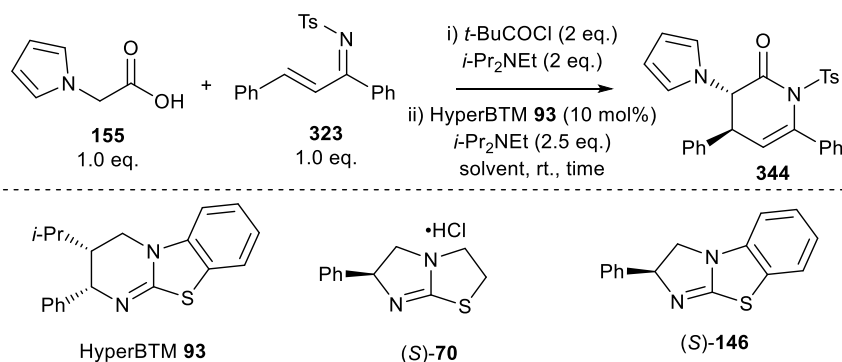
Scheme 5.6: Synthesis of saccharin-derived Michael acceptors

5.4. Acyclic α,β -unsaturated ketimines as Michael acceptors

5.4.1. Reaction conditions optimization

Investigation began with using 2-pyrrolyl acetic acid **155** and acyclic α,β -unsaturated ketimine **323** in the Michael addition-lactamization sequence (Table 5.1). Optimization studies used (2*S*,3*R*)-HyperBTM **93**, as this catalyst had been found to be optimal for the reactions described in Chapter 3. Started with using DMF as the solvent at room temperature, the dihydropyridinone **344** could be furnished in 54% yield, excellent dr of 95:5 and moderate er of 78:22 (entry 1). Changing the solvent to THF led to a reduced isolated yield 35% after 72 h due to incomplete consumption of starting material as shown by ¹H NMR analysis of the crude reaction mixture. **344** was isolated as a single diastereoisomer with moderate 68:32 er (entry 2). Conducting the reaction in CH₂Cl₂ resulted in comparable er (79:21) to using DMF, but a low yield of 40% was obtained (entry 3). Switching to other ethereal solvents, such as CPME and MTBE did not show any improvements in the er and yield compared with entry 1-3, with MTBE showing only trace product formation (<5%) (entry 4-5). Using two equivalents of pyrrolyl acetic acid **155** led to a higher isolated yield in EtOAc, with the desired

dihydropyridinone **344** isolated in 85% yield and 77:23 er (entry **6**). A slightly improved er of 82:18 was observed using *i*-PrOAc as solvent, albeit with a lower isolated yield of 65% (entry **7**). Finally, the use of MeCN was found to be the optimal solvent, giving a balance between a high isolated yield (90%) and er (76:24) (entry **8**). Unfortunately, the use of other isothiourea catalysts, such as (*S*)-tetramisole **70** or (*S*)-benzotetramisole **146**, provided the dihydropyridinone **344** in lower yields (55% and 40%) and reduced enantioselectivity (62:38 er) (entry **9-10**). Without catalyst, no background reaction was observed in MeCN (entry **11**). The er values reported here for Table 5.1 were obtained from HPLC traces of **344** prepared from a mixture of MeCN and isopropyl alcohol, making sure that all the material was fully dissolved. It was serendipitously observed that when preparing **344** from entry **8** in only isopropyl alcohol for HPLC analysis, a cloudy mixture was obtained, and the HPLC traces of the filtrate after removing the insoluble material revealed a manual enhancement of the er from 76:24 to 97:3 (3*S*,4*S*:3*R*,4*R*). HPLC analysis of the insoluble material revealed a reduced er of 45:55 (3*S*,4*S*:3*R*,4*R*). This process can be used to enhance product er but does not reflect the real er from the reaction mixture.



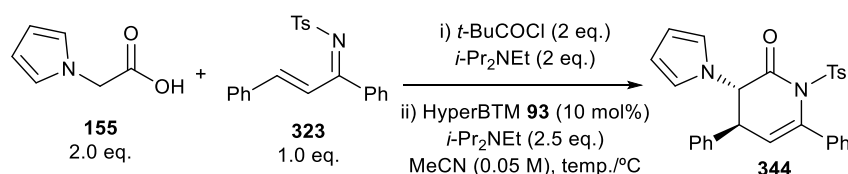
Entry	Solvent (conc.)	Time/ h	dr ^a	Yield ^b	er ^c
1	DMF (0.1 M)	24	>95:5	54%	78:22
2	THF (0.1 M)	72	>95:5	35%	68:32
3	CH ₂ Cl ₂ (0.1 M)	72	>95:5	40%	79:21
4	CPME (0.1 M)	72	>95:5	44%	69:31
5	MTBE (0.1 M)	72	n/d.	<5%	n/d.
6^d	EtOAc (0.1 M)	72	>95:5	85%	77:23
7^d	Isopropyl acetate (0.1 M)	72	>95:5	65%	82:18
8^d	MeCN (0.05 M)	72	>95:5	90%	76:24 ^e
9^f	MeCN (0.05 M)	72	>95:5	55%	62:38 (ent.)

10^g	MeCN (0.05 M)	72	>95:5	40%	62:38 (ent.)
11^h	MeCN (0.05 M)	72	n/d.	<5%	n/d.

*a. dr determined from ¹H NMR analysis of crude reaction mixture. b. Isolated yield. c. er determined from HPLC analysis in ratio of (3S,4S):(3R,4R). d. 2.0 equivalents acid **155** used. e. 97:3 er obtained after preparing the HPLC samples in isopropyl alcohol. f. Reaction with catalyst **70** (10 mol%). g. Reaction with catalyst **146** (10 mol%). h. Reaction without catalyst **93**. CPME = cyclopentyl methyl ether, MTBE = methyl tert-butyl ether.*

Table 5.1: Solvent and catalyst optimization

Screening of other reaction parameters, such as the reaction temperature and the order of addition, were performed next (Table 5.2). To remove the effect of moisture in the reaction system, the reaction was carried out under strictly anhydrous conditions with freshly distilled MeCN instead of using commercially available dry MeCN. In this case, dihydropyridinone **344** was obtained in similar yield (92%) and er (78:22) (entry 1). Adding molecular sieves did not lead to an improvement in er, and the yield dropped slightly to 80% (entry 2). Lowering the reaction temperature to 0 °C resulted in a slightly increased er of 80:20, but a 96 h reaction time was required to obtain **344** in 85% yield (entry 3). Further improvements in the er to 86:14 could be achieved with the reaction temperature decreased to -40 °C, however only 50% isolated yield of **344** was obtained, with the low solubility of ketimine **323** at -40 °C potentially contributing to this low yield (entry 4). Dropwise addition of a premixed solution of ketimine **323** and HyperBTM **93** in THF (due to solubility) to a solution of the pre-formed mixed anhydride in MeCN (from 2-pyrrolyl acetic acid **155** and *t*-BuCOCl) at room temperature resulted in a higher isolated yield of 74%, but the er was still remained moderate (74:26) (entry 5).



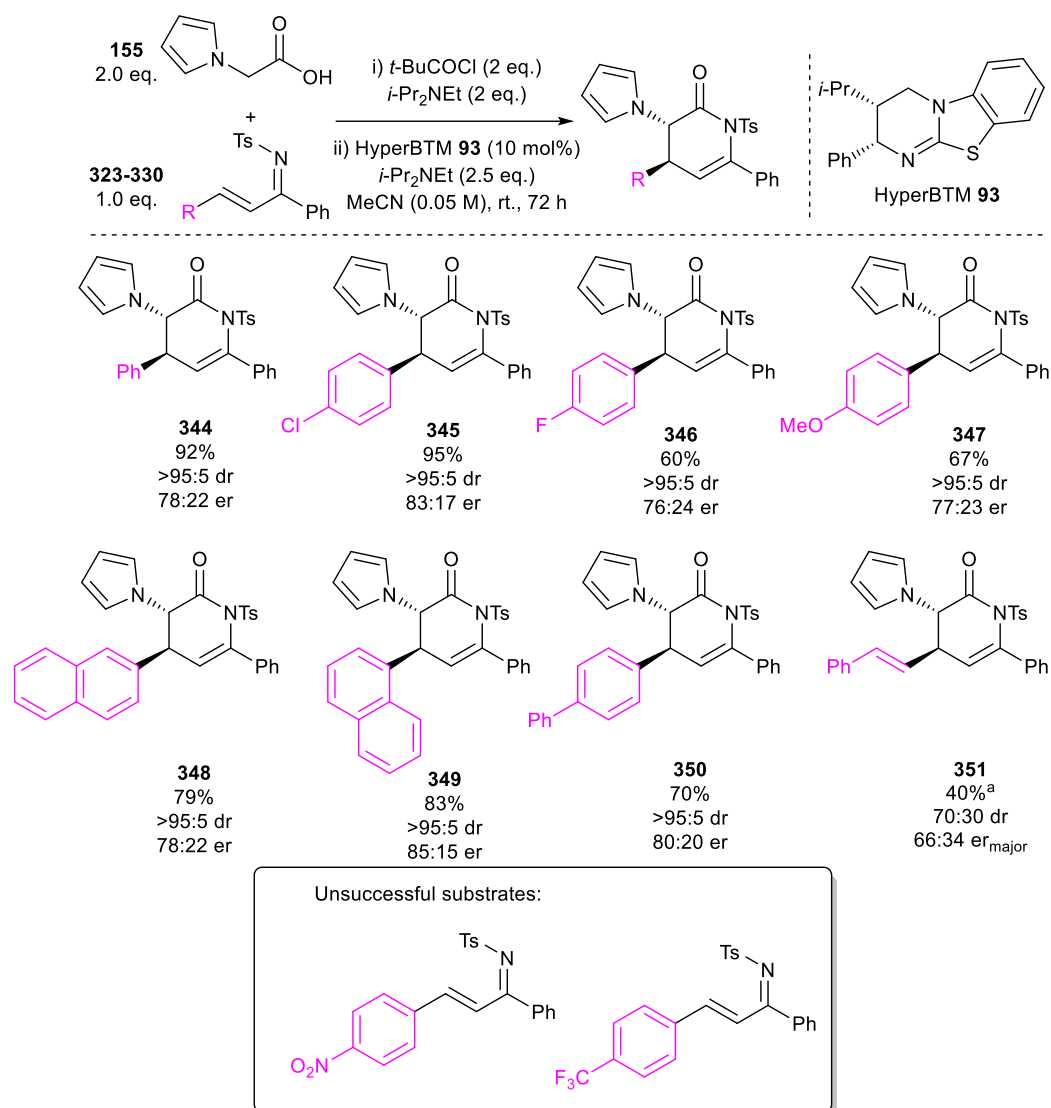
Entry	Temp.	Time/ h	Yield ^a	dr ^b	er ^c
1^d	rt	72	92%	>95:5	78:22
2^{d,e}	rt	72	80%	>95:5	75:25
3^d	0 °C	96	85%	>95:5	80:20
4^d	-40 °C	100	50%	>95:5	86:14
5^{d,f}	rt	72	74%	>95:5	74:26

*a. Isolated yield. b. dr determined from ¹H NMR analysis of crude reaction mixture. c. er determined from HPLC analysis in ratio of (3S,4S):(3R,4R). d. Reaction with MeCN freshly distilled from CaH₂. e. Reaction with 4Å molecular sieves. f. Pre-formed solution of ketimine **323** and HyperBTM **93** in dry THF added dropwise to a mixture of acid **155**, t-BuCOCl and i-Pr₂NEt in MeCN.*

Table 5.2: Optimization on reaction conditions

5.4.2. Scope analysis

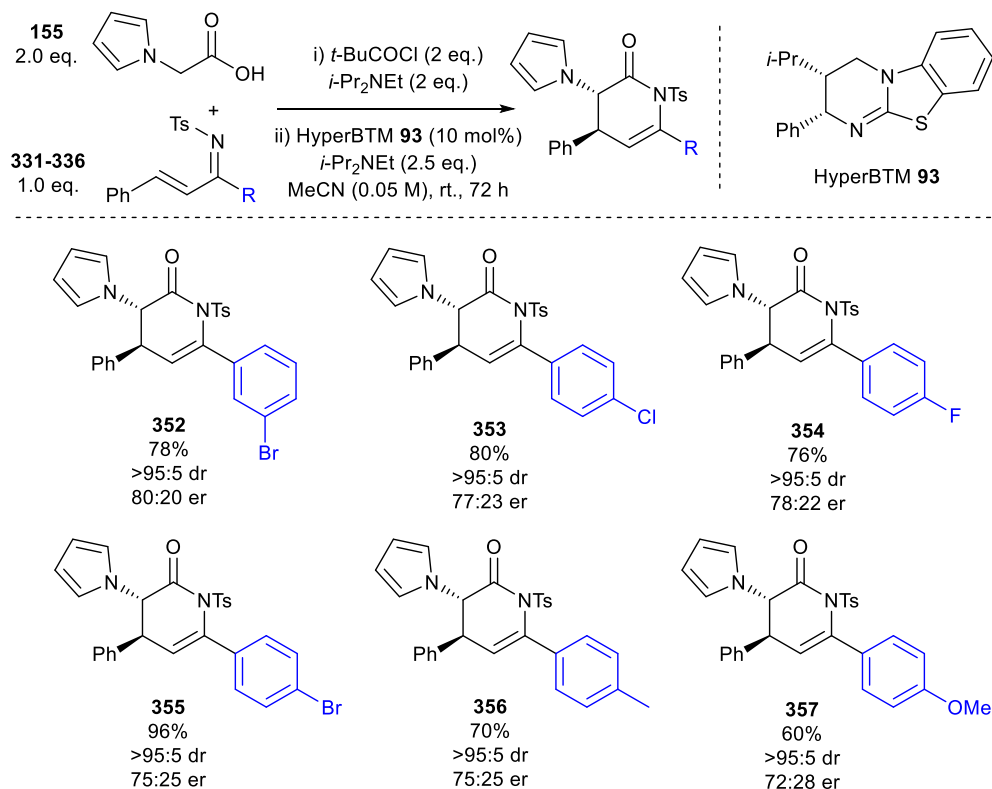
With the optimized condition (Table 5.2, entry 1) in hand, subsequent studies focused on probing the generality of the Michael addition-lactamization process by initially varying the β-aryl substituent within the ketimine substrate (Scheme 5.7). Under the developed reaction conditions, inductively electron withdrawing 4-Cl and 4-F substituents at the 4-position of the β-aryl ring were readily accommodated, afforded products **345** and **346** in good to excellent yield (95% and 60%), >95:5 dr and moderate er (83:17 and 76:24 respectively). An electron donating 4-OMe substituent was also tolerated, giving **347** as a single diastereoisomer in 67% yield with moderate enantioselectivity (77:23 er). The process also accommodated bulky β-substituents, with 2-naphthyl, 1-naphthyl and biphenyl substituents giving products **348-350** in up to 83% yield, consistently high dr (>95:5) and 78:22 to 85:15 er. The incorporation of an alkenyl substituent was not well tolerated, resulting in low isolated 40% yield due to the generation of several unidentified side products, as well as reduced dr (70:30) and er (66:34). Notably, ketimines substrates bearing strongly electron withdrawing 4-NO₂ and 4-CF₃ groups showed no formation of the desired Michael addition-lactamization product, with a complex mixture observed instead.



a. Combined yield of inseparable mixture of diastereoisomers. *b.* Isolated yield of >95:5 dr unless stated otherwise. *dr* was determined from ¹H NMR of crude reaction mixture. *er* was determined from chiral HPLC.

Scheme 5.7: Scope on varying the β-aryl substituents of the unsaturated ketimines^b

Variation of the C(1) substituent within the α,β-unsaturated ketimine was also explored (Scheme 5.8). Electron-withdrawing halogen substituents at the 3- or 4-position in the C(1) aryl ring of the α,β-unsaturated ketimine were tolerated, giving **352** to **355** in good yields of up to 96% and up to 80:20 er. Incorporating electron donating 4-Me and 4-OMe substituents gave comparable results (60%-70% yields), >95:5 dr with again moderate er (75:25 and 72:28 respectively).



Isolated yield of >95:5 dr unless stated otherwise. dr was determined from ^1H NMR of crude reaction mixture. er was determined from chiral HPLC.

Scheme 5.8: Scope on varying the C(1) substituents of the unsaturated ketimines

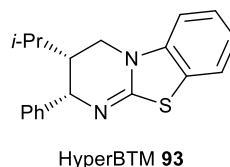
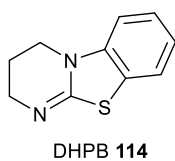
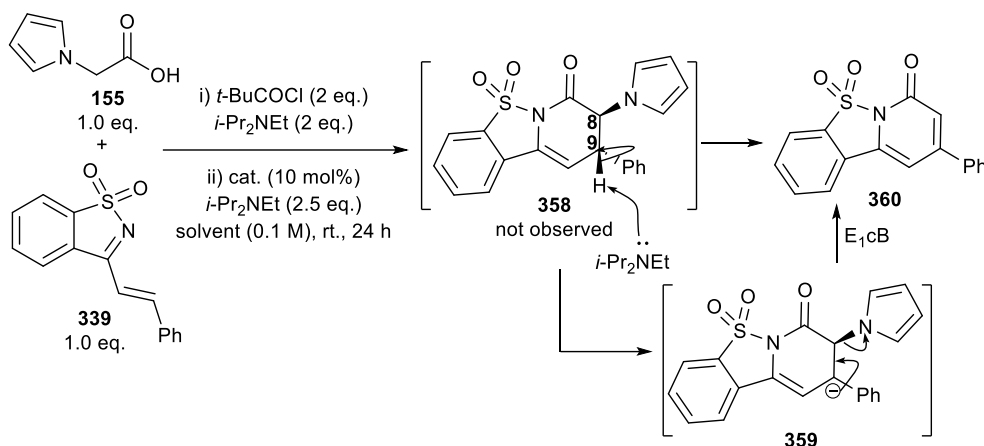
Due to a general moderate level of enantioselectivity observed, the dihydropyridinone products were not derivatized further. The use of the cyclic saccharin-derived Michael acceptors was next investigated.

5.5. Synthesis of dihydropyridinones using saccharin-derived ketimines

5.5.1. Reaction optimization with 2-pyrrolyl acetic acid

Initial experiments started with 1 equivalent of pyrrolyl acetic acid **155** and saccharin-derived α,β -unsaturated ketimine **339** at room temperature in DMF using DHPB **114** as the isothiourea catalyst. However, instead of isolating the Michael addition-lactamization product **358**, the unexpected elimination of the pyrrole group was observed during the course of the reaction, leading to the isolation of pyridone **360** as the only product in 73% yield (Table 5.3, entry 1). Formation of this unexpected side-product may be explained by deprotonation of the second acidic proton at C(9) in dihydropyridinone **358**, followed by elimination of pyrrole. Assuming the formation of *trans*-dihydropyridinone **358** with high diastereoselectivity, the *syn*-

relationship between the proton at C(9) and the eliminated pyrrole group indicated that the E₁cB elimination pathway was the dominant mechanism.²³ However, the existence of an epimerization at C(8) followed by E2 elimination could not be ruled out. Conducting the reaction in either dichloromethane or MeCN at room temperature using HyperBTM also led to the elimination product **360** being obtained in 40% and 65% yield respectively (entry 2-3).

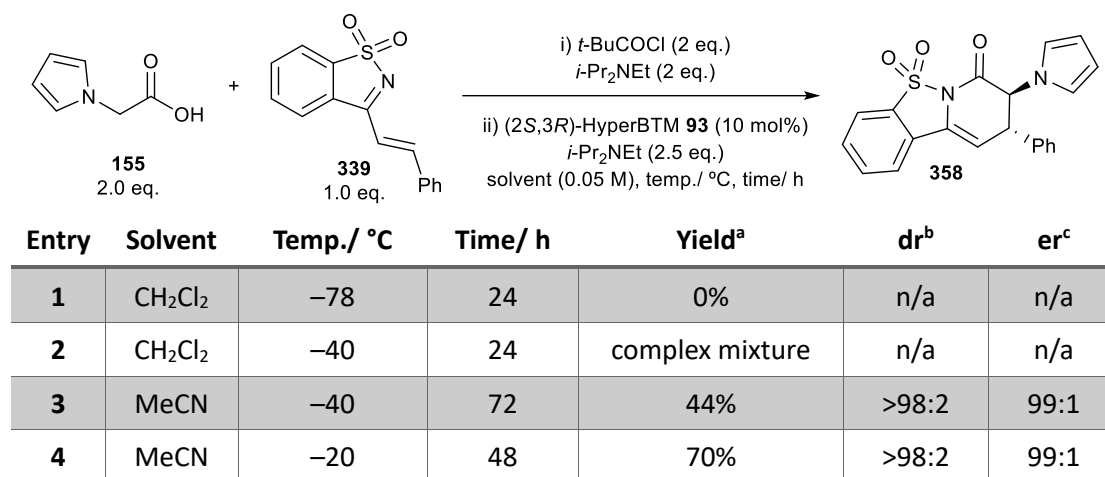


Entry	Catalyst	Solvent	Yield of 360 ^a
1	144	DMF	73%
2^b	93	CH ₂ Cl ₂	40%
3^b	93	MeCN	65%

a. Isolated yield after column chromatography. b. With 2.0 equivalents of acid **155** and 0.05 M solvent.

Table 5.3: Initial condition screenings

The reaction was next performed at low temperature, as an alternative method to prevent elimination (Table 5.4). Performing the transformation in CH₂Cl₂ at -78 °C gave no conversion of the starting material while at -40 °C an unidentified complex mixture was observed (entry 1-2). Switching the solvent to MeCN at -40 °C resulted in the isolation of the desired dihydropyridinone **358** in 44% yield within 72 hours, with excellent dr (>98:2) and er (99:1) (entry 3), with no elimination product **360** detected. An improvement in the isolated yield to 70% after 48 hours was observed when the temperature was raised to -20 °C, with no erosion in enantio- and diastereoselectivity (>98:2 dr, 99:1 er) (entry 4).

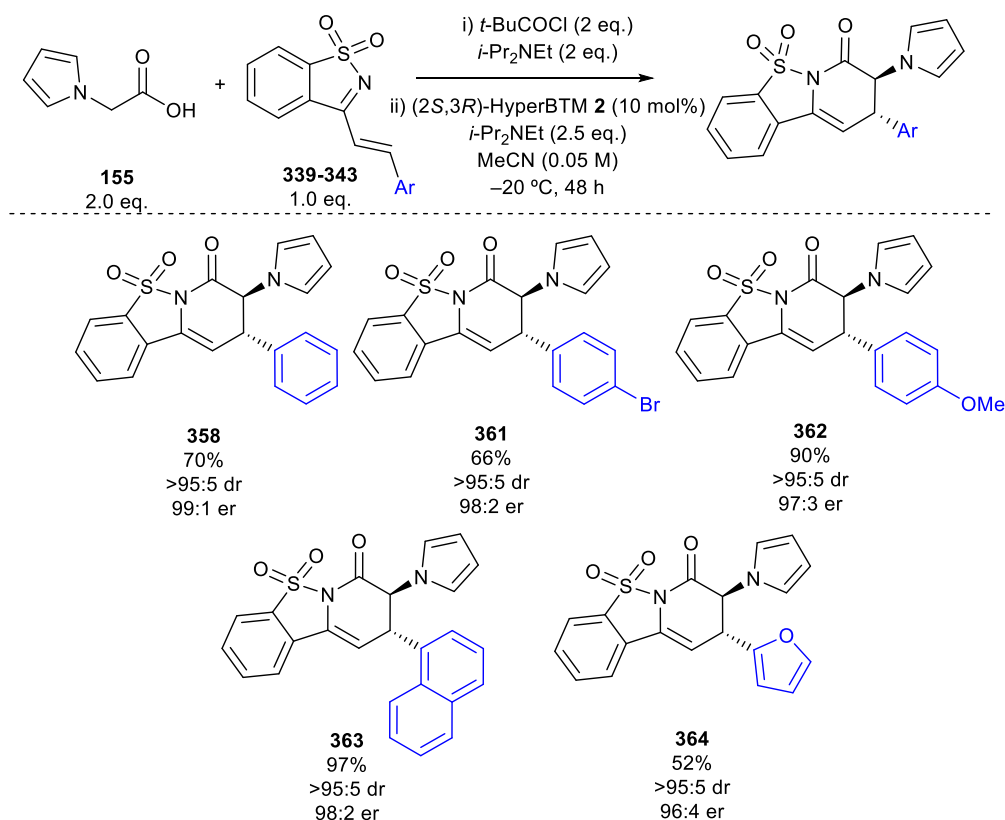


a. Isolated yield. b. dr determined from ¹H NMR of crude reaction mixture. c. er determined from HPLC analysis of isolated **358** (>95:5 dr).

Table 5.4: Optimization on reaction temperatures with different solvents

5.5.2. Substrate scope with 2-pyrrolyl acetic acid

The scope of this transformation was next explored under the optimized condition (Scheme 5.9). In general, changing the substituents on the β-aryl ring of saccharin derived α,β-unsaturated ketimine to 4-Br, 4-OMe, 1-naphthyl or 2-furyl was well tolerated, and the corresponding dihydropyridinone **361-364** was afforded in 52-97% yield with consistently high dr (>95:5) and er (96:4 to 99:1).



Yield referred to isolated yield of >95:5 dr. dr was determined from ^1H NMR analysis of crude reaction mixture. er was determined from chiral HPLC.

Scheme 5.9: Substrate scope with 2-pyrrolyl acetic acid

Single crystal x-ray analysis was performed on the major diastereoisomer of **362** (Fig. 5.3),²⁴ allowing the relative and absolute stereochemistry for the major diastereoisomer to be assigned as (8*S*,9*S*), with the stereochemistry of all other dihydropyridinones assigned by analogy.

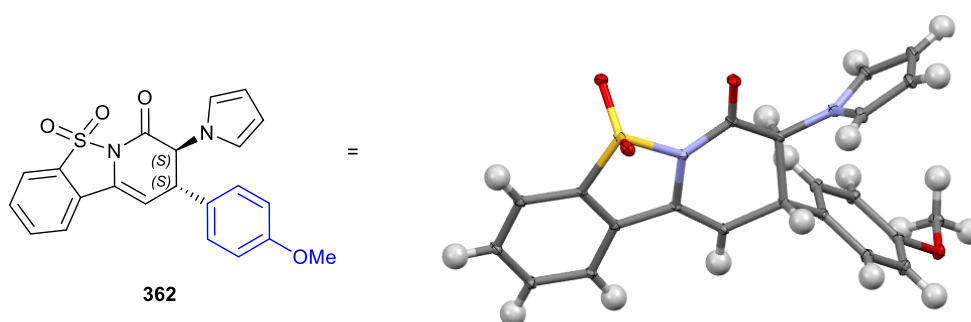
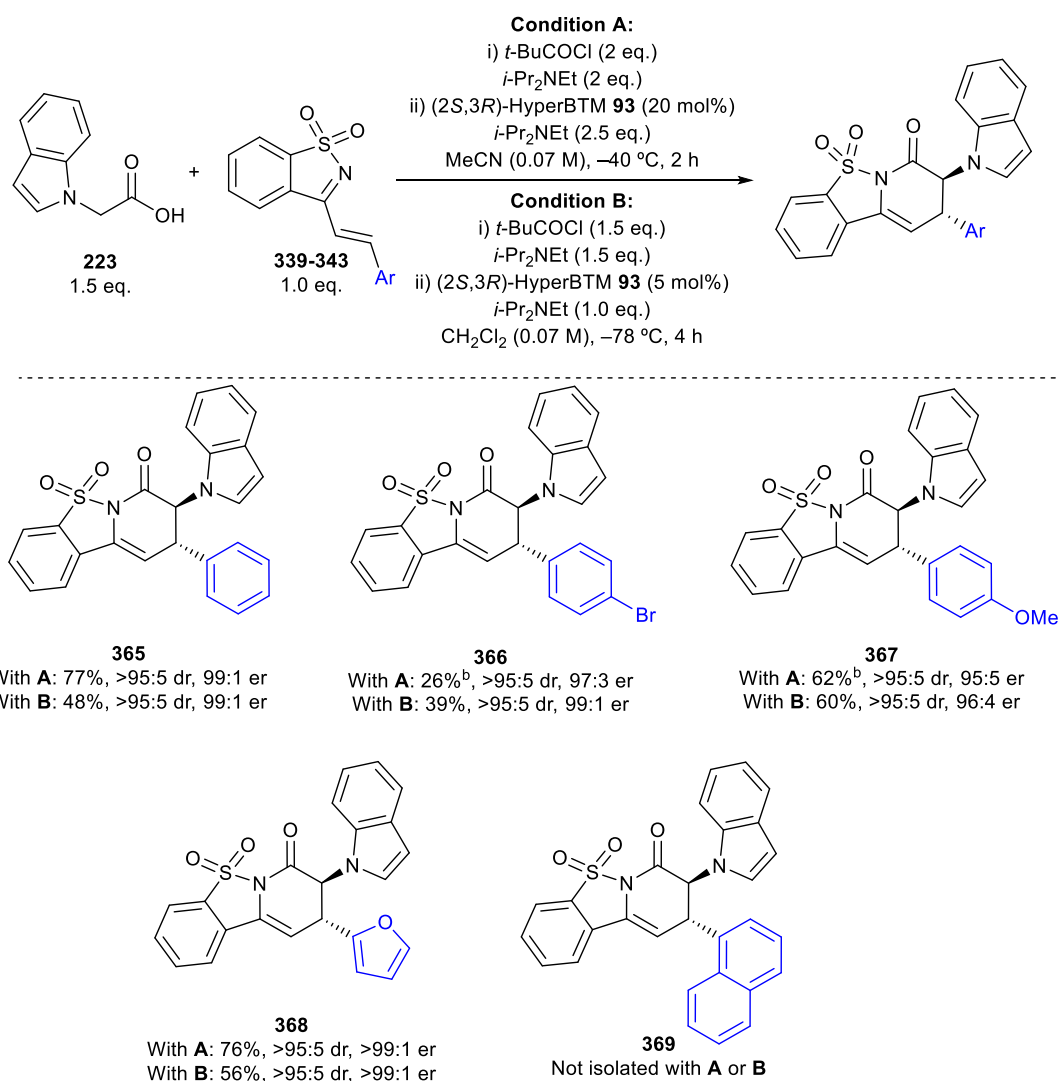


Fig. 5.3: Single crystal of **362**

5.5.3. Substrate scope with 2-indolyl acetic acid

In collaboration with Lucas Bacheley, a summer placement student from France, the scope of this Michael addition-lactamization was explored further by employing 2-indolyl acetic acid **223**. Interestingly, in this case the use of either MeCN or CH_2Cl_2 as a solvent provided the expected dihydropyridinones at low temperature in a yield ranging from 26% to 77% (Scheme 5.10). When using MeCN as solvent at $-40\text{ }^\circ\text{C}$, dihydropyridinone **365** was obtained in 77% yield within 2 h, whilst a lower 48% yield was obtained in CH_2Cl_2 at $-78\text{ }^\circ\text{C}$ within 4 h. Both sets of reaction conditions gave **365** with excellent enantioselectivity (99:1 er) and high diastereoselectivity (>95:5 dr). Saccharin derived α,β -unsaturated ketimine with an electron-withdrawing 4-Br substituent in the β -aryl ring was tested under both sets of reaction conditions (MeCN at $-40\text{ }^\circ\text{C}$ and CH_2Cl_2 at $-78\text{ }^\circ\text{C}$), with the former condition gave **366** in a low yield of 26% while the latter condition gave **366** in a moderate yield of 39%. Excellent dr (>95:5) and er (97:3 and 99:1 respectively) for **366** was observed. The reduced yield was ascribed to the observed formation (via ^1H NMR analysis of the crude reaction mixture) of the corresponding indole elimination product after 48 h reaction time although this could not be

readily isolated. The incorporation of an electron-donating 4-OMe β -aryl resulted in the isolation of **367** in good yield in both MeCN and CH_2Cl_2 (62% and 60% respectively) with high dr (>95:5) and excellent er (95:5 and 96:4). With a 2-furyl substituent, dihydropyridinone **368** was isolated in excellent dr and er (>95:5 dr, >99:1 er) using both MeCN (76% yield) and CH_2Cl_2 (56% yield). Unfortunately, unlike the reaction with 2-pyrrolyl acetic acid **223**, the incorporation of a 1-naphthyl group at the β - of the ketimine was not tolerated. In CH_2Cl_2 , no conversion of the Michael acceptor into the corresponding dihydropyridinone **369** was observed by ^1H NMR. In MeCN full conversion into **369** was observed but unfortunately attempted chromatographic purification was unsuccessful, potentially due to decomposition or elimination. In general, a shorter reaction time was required for the 2-indolyl system to prevent the indole elimination side reactivity which was not observed for 2-pyrrolyl system at low reaction temperatures.

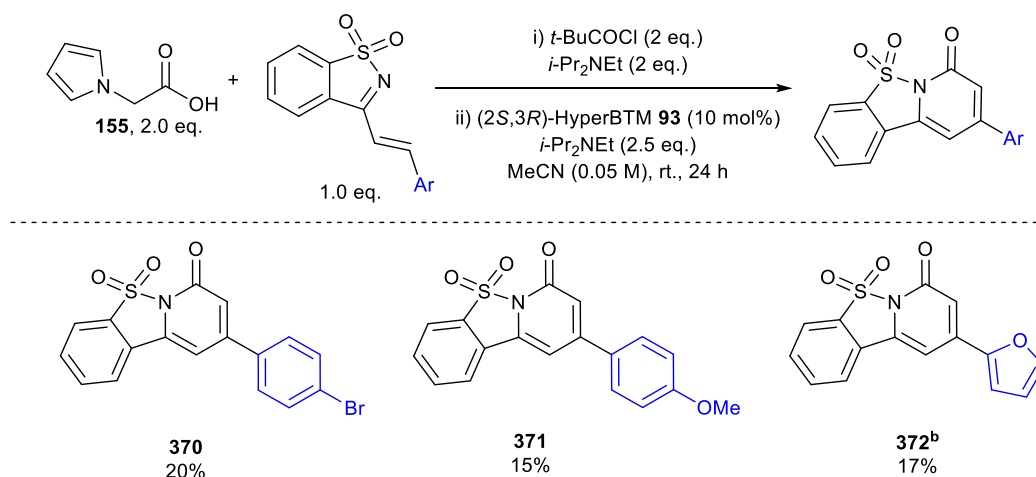


a. Yield referred to isolated yield of >95:5 dr. dr was determined from ^1H NMR analysis of crude reaction mixture. er was determined from chiral HPLC. b. Reaction after 48 h.

Scheme 5.10: Substrate scope with 2-indolyl acetic acid (by Lucas Bacheley)^a

5.6. Exploring the elimination of pyrrole or indole to give pyridones

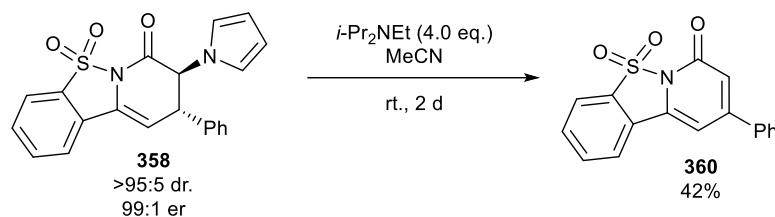
The generality of the one-pot isothioureia-catalyzed Michael addition-lactamization/elimination protocol as a new synthetic route towards fused pyridones was investigated. By repeating the Michael addition-lactamization protocol with 2-pyrrolyl acetic acid at room temperature, saccharin-derived Michael acceptors suggested the formation of the desired pyridones **370-372** upon ^1H NMR analysis of the crude reaction mixture. Attempted chromatographic purification led to the decomposition of the product on the silica. Thus, a recrystallization was performed in Et₂O/pentane solvent mixture, but resulted in very low isolated yields (between 15% and 20%) (Scheme 5.11), with **372** being isolated only using 2-indolyl acetic acid **223**.



a. Isolation yield after recrystallization. b. Work by Lucas Bacheley with 1.5 eq. 2-indolyl acetic **223**.

Scheme 5.11: Formation of the elimination product^a

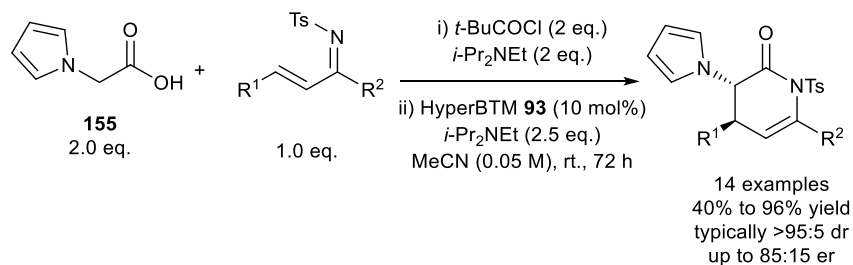
A control reaction was performed by taking the isolated dihydropyridinone **358** and treating with an excess of *i*-Pr₂NEt in MeCN. The elimination product **360** could be obtained in 42% isolated yield (Scheme 5.12). A close examination of the ^1H NMR spectra of the crude reaction product revealed the presence of the eliminated pyrrole group. This confirmed the previously proposed mechanistic explanation for the formation of **360** (Table 5.3), and potentially provided a more synthetically useful route to access the fused pyridone structure **360**.



Scheme 5.12: Control experiment to obtain 360

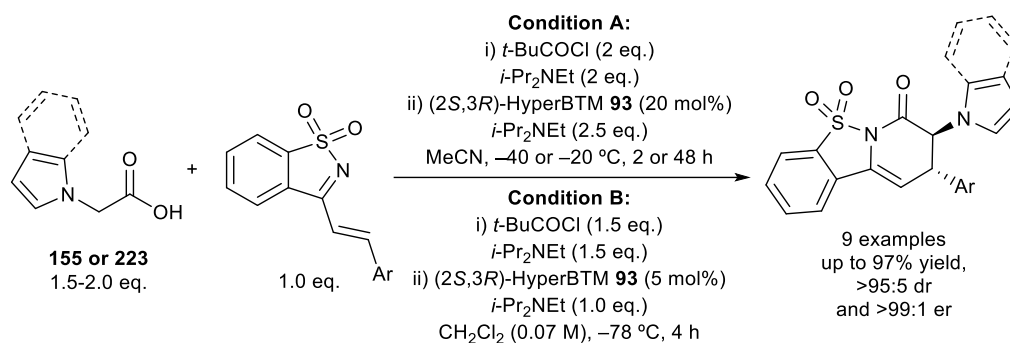
5.7. Conclusions

In conclusion, this chapter has described the Michael addition-lactamization process between heterocyclic C1-ammonium enolate precursors, 2-pyrrolyl and 2-indolyl acetic acid, and α,β -unsaturated ketimines to access core dihydropyridinone structural motifs enantioselectively. With chalcone-derived *N*-sulfonyl α,β -unsaturated ketimines as the Michael acceptors, yields of up to 96% were achieved under the optimized conditions with excellent diastereoselectivity (>95:5 dr) obtained in most cases (Scheme 5.13). Although several attempts have been made to improve the enantioselectivity, only moderate ers were obtained (between 62:38 to 85:15), possibly due to a base-mediated epimerization of the minor diastereoisomer into the minor enantiomer of the major diastereoisomer.



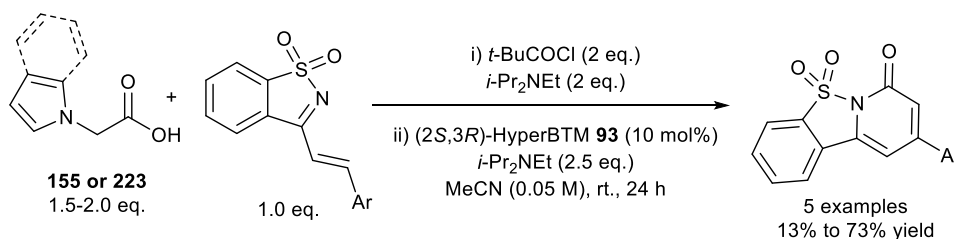
Scheme 5.13: Synthesis of dihydropyridinones from chalcone derived ketimines

Cyclic saccharin-derived α,β -unsaturated ketimine Michael acceptors were also demonstrated to be well tolerated in this process. The desired tricyclic dihydropyridinones could be obtained exclusively at low temperature with excellent diastereoselectivity and enantioselectivity (up to >95:5 dr and >99:1 er) using either 2-indolyl acetic acid **223** or 2-pyrrolyl acetic acid **155** (Scheme 5.14).



Scheme 5.14: Isothiourea catalyzed enantioselective synthesis of tricyclic dihydropyridinones

When the Michael addition reaction using saccharin-derived α,β -unsaturated ketimines was performed at room temperature, a facile elimination of the indole/pyrrole unit was observed to take place, allowing the isolation of a tricyclic pyridone. The relatively poor yields obtained were attributed to low chromatographic stability of the pyridone structure (Scheme 5.15).



Scheme 5.15: Synthesis of tricyclic pyridone via elimination of pyrrole/indole

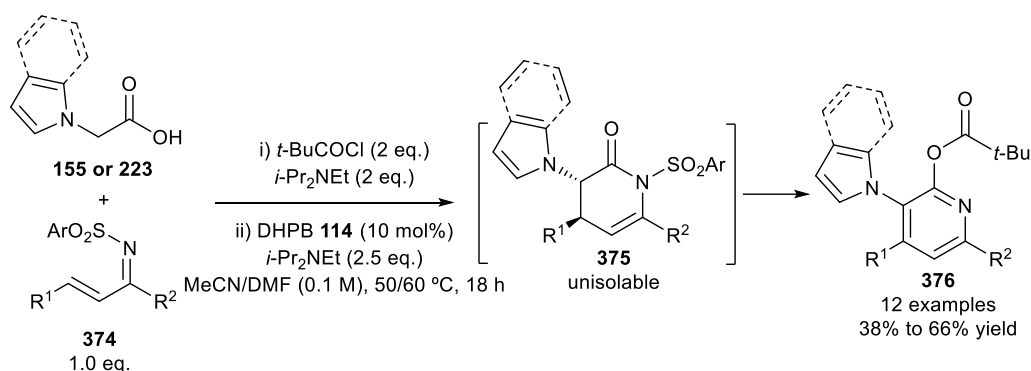
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- 24 Crystal structure determined by Alexandra Slawin, University of St Andrews.

Chapter 6: One-pot synthesis of functionalized pyridines

This chapter describes the unexpected discovery of a synthetic route to access tetrasubstituted pyridines. The initially generated *anti*-dihydropyridinone **375** from Michael addition-lactamization between 2-pyrrolyl **155** or 2-indolyl acetic acid **223** and α,β -unsaturated ketimines, in the presence of pivaloyl chloride and *i*-Pr₂NEt, is readily transformed *in situ* into tetrasubstituted pyridines **376** in up to 66% yield (Scheme 6.1). This unexpected result provides an one-pot organocatalytic protocol to access highly functionalized pyridine derivatives.



Scheme 6.1: One-pot synthesis of functionalized pyridines

6.1. Introduction

Pyridines are generally recognized as a very important class of heterocycle that exist in the core of many drug molecules and agrochemical products (Figure 6.1).^{1–3}

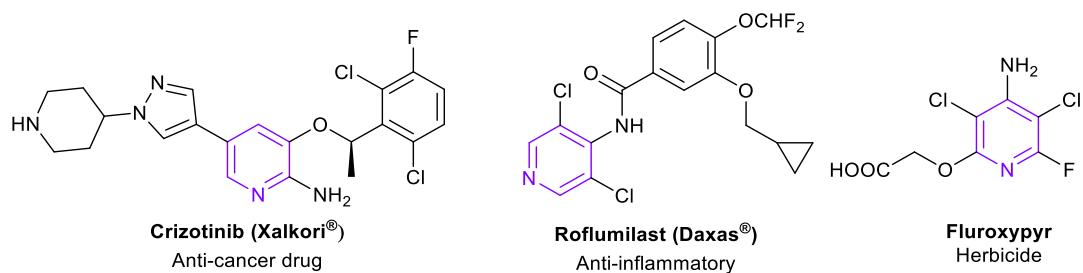
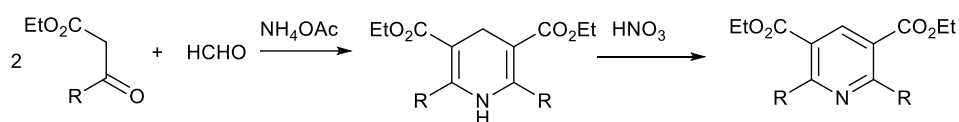


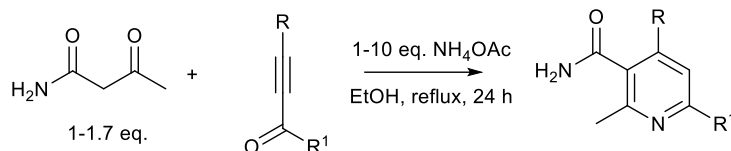
Fig. 6.1: Biologically important molecules with core pyridine structures

As a consequence, many synthetic methods have been developed to access these molecules efficiently.⁴ Historically, chemists used the condensation between carbonyl compounds and nitrogen containing molecules to obtain pyridines, including Hantzsch pyridine synthesis⁵ and Bohlmann-Rahtz pyridine synthesis (Scheme 6.2).⁶

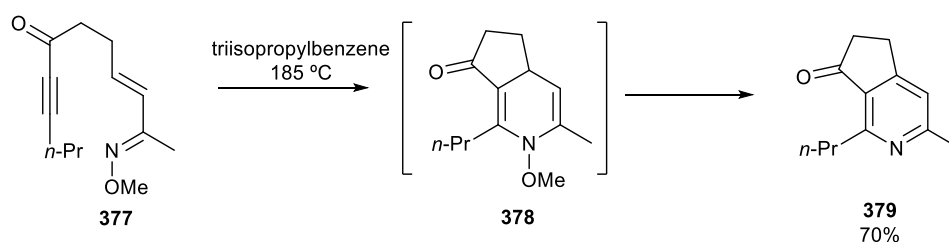
i) Hantzsch pyridine synthesis



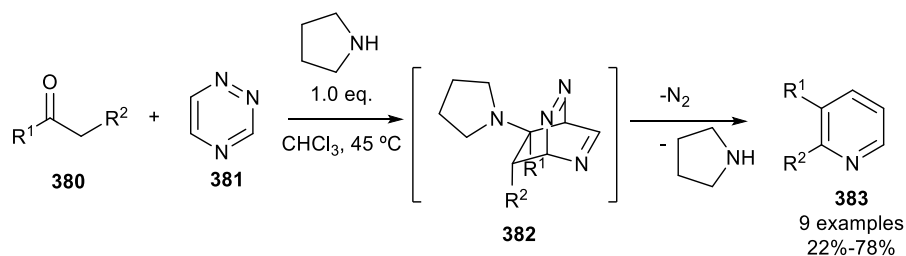
ii) Bohlmann-Rahtz pyridine synthesis


Scheme 6.2: Examples of pyridine synthesis

Besides condensation, cycloaddition chemistry is also recognized as an important strategy to construct pyridines. For example, the intramolecular hetero-Diels-Alder reaction between the electron rich azadiene and alkyne **377** afforded the intermediate **378**, which following the elimination of MeOH provides pyridine **379** in good yield (Scheme 6.3).⁷

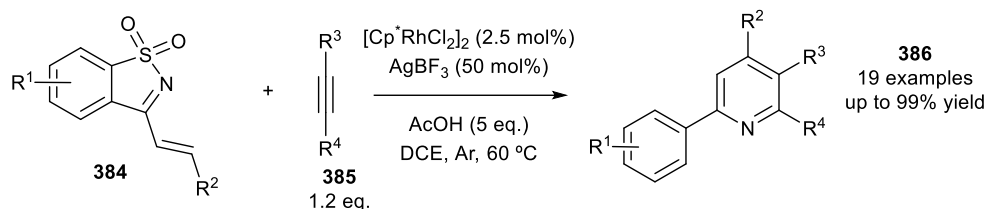

Scheme 6.3: Cycloaddition in the synthesis of pyridine

Pathways to pyridines involving the use of inverse electron demand hetero-Diels-Alder reaction followed by the release of nitrogen have also been developed. Using 1,2,4-triazine **381** and a ketone **380**, in the presence of a stoichiometric amount of pyrrolidine, the bicyclic intermediate **382** is generated. An entropy-favoured elimination of molecular nitrogen and pyrrolidine furnished the pyridine **383** in moderate to good yields (Scheme 6.4).⁸


Scheme 6.4: Synthesis of pyridines via inverse electron demand Diels Alder

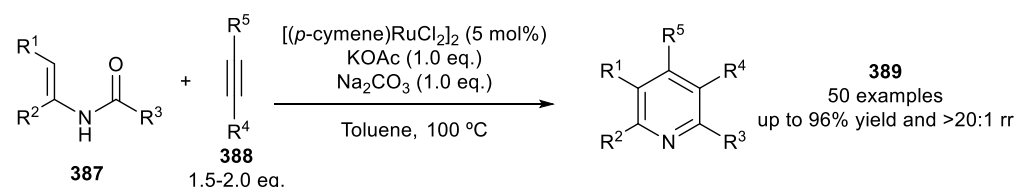
With the growing interest in the area of catalysis, methods for the transition metal catalyzed synthesis of pyridines have been explored, including the ring-closing⁹⁻¹⁴ and cross

metathesis^{15,16} strategies developed by Donohoe. One representative example afforded pyridines **386** from saccharin-derived ketimines **384** and disubstituted alkynes **385** in excellent yields. An initial C-H activation and late-stage SO₂ elimination was involved (Scheme 6.5).¹⁷

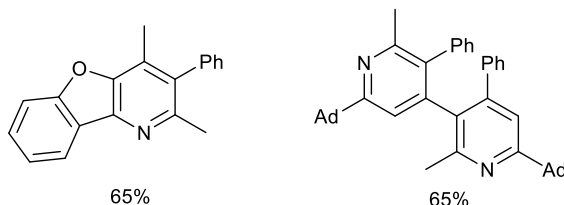


Scheme 6.5: Transition metal catalyzed pyridine synthesis

Highly substituted pyridines with 5 substituents have also been prepared by a formal dehydrative [4+2] cycloaddition using enamides **387** and alkynes **388** using Ru catalysis. The pentasubstituted pyridines could be isolated in excellent yields, with the scope of this process featuring a polycyclic and annulated examples (Scheme 6.6).¹⁸

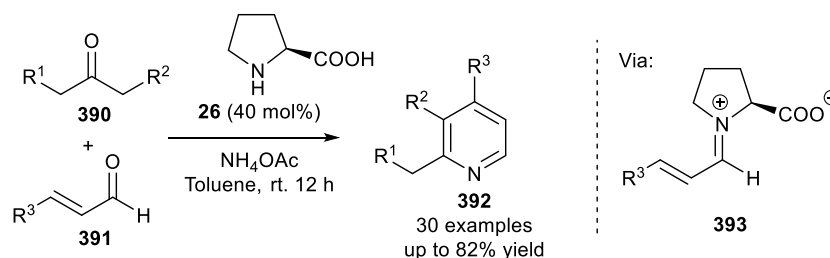


Selected examples:



Scheme 6.6: Synthesis of pentasubstituted pyridines

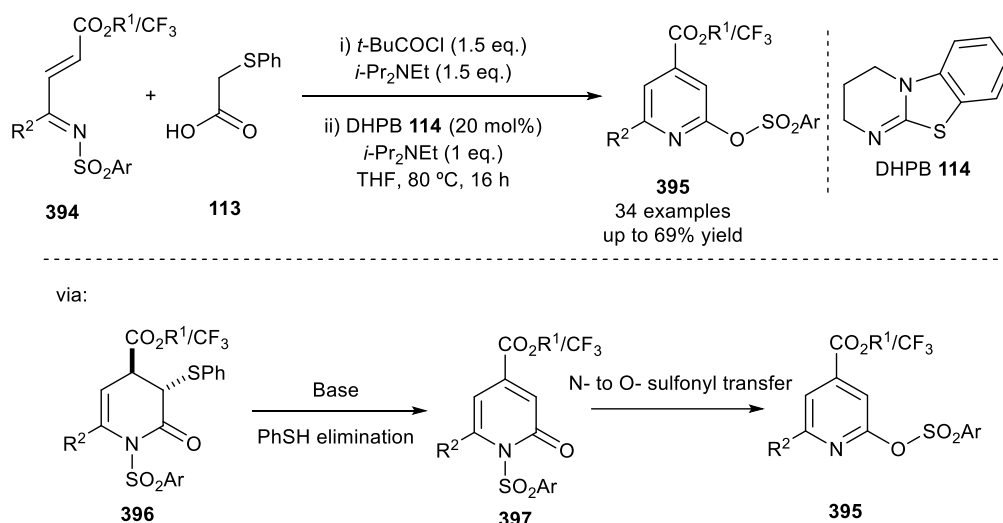
Apart from transition metal catalysis, organocatalytic approaches were also reported. In 2015, Lee developed an organocatalytic protocol using iminium ion catalysis. Condensation between enals **391** and catalytic proline **26** generates the iminium ion **393** which is then attacked by **390** to afford the pyridines **392** in good to excellent yields (Scheme 6.7).¹⁹



Scheme 6.7: Proline-catalyzed one-pot synthesis of pyridines

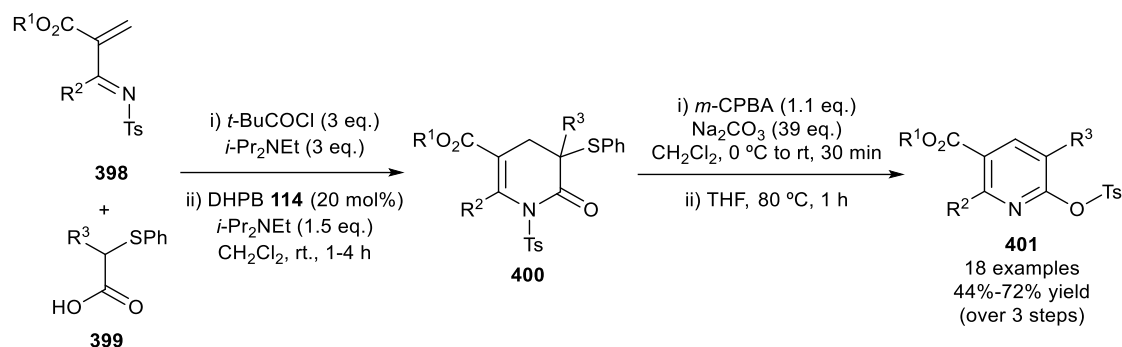
6.2. Previous work in the Smith Group

N-Heterocycles have been prepared previously in the Smith group using isothioureacatalyzed Michael addition-lactamization protocols. As previously described in Chapter 5, the synthesis of *anti*-dihydropyridinone was reported using aryl acetic acids and chalcone derived ketimines.²⁰ Following this success, the scope of applicable Michael acceptors was expanded to β -ester/ β -CF₃ substituted α,β -unsaturated ketimines.^{21,22} When using aryl acetic acids as the C1-ammonium enolate precursors, dihydropyridinone products were isolated as the major product in each case.²² However, by switching to thiophenyl acetic acid **113** as the C1-ammonium enolate precursor, pyridine products **395** were obtained in good to excellent yields with β -ester/ β -CF₃ substituted α,β -unsaturated ketimines (Scheme 6.8). It was proposed that following the Michael addition-lactamisation process to dihydropyridinone **396**, elimination of PhSH affords pyridinone **397**, which proceeded through a thermally promoted N- to O- sulfonyl migration to give the final pyridine product.²¹



Scheme 6.8: Isothiourea catalysed one-pot synthesis of pyridines

The method was later extended to provide access to tetrasubstituted pyridines, in a three-step procedure by employing α -ester- α,β -unsaturated ketimines as the Michael acceptors and α,α -disubstituted (phenylthio)acetic acids as the C1-ammonium enolate precursors. The initially formed dihydropyridinone **400** was oxidized using *m*-CPBA to give the corresponding sulfoxide, which underwent spontaneous elimination (via E₁ pathway) upon warming to room temperature.^{23,24} Subsequent thermally promoted N- to O- sulfonyl transfer was used to afford the desired functionalized pyridines **401** in moderate to good yields (Scheme 6.9).²⁵



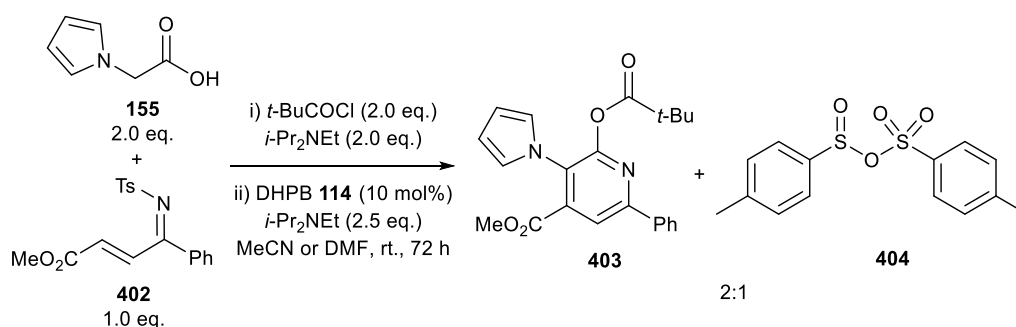
Scheme 6.9: Isothiourea catalyzed three-stage synthesis of tetrasubstituted pyridines

During the investigation of using 2-pyrrolyl acetic acid **155** and β -ester substituted α,β -unsaturated ketimine to synthesize 3,4-dihydropyridinones via Michael addition-lactamization, an unexpected pyridine formation was discovered. The observation of a sulfinic acid elimination, instead of a pyrrole elimination and N- to O- sulfonyl transfer, was significantly different to the previous work in the Smith group.

6.3. Proof of concept study

6.3.1. β -Ester- α,β -unsaturated N-tosyl ketimine

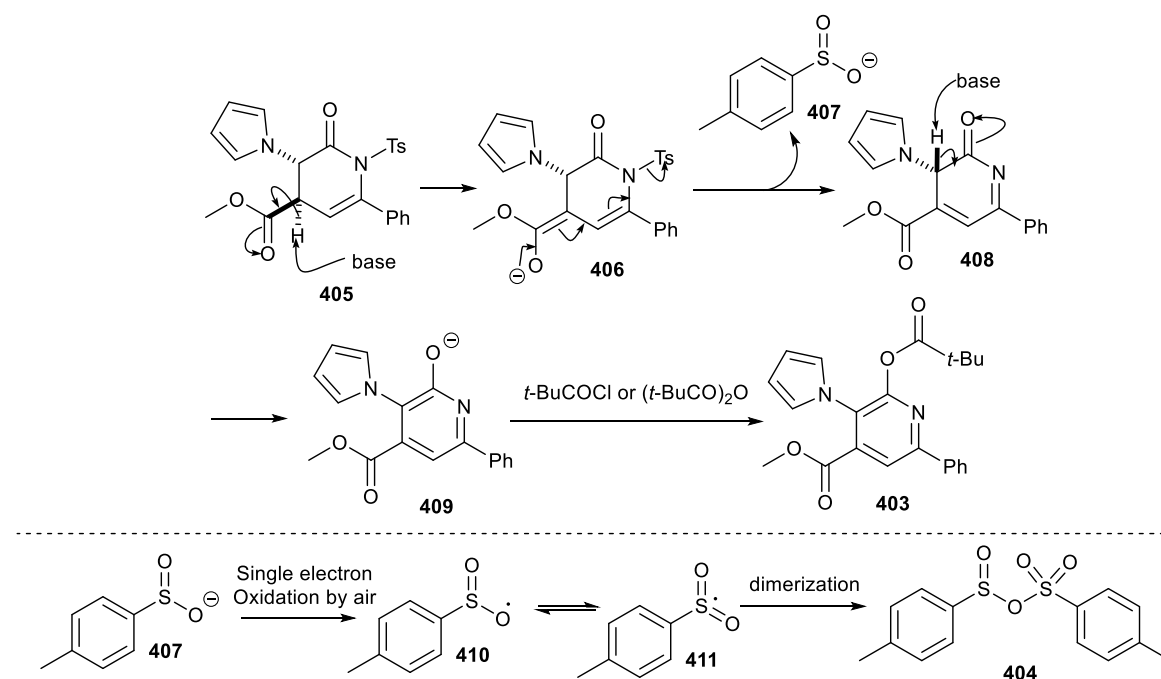
Initial reactivity tests began with 2-pyrrolyl acetic acid **155** and N-tosyl protected β -ester- α,β -unsaturated ketimine **402** with DHPB **114** as the catalyst. In either DMF or MeCN solvent at room temperature, full consumption of the ketimine **402** was observed within 72 h by ^1H NMR analysis. Purification gave an inseparable 2:1 mixture of the 2-OPiv pyridine **403** and the dimerized sulfonyl species **404** (Scheme 6.10). The structure of **404** was assigned by direct comparison to the literature.²⁶



Scheme 6.10: Initial observation with ketimine xx and 2-pyrrolyl acetic acid 155

The pyridine **403** was proposed to be generated from the corresponding 3,4-dihydropyridinone **405** (Scheme 6.11) via an ionic pathway. Following Michael addition-lactamization, deprotonation at C(4), promoted by delocalization of the resulting anion onto

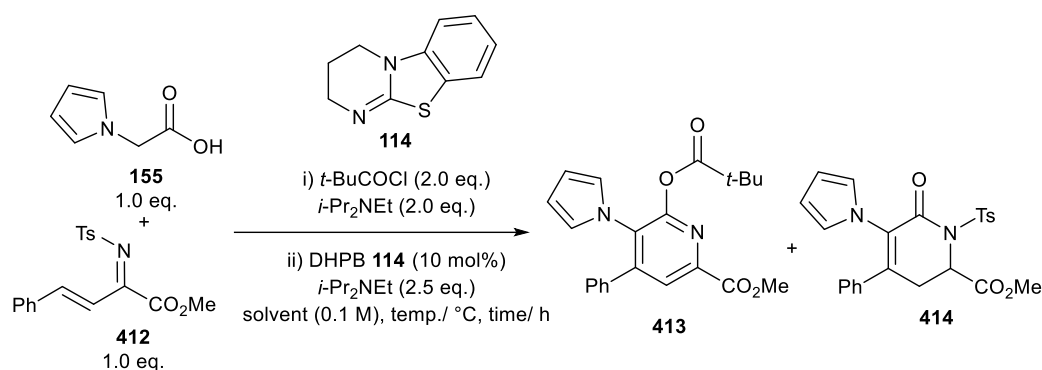
the adjacent ester carbonyl, generated enolate **406**. Sulfinate elimination ($E1_{cb}$) led to the formation of **408**. Subsequent deprotonation of the most acidic proton at C(3) of **408** gave hydroxypyridine **409** that was acylated with unreacted $t\text{-BuCOCl}$ or $(t\text{-BuCO})_2\text{O}$ to form the final tetrasubstituted pyridine **403**. The eliminated sulfinate **407** was presumably oxidized by air to afford a sulfonyl radical **411** that dimerized readily to form the byproduct **404**.^{26–29}



Scheme 6.11: Proposed mechanistic formation of pyridine **403** and **404**

6.3.2. α -Imino- β,γ -unsaturated ester

One of the α -keto- β,γ -unsaturated ester substrates used in Chapter 4, was next converted to the corresponding *N*-tosyl ketimine **412** using a literature protocol with TsNH_2 , NEt_3 and TiCl_4 .²¹ Applying the ketimine derivative **412** in the catalytic reaction using DHPB **114** (10 mol%) at room temperature in MeCN gave a 1:1 mixture of 2-OPiv pyridine **413** and the 5,6-dihydropyridinone **414** (Table 6.1, entry 1). Raising the temperature to 60 °C in MeCN afforded the pyridine **414** in 42% yield within 4 hours, giving an improved product ratio of 65:35 (entry 2). Switching the solvent to EtOAc, isopropyl acetate or THF, and conducting the reaction at elevated temperature of 60 °C (entry 3–5) gave preferential formation of 5,6-dihydropyridinone **414** rather than the desired 2-OPiv pyridine **413**.

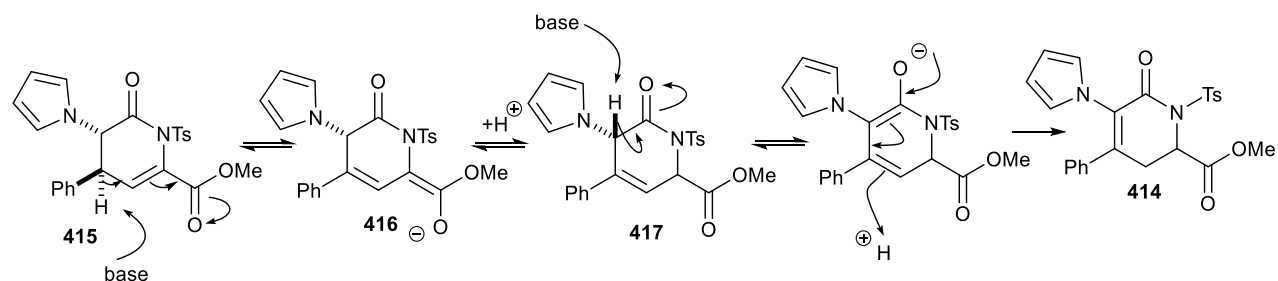


Entry	Solvent	Temp.	Time/h	Ratio 413:414	Yield of 413 ^a
1	MeCN	rt.	72	44:56	38%
2	MeCN	60 °C	4	65:35	42%
3	EtOAc	60 °C	16	22:78	n/d
4	Isopropyl acetate	60 °C	16	17:83	n/d
5	THF	60 °C	16	30:70	n/d

a. Ratio determined from ¹H NMR analysis of crude material. b. Isolation yield

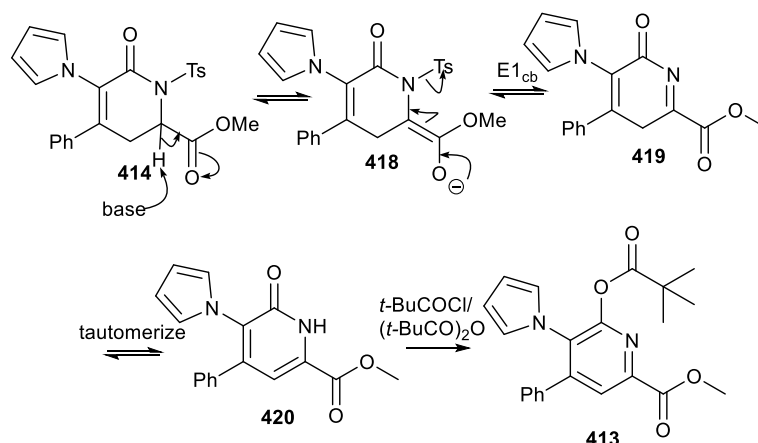
Table 6.1: Screening of solvents and temperatures

The isomerized 5,6-dihydropyridinone **414** (Scheme 6.12) presumably arises from initially formed 3,4-dihydropyridinone **415**, with deprotonation at C(4) giving enolate **416**. Subsequent α -protonation, followed by tautomerization, affords 5,6-dihydropyridinone **414**.



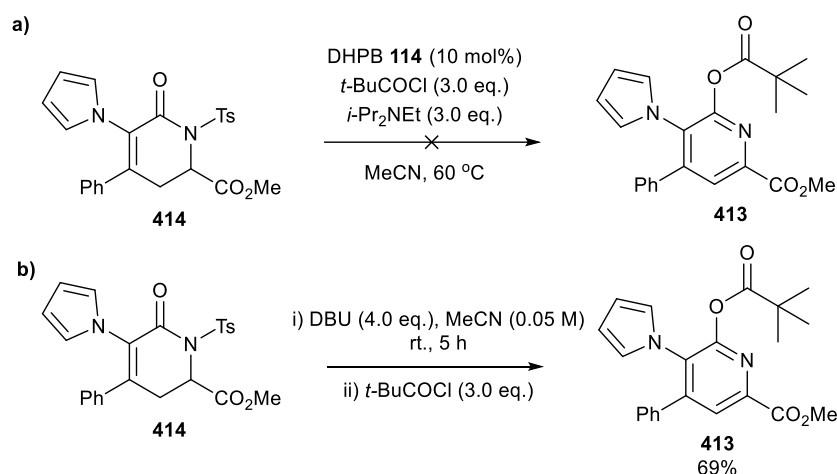
Scheme 6.12: Proposed mechanistic pathways for the isomerization

Conceivably 5,6-dihydropyridinone **414** could also be transformed into the final pyridine product **413** through an E1_{cb} elimination of the sulfonic acid followed by tautomerization (Scheme 6.13). Therefore, depending on whether this pathway is operative under the reaction conditions would determine if 5,6-dihydropyridinone **414** should be considered as a reaction side-product, or an intermediate on the way to forming the final pyridine product **413**.



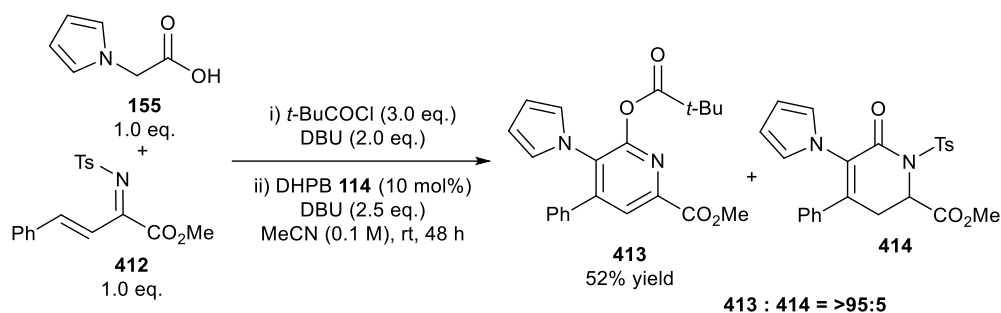
Scheme 6.13: Proposed formation of pyridine 413 from 5,6-dihydropyridinone 414

A control reaction was therefore performed by treating the isolated **414** with *i*-Pr₂NEt, DHPB (10 mol%) and *t*-BuCOCl in MeCN at 60 °C. Less than 5% conversion to pyridine **413** was determined by ¹H NMR analysis of the crude mixture, with more than 95% starting material being observed (Scheme **6.14a**). This suggested that 5,6-dihydropyridinone **414** was a side product that could not be transformed into pyridine **413** under the standard reaction conditions. With a stronger base DBU ($pK_a^H \sim 13.5$ in H₂O, *cf.* 10.9 for *i*-Pr₂NEt in H₂O), the final pyridine **413** could be isolated in 69% yield (Scheme **6.14b**). This confirmed that DBU could effectively ‘switch on’ the pathway detailed in Scheme **6.13**. It was then hypothesized that if DBU was used as the base in the catalytic reaction, more efficient access to the pyridine **413** could be achieved, by promoting conversion of 5,6-dihydropyridinone **414** to pyridine **413**.



Scheme 6.14: Control reactions in product transformation

To test this hypothesis, using DBU in place of *i*-Pr₂NEt led to an improved isolated yield of 52% for pyridine **413** (Scheme 6.15), with no 5,6-dihydropyridinone **414** detected by ¹H NMR analysis.

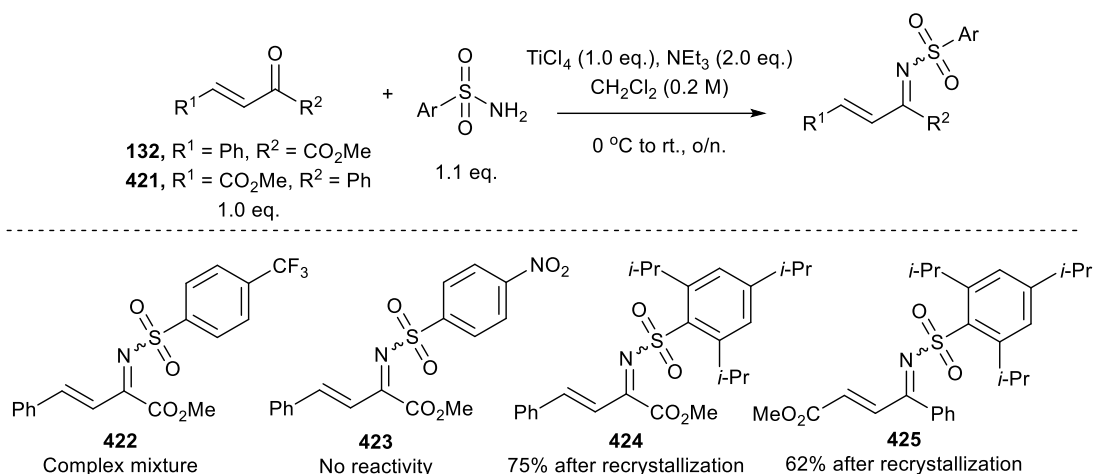


Scheme 6.15: DBU mediated pyridine synthesis

As both the purification (α -imino group slowly hydrolysed under chromatographic conditions) and handling of the α -imino- β,γ -unsaturated ester **412** (a highly viscous yellow oil) was difficult, not all the “mass” of the substrate added was “pure” ketimine. Therefore, the calculated isolated yields underestimated the likely true yield of the reactions, and a better substrate, such as a bench-stable solid, was needed.

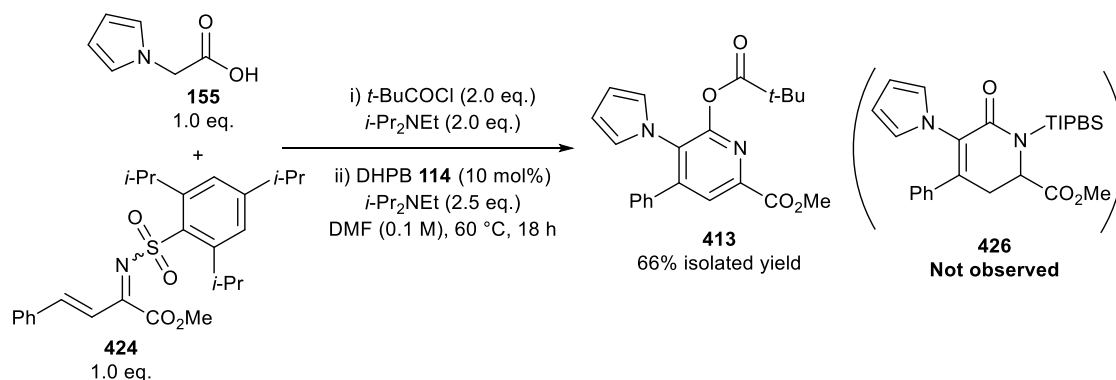
6.3.3. Unsaturated ketimines with alternative *N*-sulfonyl substituents

Different *N*-protected ketimines were synthesized from the corresponding sulfonamides (Scheme 6.16). Based on the proposed mechanism of pyridine formation (Scheme 6.13), it was rationalized that *N*-sulfonyl substituents bearing electron-withdrawing groups would be optimal to promote elimination of the sulfinic acid. Both 4-CF₃ and 4-NO₂ benzenesulfonamides were subjected to the reaction conditions. However, with 4-CF₃ benzenesulfonamide, a full consumption of the α -keto- β,γ -unsaturated ester **132** into an unidentified complex mixture was observed, while no conversion of α -keto- β,γ -unsaturated ester **132** was observed with 4-NO₂ benzenesulfonamide. Changing to electron-rich 2,4,6-triisopropylbenzenesulfonamide (TIPBS) under the reaction conditions with α -keto- β,γ -unsaturated ester **132** successfully afforded the α -imino- β,γ -unsaturated ester **424** in 75% yield after recrystallisation as a white crystalline solid. Meanwhile, β -ester- α,β -unsaturated ketimine **421** was synthesized from TIPBS and β -ester- α,β -unsaturated ketone **425** in 62% yield after recrystallisation as a white crystalline solid.



Scheme 6.16: Synthesis of unsaturated ketimines bearing different *N*-substituents

Using ketimine **424** with 2 equivalents *t*-BuCOCl, 10 mol% DHPB and 4.5 equivalents *i*-Pr₂NEt in DMF (0.1 M) at 60 °C, gave the pyridine **413** in 66% yield (Table 6.2) with no 5,6-dihydropyridinone **426** detected in the crude reaction mixture. Switching the base from *i*-Pr₂NEt (4.5 eq.) to DBU (4.5 eq.) did not improve the isolated yield of pyridine **413** (50%) (entry 1). Switching the solvent from DMF to either MeCN or THF at elevated temperature did not show improvements in the isolated yield (entry 2-3). Increasing the amount of activating agent *t*-BuCOCl from 2.0 eq. to 3.0 eq. afforded pyridine **413** only in 45% NMR yield (entry 3).

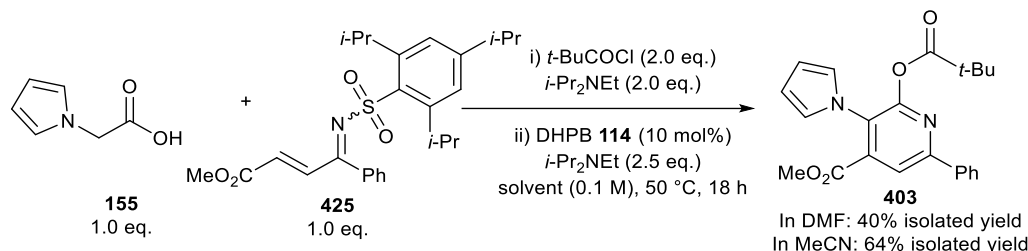


Entry	Variation from standard conditions	Isolated yield / (NMR yield ^a)
1	DBU (2.0 + 2.5 eq.)	50% / (-)
2	THF (0.1 M), 60 °C, 18 h	30% / (-)
3	MeCN (0.1 M), 50 °C, 18 h	43% / (-)
4	<i>t</i> -BuCOCl (3 eq.), 50 °C, 24 h	- / 45%

a. Calculated from crude ¹H NMR of reaction mixture using 1,4-dinitrobenzene as the internal standard.

Table 6.2: Optimizations with *N*-TIPBS ketimine **424**

These conditions were used with β -ester- α,β -unsaturated ketimine **425**, giving the pyridine **403** in 64% isolated yield in MeCN, compared to 40% yield with DMF as the solvent (Scheme 6.17).

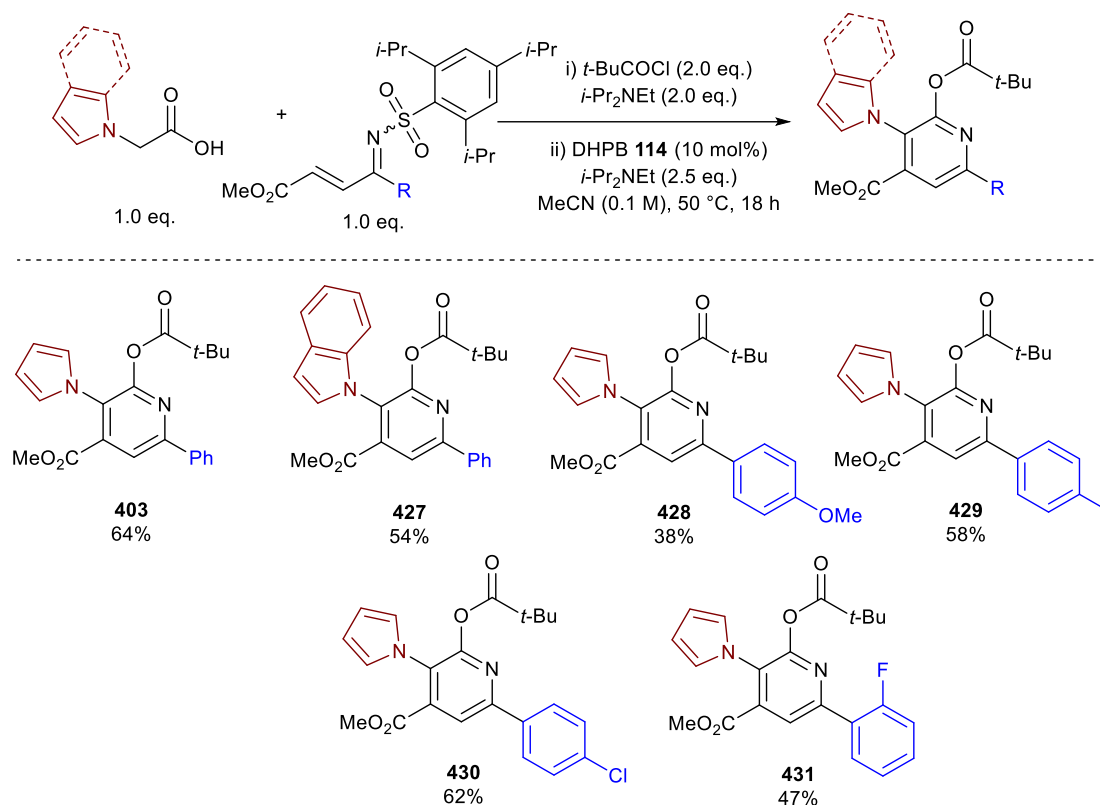


Scheme 6.17: Optimized conditions with β -ester- α,β -unsaturated ketimine **425**

6.4. Substrate scope of pyridine synthesis

6.4.1. Scope study with β -ester- α,β -unsaturated ketimines

With the established optimized conditions, the scope of this process was explored by varying the C(1) aryl ring on the β -ester- α,β -unsaturated ketimines (Scheme 6.18). With 2-pyrrolyl and 2-indolyl acetic acid, C(1)-Phenyl substituted ketimine afforded the pyridines **403** and **427** in 64% and 54% isolated yield respectively. Ketimines with electron-donating 4-OMe or 4-Me substituent on C(1) aryl ring were tolerated, afforded the corresponding pyridines **428** and **429** in 38% and 58% yield with 2-pyrrolyl acetic acid. Installing electron-withdrawing 4-Cl group on C(1) aryl ring of the ketimine afforded the pyridine **430** in 62% yield with 2-pyrrolyl acetic acid. 2-F substituted C(1) aryl ketimine was also tolerated, giving the corresponding pyridine **431** in similar 47% yield with 2-pyrrolyl acetic acid.



Scheme 6.18: Scope with β -ester- α,β -unsaturated ketimines

An X-ray crystal structure was obtained for **403**,³⁰ despite the *t*-Bu group being disordered. This data provides confirmation of the products connectivity, demonstrating that the pivalate group is attached to oxygen, and not nitrogen (Fig. 6.2).

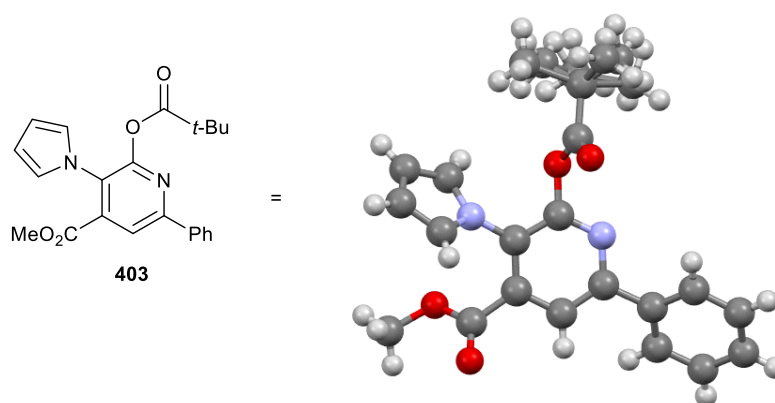
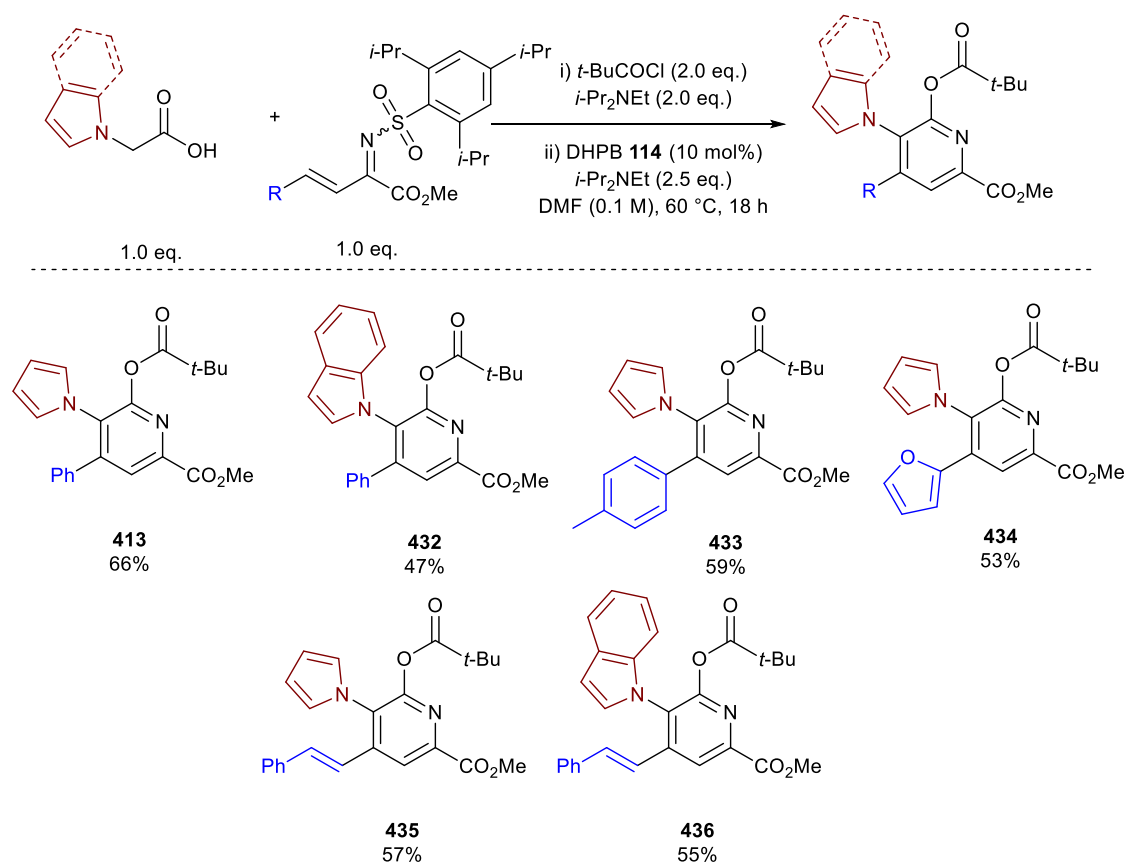


Fig. 6.2: Crystal structure of **403**

6.4.2. Scope with α -imino- β,γ -unsaturated esters

The scope was studied further with α -imino- β,γ -unsaturated esters (Scheme 6.19). Using both 2-pyrrolyl and 2-indolyl acetic acids with γ -Ph-substituted imino ester, the corresponding pyridines **413** and **432** could be isolated in good yields of 66% and 47% respectively. An

electron-donating 4-Me substituent on the γ -aryl ring of imino ester was well tolerated, giving pyridine **433** in 59% yield with 2-pyrrolyl acetic acid while the pyridine product from 2-indolyl acetic acid could not be separated from the crude reaction mixture. Incorporation of a heteroaryl (2-furyl) group on the γ position of the imino ester resulted in pyridine **434** being isolated in 53% yield with 2-pyrrolyl acetic acid, however a complex mixture of starting material and several other species were identified by ^1H NMR with 2-indolyl acetic acid and this was not pursued further. Finally, when a γ -alkenyl substituted imino ester was tested under the reactions, similar yields for pyridines **435** and **436** were obtained with both acids (57% and 55%).



Scheme 6.19: Scope with α -imino- β,γ -unsaturated esters

A crystal structure was also obtained for pyridine **413**, providing further confirmation of the identity and connectivity present within these pyridine products (Fig. **6.3**).

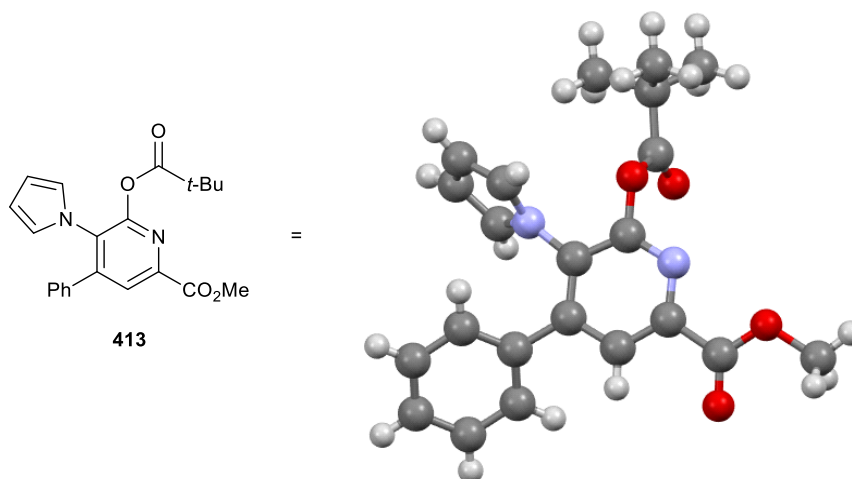
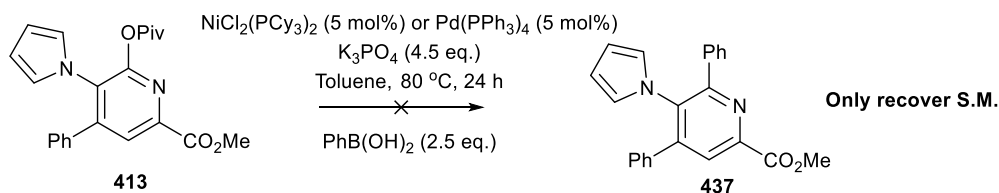


Fig. 6.3: Crystal structure of 413

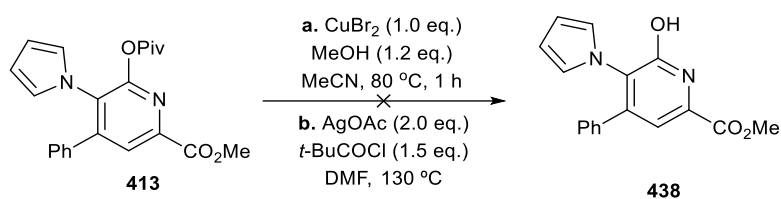
6.5. Product derivatization

Initially, it was envisioned that, by selecting an appropriate transition metal catalyst, the 2-pivaloyloxy pyridine could be directly functionalized via Suzuki-Miyaura cross coupling.³¹ Following a literature procedure using $\text{NiCl}_2(\text{PCy}_3)_2$ and phenyl boronic acid to functionalize aryl pivalates,³² the same catalytic system was tested with 2-pivalate pyridine **413**. Unfortunately, only starting material was recovered and no cross-coupling product **437** was isolated (Scheme 6.20).

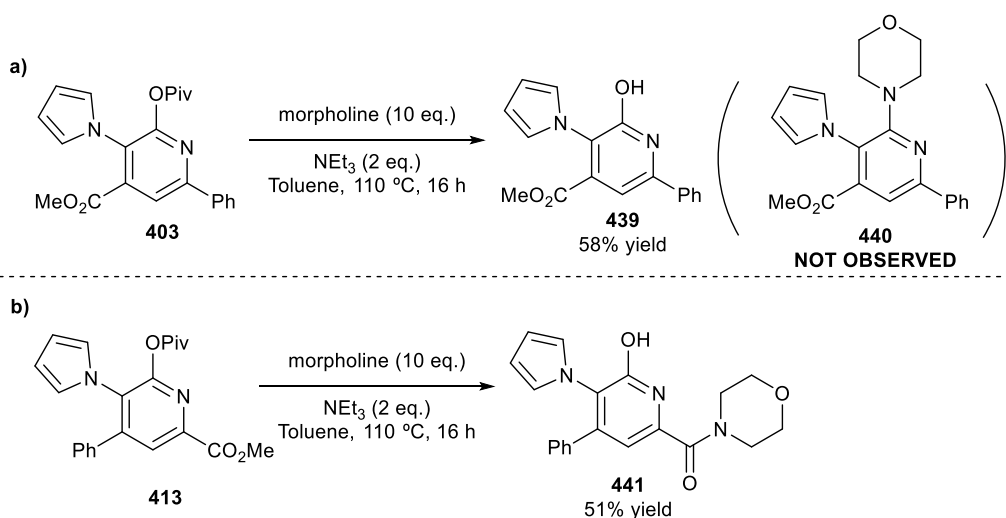


Scheme 6.20: Attempts on cross coupling

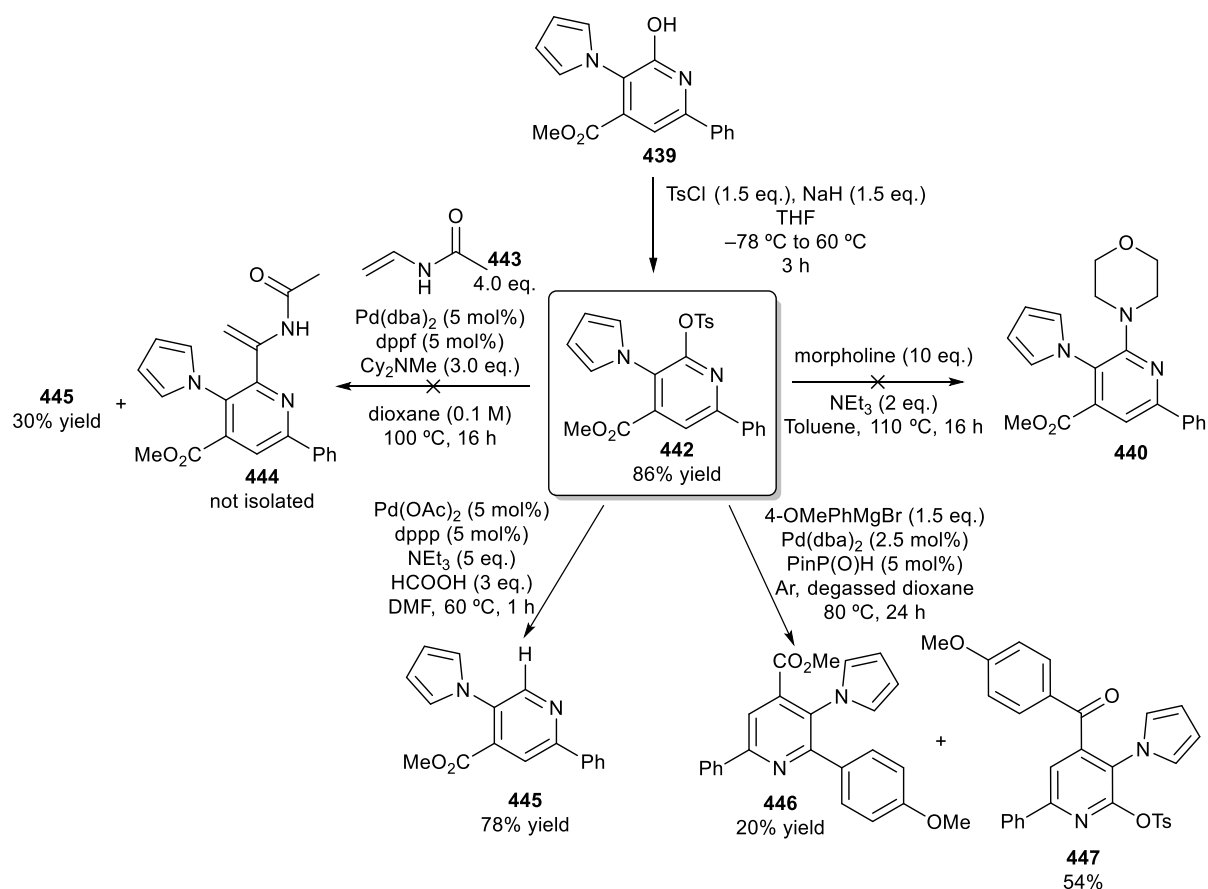
Since no other reported literature was found on the cross-coupling with a pivalate installed on the 2-position of the pyridine, attention turned to hydrolyzing the pivalate and transforming it into another leaving group suitable for the cross coupling. Inspired by literature procedures,^{33,34} the use of Lewis acids CuBr_2 and AgOAc in the presence of a nucleophile was investigated (Scheme 6.21). Unfortunately, based on the inspection of the ^1H NMR of the crude mixture, a complex mixture was identified with full consumption of starting pyridine **413**.

Scheme 6.21: Attempts at hydrolysis of **413**

With the hydrolysis of **413** proving unsuccessful, nucleophilic aromatic substitution (S_NAr) with morpholine was attempted as an alternative way to functionalize the pyridine.²¹ Using 10 equivalents of morpholine as the nucleophile and NEt_3 as the base in toluene, heating at reflux for 16 hours provided none of the expected S_NAr product **440**. Instead, the hydrolysis product, 2-hydroxypyridine **439**, was isolated in 58% yield (Scheme 6.22a), and the by-product *N*-pivaloyl morpholine was detected by analyzing the 1H NMR of the crude reaction mixture. In the absence of morpholine, no conversion of **403** to the corresponding 2-hydroxypyridine **439** was detected, consistent with morpholine acting as a nucleophile to remove the pivalate. Other nucleophiles, such as MeOH, returned only the starting material **403**. The structure of **439** was tentatively assigned to be the 2-hydroxypyridine rather than its 2-pyridone tautomer, as in solution only small energy differences between the two tautomers is exceeded (8.83 kJ/mol, measured by IR spectroscopy).^{35,36} When pyridine **413**, bearing the ester group at the C(6) position, was applied under the same conditions, hydrolysis and amidation of the C(6) ester was observed, giving amide **441** in 51% yield (Scheme 6.22b). The absence of S_NAr product suggested that the pivalate carbonyl was relatively more electrophilic than the C(2) position on the pyridine.

Scheme 6.22: Hydrolysis products from attempted S_NAr reactions

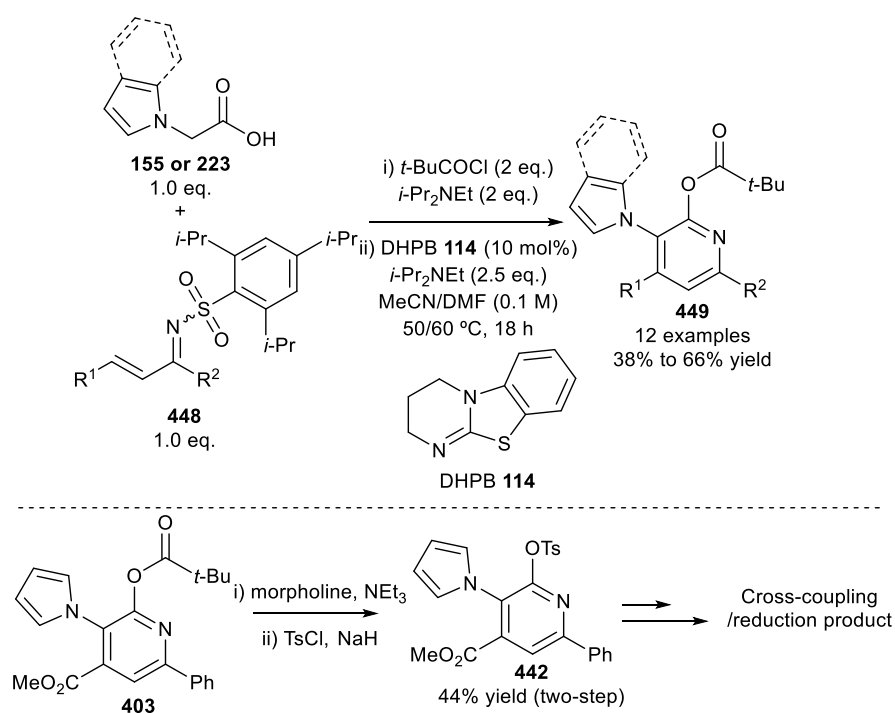
After obtaining 2-hydroxypyridine **439**, it was transformed into the 2-tosyl-pyridine **442**, to investigate if the OTs group could be used for further derivatization (Scheme 6.23). Initially an attempted S_NAr reaction with 2-OTs pyridine **442** and morpholine afforded a mixture of starting material and other products,³⁷ with none of the desired product **440** able to be isolated. Mizoroki–Heck reaction using *N*-vinyl-acetamide **443** was next tested,³⁸ however under these conditions none of the cross-coupling product **444** was observed, with only trisubstituted pyridine **445** and starting material **442** being isolated. Next, reduction of the 2-OTs group was attempted using $Pd(OAc)_2$ and formic acid.³⁹ Trisubstituted pyridine **445** was isolated in 78% yield after 1 h. The success of this reduction indicated that the oxidative addition of Pd into 2-OTs group was happening, which was potentially useful for other derivatizations. Finally, Kumada cross-coupling⁴⁰ using 4-methoxyphenylmagnesium bromide afforded the corresponding coupling product **446** in 20% yield, with the major side-product **447**, arising from addition of the Grignard reagent to the methyl ester, isolated in 54% yield.



Scheme 6.23: Derivatization study

6.6. Conclusions

In conclusion, a one-pot synthesis of tetrasubstituted pyridines has been developed. Using either 2-pyrrolyl or 2-indolyl acetic acid with *N*-TIPBS derived unsaturated ketimines **448** in MeCN or DMF at elevated temperature (50-60 °C), a range of 2-pivaloyloxy pyridines **449** were isolated in 30-66% yield (Scheme 6.24). The 2-pivaloyloxy substituent proved unreactive in model cross-coupling reactions, so attempts were made to deprotect the pivalate group. A two-step process with morpholine/TsCl afforded the corresponding 2-OTs pyridine **442**. Cross-coupling reactions and a reduction were tested, with Kumada coupling giving the coupling product in 20% yield, and Pd-catalysed reduction using formic acid affording the trisubstituted pyridine **445** in 78% yield.



Scheme 6.24: One-pot synthesis of pyridines

6.7. References

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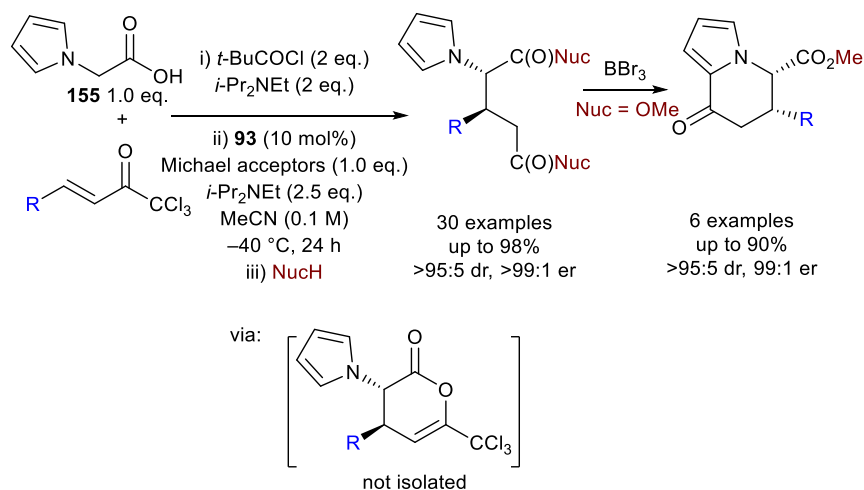
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Chapter 7: Conclusions and future work

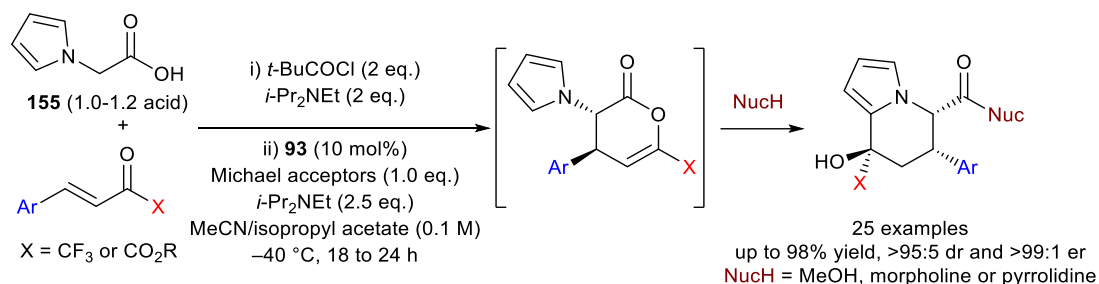
To conclude this thesis, N-substituted C(1)-ammonium enolate precursors, especially 2-pyrrolyl and 2-indolyl acetic acid, have been successfully applied in isothiurea-catalyzed Michael addition-lactonization/lactamizations with a wide variety of Michael acceptors. Importantly, the installation of this N-linked substituents serves as a functional handle for further synthetic transformations.

Firstly, the use of electron-deficient CCl_3 Michael acceptors was demonstrated with 2-pyrrolyl acetic acid. Even through the intermediate 3,4-dihydropyranone generated as the catalysis product proved troublesome to purify due to chromatographic instability, *in situ* nucleophilic ring-opening facilitated the isolation of stable derivatives of this intermediate. CCl_3 displacement by nucleophiles allowed the isolation of stable ring-opening derivatives as a range of 30 diesters and diamides in up to 98% yield, >95:5 dr and >99:1 er. The substrate scope was examined by varying the β -substituent in CCl_3 enone. Further demonstration of the synthetic utility of this ring-opening derivatives was achieved with an intramolecular Friedel-Crafts acylation utilizing the electron-rich nature of pyrrole to afforded dihydroindolizinone derivatives in up to 90% yield with no erosion in stereoselectivity (Scheme 7.1).



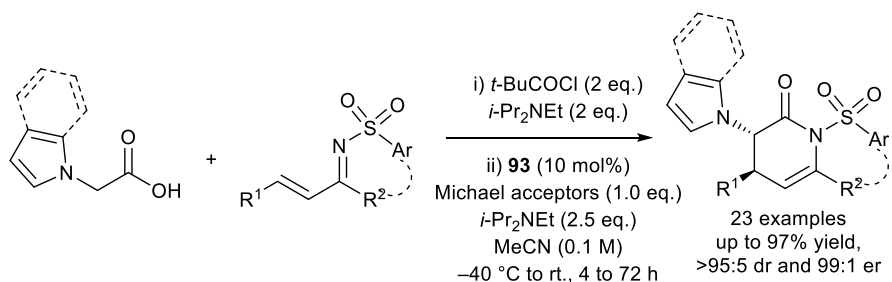
Scheme 7.1: Enantioselective Michael addition-lactonization with CCl_3 Michael acceptors

In the case of using either α,β -unsaturated trifluoromethyl ketones or α -keto- β,γ -unsaturated esters as the Michael acceptors, *in situ* nucleophilic ring-opening followed by spontaneous intramolecular cyclization with pyrrole afforded the corresponding tetrahydroindolizine derivatives in up to 98% yield, >95:5 dr and >99:1 er (Scheme 7.2).



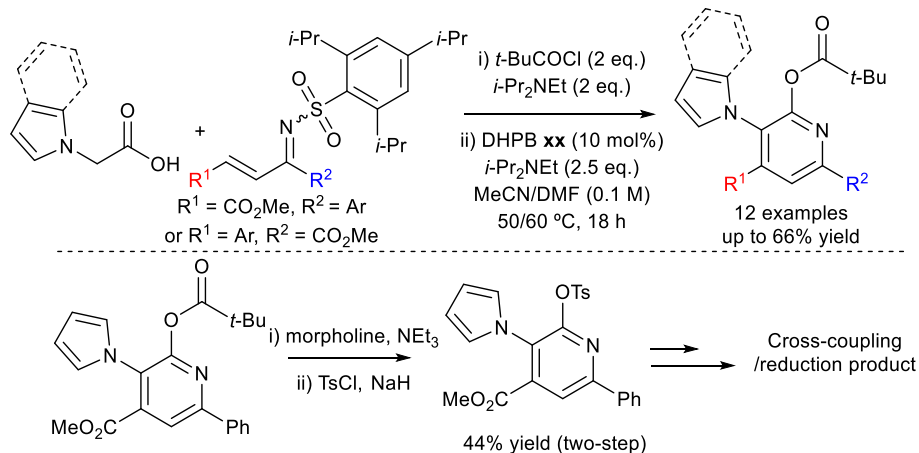
Scheme 7.2: One-pot synthesis of enantioenriched tetrahydroindolizine derivatives

Having shown that 2-pyrrolyl acetic acid is an effective C(1)-ammonium enolate precursor, its reaction with α,β -unsaturated ketimines was investigated next. With 2-pyrrolyl and 2-indolyl acetic acid, both chalcone-derived *N*-Ts ketimines and unsaturated cyclic sulfonamides derived from saccharin afforded a range of 23 chromatographic stable dihydropyridinones in up to 97% yield, >95:5 dr and >99:1 dr (Scheme 7.3).



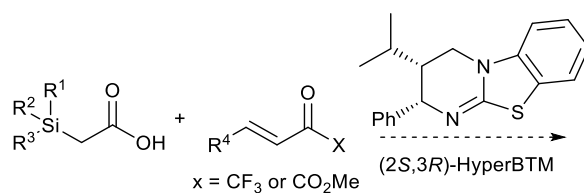
Scheme 7.3: Summary of isothiurea catalyzed synthesis of dihydropyridinones

During the course of investigating a variety of α,β -unsaturated ketimines bearing esters, an unexpected elimination of the nitrogen-sulfonyl substituent was discovered, leading to the formation of tetrasubstituted pyridines in up to 66% yield with 2-indolyl and 2-pyrrolyl acetic acid (Scheme 7.4). Further derivatization via transforming the 2-pivaloyloxy group into 2-OTs group in a two-step process enabled Pd-catalyzed cross coupling and reduction.



Scheme 7.4: Synthesis of tetrasubstituted pyridines and further derivatization

Inspired by the results outlined in this thesis, future work will likely focus on probing other heteroatom linked C(1)-ammonium enolate precursors, such as α -Si, O or B linked acids, with isothiourea catalysts and electron deficient Michael acceptors (Scheme 7.5). Further application of the methodologies described in the thesis to natural product synthesis will be investigated.



Scheme 7.5: Overview of the future work envisaged in Si-linked C(1)-ammonium enolate precursors

Experimentals

8.1. General Information

Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (N₂ or Ar) using standard vacuum line techniques. Anhydrous solvents (Et₂O, CH₂Cl₂, THF and PhMe) were obtained after passing through an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40–60 °C. All other solvents and commercial reagents were used as received without further purification unless otherwise stated.

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 –78 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reaction involving heating were performed using DrySyn blocks and a contact thermocouple.

Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a Büchi V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with an IKA HB10 heating bath and ILMVAC vacuum controller, or an IKA RV10 rotary evaporator with a IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL601 Recirculating Coolers filled with ethylene glycol and set to –5 °C.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm) and/or staining with aqueous KMnO₄ solution followed by heating. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated.

Melting points were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained on a Shimadzu HPLC consisting of a DGU-20A_s degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven. Separation was achieved using either DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS- H, IA and IB columns using the method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra.

Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wavenumbers (ν_{\max}) reported in cm^{-1} .

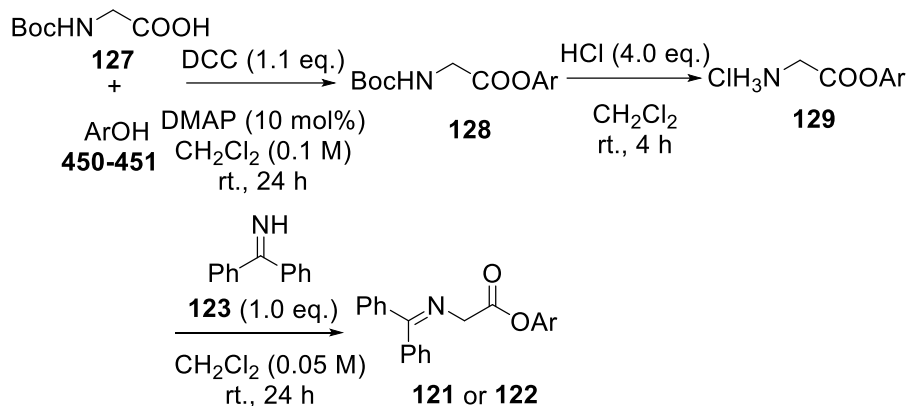
^1H , $^{13}\text{C}\{^1\text{H}\}$, ^{19}F and $^{19}\text{F}\{^1\text{H}\}$ NMR spectra were acquired on either a Bruker AV300 with a BBFO probe (^1H 300 MHz; $^{13}\text{C}\{^1\text{H}\}$ 75 MHz; $^{19}\text{F}\{^1\text{H}\}$ 282 MHz), a Bruker AV400 with a BBFO probe (^1H 400 MHz; $^{13}\text{C}\{^1\text{H}\}$ 101 MHz; $^{19}\text{F}\{^1\text{H}\}$ 377 MHz), a Bruker AVII 400 with a BBFO probe (^1H 400 MHz; $^{13}\text{C}\{^1\text{H}\}$ 101 MHz; $^{19}\text{F}\{^1\text{H}\}$ 376 MHz), a Bruker AVIII-HD 500 with a SmartProbe BBFO+ probe (^1H 500 MHz; $^{13}\text{C}\{^1\text{H}\}$ 126 MHz; $^{19}\text{F}\{^1\text{H}\}$ 470 MHz) or a Bruker AVIII 500 with a CryoProbe Prodigy BBO probe (^1H 500 MHz; $^{13}\text{C}\{^1\text{H}\}$ 126 MHz; ^{19}F 470 MHz) in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, J , are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples thereof. The abbreviation Ar denotes aromatic and app denotes apparent. NMR peak assignments were confirmed using 2D ^1H correlated spectroscopy (COSY), 2D ^1H - ^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D ^1H - ^{13}C heteronuclear single quantum coherence (HSQC) where necessary.

Mass spectrometry (m/z) data were acquired by either electrospray ionisation (ESI), chemical ionisation (CI), electron impact (EI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionization (APCI) or nanospray ionisation (NSI) at either the University of St Andrews Mass Spectrometry Facility ([A] quoted) or at the EPSRC UK National Mass Spectrometry Facility at Swansea University ([A]⁺ or [A]⁻ quoted).

8.2. Experimentals for Chapter 2

8.2.1. General Procedures

General procedure A: Synthesis of glycine-derived Schiff base esters

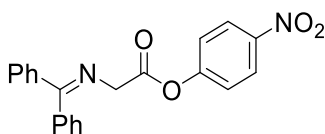


To a round-bottom flask containing *N*-Boc glycine **127** (1.0 eq.), aromatic alcohol **450-451** (1.0 eq.), DCC (1.1 eq.) and DMAP (10 mol%) was added anhydrous CH_2Cl_2 (0.1 M) under Ar. The resulting mixture was stirred vigorously at room temperature for 24 h, before it was filtered through a Celite pad. The filtrate was collected, and HCl solution (2 M in Et_2O , 4.0 eq.) was added to the filtrate. The mixture was stirred at rt. for further 4 hours. Solid **128** was collected through a sinter funnel and dried under vacuum.

To a round-bottom flask charged with ammonium salt **129** from last step, anhydrous CH_2Cl_2 (0.1 M) was added, followed by benzophenone imine **123** (1.0 eq.) under Ar. The mixture was allowed to stir vigorously at rt. for 24 h. Upon completion of the reaction, the mixture was filtered through a pad of Celite. The filtrate was collected and concentrated *in vacuo*. Purification via either trituration in Et_2O or flash chromatography afforded the final product

8.2.2. Substrate synthesis and characterization data

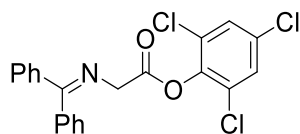
4-Nitrophenyl 2-((diphenylmethylene)amino)acetate (**121**)



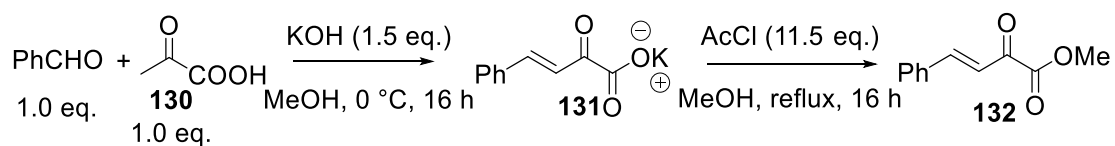
Following **general procedure A**, *N*-Boc glycine **127** (2.63 g, 15 mmol, 1.0 eq.), 4-nitrophenol **450** (2.09 g, 15 mmol, 1.0 eq.), DCC (3.41 g, 16.5 mmol, 1.1 eq), DMAP (183.3 mg, 1.5 mmol,

10 mol%) and benzophenone imine **123** (2.72 g, 15 mmol, 1.0 eq.) gave the titled compound **121** (2.59 g, 48% yield over three-step), after trituration in Et₂O, as white needles. mp 101–103 °C; ν_{\max} (film, cm⁻¹) 3076 (CH stretch), 1780 (ester C=O), 1624 (C=N), 1614 (C=C), 1522 (N–O stretch); ¹H NMR (400 MHz, CDCl₃) δ_{H} : 4.49 (2H, s, CH₂), 7.21–7.25 (2H, m, C(2)N=CArH), 7.30–7.33 (2H, m, C(1)OArC(2,6)H), 7.35–7.39 (2H, m, C(2)N=CArH), 7.42–7.47 (1H, m, C(2)N=CArH), 7.50–7.54 (3H, m, C(2)N=CArH), 7.69–7.71 (2H, m, C(2)N=CArH), 8.25–8.29 (2H, m, C(1)OArC(3,5)H); ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 55.6 (CH₂), 122.5 (C(1)OArC(2,6)H), 125.4 (C(1)OArC(3,5)H), 127.7 (C(2)N=CArC), 128.4 (C(2)N=CArC), 129.0 (C(2)N=CArC), 129.1 (C(2)N=CArC), 129.3 (C(2)N=CArC), 131.0 (C(2)N=CArC), 135.9 (C(2)N=CArC), 139.0 (C(2)N=CArC), 145.5 (C(1)OArC(1)), 155.4 (C(1)OArC(4)), 168.4 (C(1)), 173.1 (C(2)N=C); HRMS (ESI⁺) C₂₁H₁₆O₄N₂Na [M+Na]⁺ found 383.0994, requires 383.1002 (-2.2 ppm).

2,4,6-Trichlorophenyl 2-((diphenylmethylene)amino)acetate (**122**)

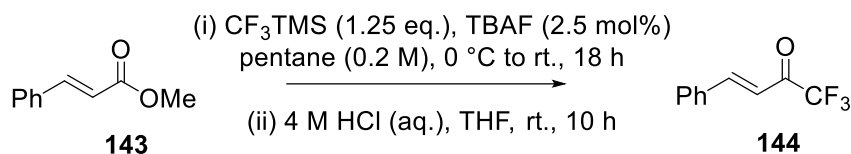


Following **general procedure A**, *N*-Boc glycine (2.63 g, 15 mmol, 1.0 eq.), 2,4,6-trichlorophenol **451** (2.96 g, 15 mmol, 1.0 eq.), DCC (3.41 g, 16.5 mmol, 1.1 eq.), DMAP (183.3 mg, 1.5 mmol, 10 mol%) and benzophenone imine **123** (2.72 g, 15 mmol, 1.0 eq.) gave the titled compound **122** (2.39 g, 38% yield over three-step), after flash column chromatography (10:90 EtOAc:petrol, *R_f* 0.31), as white solids. mp. 79–83 °C; ν_{\max} (film, cm⁻¹) 3080 (CH stretch), 1788 (ester C=O), 1657 (C=N), 1624 (Ar C=C); ¹H NMR (400 MHz, CDCl₃) δ_{H} : 4.60 (2H, s, CH₂), 7.24–7.28 (2H, m, C(2)N=CArH), 7.36–7.40 (4H, m, C(2)N=CArH + C(1)OArC(3,5)H), 7.43–7.47 (1H, m, C(2)N=CArH), 7.50–7.56 (3H, m, C(2)N=CArH), 7.71–7.74 (2H, m, C(2)N=CArH); ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 54.9 (CH₂), 127.8 (C(2)N=CArC), 128.2 (C(1)OArC(3)H), 128.3 (C(1)OArC(3)H), 128.4 (C(2)N=CArC), 128.7 (C(2)N=CArC), 129.0 (C(2)N=CArC), 129.0 (C(2)N=CArC), 129.2 (C(2)N=CArC), 129.7 (C(2)N=CArC), 130.2 (C(2)N=CArC), 130.9 (C(2)N=CArC), 132.2 (C(2)N=CArC), 132.6 (C(2)N=CArC), 135.8 (C(1)OArC(1)), 139.1 (C(1)OArC(2,6)), 142.9 (C(1)OArC(4)), 167.1 (C(1)), 173.4 (C(2)N=C); HRMS (ESI⁺) C₂₁H₁₄O₂N³⁵Cl₃Na [M+Na]⁺ found 439.9973, requires 439.9982 (-2.1 ppm).

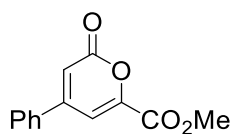
Methyl (*E*)-2-oxo-4-phenylbut-3-enoate (132**)**

To a solution of pyruvic acid **130** (3.52 mL, 50 mmol, 1.0 eq.) and benzaldehyde (5.09 mL, 50 mmol) in MeOH (5 mL) at 0 °C was added a solution of KOH (4.21 g, 75 mmol, 1.5 eq.) in MeOH (15 mL). The first 1 eq. of the KOH solution was added dropwise over 30 minutes. The last 0.5 eq. was added as one portion and the reaction mixture was stirred at 40 °C for 1 h followed by 0 °C for 16 h. The precipitate was collected by filtration, washed twice with cold MeOH, once with Et₂O and dried under vacuum to furnish the potassium salt **131** (9.01 g, 84%) as a yellow solid. Spectroscopic data were in accordance with the literature.¹ mp 248–249 °C {Lit.¹ 248 °C}; ¹H NMR (400 MHz, D₂O) δ_H: 6.82 (1H, d, *J* 16.5, C(3)*H*), 7.37–7.47 (3H, m, ArC(3,5)*H* and ArC(4)*H*), 7.60–7.66 (3H, m, ArC(2,6)*H* and C(4)*H*).

Acetyl chloride (28.6 mL, 400 mmol, 11.5 eq.) was added to MeOH (200 mL) at 0 °C to generate HCl. Potassium salt **131** (7.48 g, 35.0 mmol, 1.0 eq.) was added and the mixture stirred at 0 °C for 30 min then warmed to rt for 2 h before heating at reflux for 16 h. Concentration *in vacuo* gave a sticky solid which was dissolved in H₂O (50 mL) and extracted with CH₂Cl₂ (50 mL x 3). The combined organics were washed with saturated aq. NaHCO₃ (25 mL), H₂O (25 mL) and brine (25 mL) before being dried with MgSO₄. Concentration *in vacuo* afforded the crude reaction mixture which was purified by flash column chromatography (10:90 EtOAc:petrol) to afford **132** as a yellow solid (2.80 g, 42%). Spectroscopic data were in accordance with the literature.¹ mp 68–70 °C (MeOH) {Lit.¹ 69–70 °C (MeOH)}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.89 (3H, s, CH₃), 7.34 (1H, d, *J* 16.1, C(3)*H*), 7.34–7.44 (3H, m, ArC(3,5)*H* and ArC(4)*H*), 7.56–7.61 (2H, m, ArC(2,6)*H*), 7.82 (1H, d, *J* 16.1, C(4)*H*).

(E)-1,1,1-Trifluoro-4-phenylbut-3-en-2-one (144)

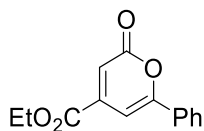
To a solution of methyl cinnamate **143** (2.0 g, 12.4 mmol, 1.0 eq.) in pentane (60 mL, 0.2 M) at room temperature under Ar was added trifluoromethyltrimethylsilane (2.28 mL, 15.4 mmol, 1.25 eq.). The mixture was cooled to 0 °C, before a 1 M solution of TBAF in THF (0.31 mL, 0.31 mmol, 2.5 mol%) was added. The resulting mixture was warmed to room temperature and stirred for 18 h. Then, the solvent was removed *in vacuo*, and the residue was redissolved in THF (10 mL) and treated with 4 M aqueous HCl (10 mL). After stirring at rt. for another 10 h, the reaction mixture was diluted with Et₂O (80 mL) and washed with brine (40 mL). The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to give the crude material. Purification by flash column chromatography (5:95 to 10:90 CH₂Cl₂:petrol) gave the titled compound **144** (1.17 g, 47%) as a light yellow. Spectroscopic data was in accordance with the literature.² ¹H NMR (400 MHz, CDCl₃) δ_H: 7.05 (1H, dq, *J* 16.0, 0.9, C(3)*H*), 7.41–7.58 (3H, m, Ar*H*), 7.64–7.71 (2H, m, Ar*H*), 8.00 (1H, d, *J* 16.0, C(4)*H*); ¹⁹F NMR (376 MHz, CDCl₃) δ_F: -77.6 (3F, s, CF₃).

Methyl 2-oxo-4-phenyl-2H-pyran-6-carboxylate (135)

To a flame-dried Schlenk tube containing 4-nitrophenyl ester **121** (97.9 mg, 0.272 mmol, 1.0 eq.), ketoester **132** (51.7 mg, 0.272 mmol, 1.0 eq.) and *rac*-tetramisole·HCl **133** (13.1 mg, 20 mol%) under Ar, CH₂Cl₂ (2.7 mL, 0.1 M) was added followed by *i*-Pr₂NEt (118 μL, 0.68 mmol, 2.5 eq.). The resulting mixture was allowed to stir at room temperature for 24 h, and the progress of the reaction was monitored by TLC analysis. Upon complete consumption of the starting Michael acceptor, the reaction mixture was quenched with 0.1 M aqueous HCl (5 mL), extracted with CH₂Cl₂ (3 x 10 mL), dried over MgSO₄ and concentrated *in vacuo*. Flash column chromatography (30:70 Et₂O:petrol, R_f 0.37) gave the titled compound **135** as a light yellow

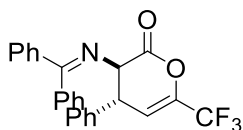
solid (37.6 mg, 60%). mp 89-91 °C; ν_{\max} (film, cm^{-1}) 3061 (C-H), 2961 (C-H), 1742 (C=O ester), 1709 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 3.97 (3H, s, CH_3), 6.73 (1H, d, J 1.7, C(3) H), 7.47 (1H, d, J 1.7, C(5) H), 7.50–7.55 (3H, m, C(4)ArC(3,4,5) H), 7.62–7.65 (2H, m, C(4)ArC(2,6) H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 53.2 (CH_3), 110.3 (C(5) H), 115.0 (C(3) H), 126.7 (C(4)ArC(2,6) H), 129.5 (C(4)ArC(3,5) H), 131.3 (C(4)ArC(4) H), 134.4 (C(4)ArC(1)), 148.8 (C(4)), 153.5 (C(6)), 160.1 (C(2)), 160.6 (C(6)CO₂Me); HRMS (ESI⁺) C₁₃H₁₀O₄Na [M+Na]⁺ found 253.0466, requires 253.0471 (-2.1 ppm).

Ethyl 2-oxo-6-phenyl-2H-pyran-4-carboxylate (**141**)



To a flame-dried Schlenk tube containing 4-nitrophenyl ester **121** (103 mg, 0.285 mmol, 1.0 eq.), β -ester enone **139** (58.2 mg, 0.285 mmol, 1.0 eq.) and *rac*-tetramisole·HCl **133** (6.91 mg, 10 mol%) under Ar, CH_2Cl_2 (2.9 mL, 0.1 M) was added followed by *i*-Pr₂NEt (123 μL , 0.712 mmol, 2.5 eq.). The resulting mixture was allowed to stir at room temperature for 24 h, and the progress of the reaction was monitored by TLC analysis. Upon complete consumption of the starting Michael acceptor, the reaction mixture was quenched with 0.1 M aqueous HCl (5 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over MgSO_4 and concentrated *in vacuo*. Flash column chromatography (30:70 Et₂O:petrol, R_f 0.40) gave the titled compound **141** as a light yellow solid (23.6 mg, 36%). Spectroscopic data was in accordance with the literature.³ mp 73-74 °C; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.42 (3H, t, J 7.1, CH_3), 4.42 (2H, q, J 7.1, CH_2), 6.90 (1H, d, J 1.3, C(3) H), 7.12 (1H, d, J 1.3, C(5) H), 7.46–7.50 (3H, m, Ar H), 7.86–7.90 (2H, m, Ar H).

3-((Diphenylmethylene)amino)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one
(145)



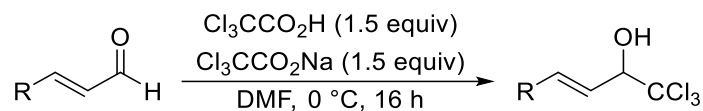
To a flame-dried Schlenk tube containing 4-nitrophenyl ester **121** (164 mg, 0.456 mmol, 1.0 eq.), CF₃ enone **144** (91.3 mg, 0.456 mmol, 1.0 eq.) and (*S*)-BTM **146** (23.0 mg, 20 mol%) under Ar, CH₂Cl₂ (4.6 mL, 0.1 M) was added. The resulting mixture was allowed to stir at rt for 24 h before it was concentrated *in vacuo* and then filtered directly through a short column of silica using CH₂Cl₂ eluent (ca. 20 mL). The filtrate was concentrated *in vacuo* to give the crude product (87:13 dr *anti:syn*) which was purified via flash column chromatography (30:70 Et₂O:petrol, R_f 0.33) to give the titled compound **145** as a light brown oil in >95:5 dr (77 mg, 40%). Chiral HPLC analysis, Chiralpak OD-H (99:1 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 13.0 min, t_R(minor): 7.7 min, 58:42 er; v_{max} (film, cm⁻¹) 3061 (CH stretch), 1717 (C=O), 1655 (C=N), 1597 (C=C), 1578 (C=C); ¹H NMR (400 MHz, CDCl₃) δ_H: 4.20 (1H, d, *J* 11.2, C(3)*H*), 4.29–4.34 (1H, m, C(4)*H*), 6.02 (1H, d, *J* 2.3, C(5)*H*), 7.04–7.07 (2H, m, Ar*H*), 7.31–7.42 (11H, m, Ar*H*), 7.53–7.55 (2H, m, Ar*H*); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C: 44.3 (C(4)*H*), 65.4 (C(3)*H*), 110.1 (q, *J* 3.7, C(5)*H*), 119.9 (q, *J* 270.1, CF₃), 127.4 (ArCH), 128.0 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.5 (ArCH), 128.7 (ArCH), 128.9 (ArCH), 129.0 (ArCH), 129.3 (ArCH), 131.0 (ArCH), 135.0 (C(3)ArC(1)), 135.2 (NCAr^aC(1)), 135.6 (NCAr^bC(1)), 140.8 (q, *J* 38.2, C(6)), 164.2 (C(2)), 173.8 (C=N); ¹⁹F NMR (376 MHz, CDCl₃) δ_F: -72.1 (3F, s, CF₃). Characterization was not carried out further due to product instability.

Data for the minor diastereoisomer: Chiral HPLC analysis, Chiralpak OD-H (99:1 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 22.2 min, t_R(minor): 9.4 min, 51:49 er; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.94–3.98 (1H, m, C(4)*H*), 4.46 (1H, d, *J* 5.4, C(3)*H*), 6.17 (1H, d, *J* 3.8, C(5)*H*), 7.10–7.12 (2H, m, Ar*H*), 7.31–7.42 (11H, m, Ar*H*), 7.46–7.48 (2H, m, Ar*H*); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C (selected): 43.4 (C(4)), 63.4 (C(3)), 110.0 (q, *J* 3.7, C(5)), 164.4 (C(2)), 173.2 (C=N); ¹⁹F NMR (376 MHz, CDCl₃) δ_F: -72.0 (3F, s, CF₃).

8.3. Experimentals for Chapter 3

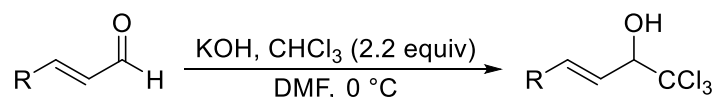
8.3.1. General Procedures

General Procedure A: Synthesis of trichloromethyl carbinols using trichloroacetate



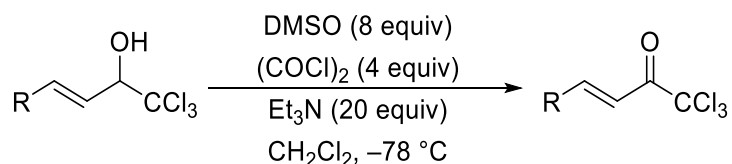
Trichloroacetic acid (1.5 equiv) and sodium trichloroacetate (1.5 equiv) were added to a solution of the appropriate aldehyde (1 equiv) in DMF (1.3 M) at 0 °C. The reaction was allowed to warm slowly to rt over 16 h before being diluted with water and extracted with EtOAc (×3). The combined organics were washed with water (×3) and NaHCO₃, dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography.

General Procedure B: Synthesis of trichloromethyl carbinols using CHCl₃



A solution of KOH (1.0 equiv) in EtOH (4 mL) was added dropwise to a stirred solution of the appropriate aldehyde (1.0 equiv) and chloroform (2.2 equiv) in DMF (1.3 M) at 0 °C. The solution turned deep red and was stirred at 0 °C for until complete by TLC analysis (*ca.* 30 min to 1 h). The solution was acidified with 2 M HCl to pH 5-7 and extracted with EtOAc (×3). The combined organics were washed with water dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography.

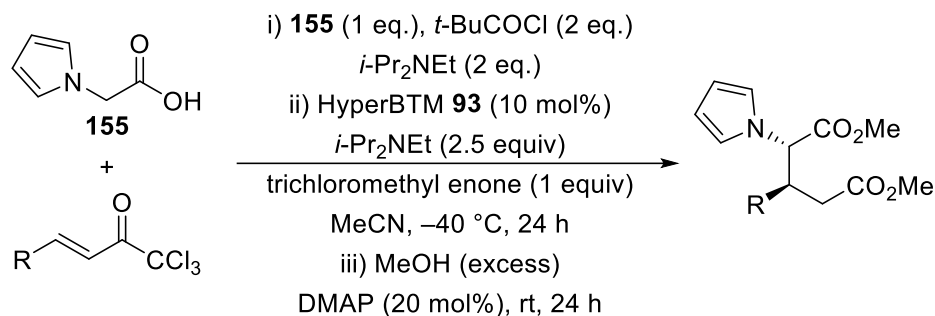
General Procedure C: Synthesis of α,β -unsaturated trichloromethyl ketones



A solution of DMSO (8 equiv) in anhydrous CH₂Cl₂ (4.4 M) was added dropwise to a solution of oxalyl chloride (4 equiv) in CH₂Cl₂ (0.25 M) at -78 °C. After 2 min, a solution of the appropriate alcohol (1 equiv) in CH₂Cl₂ (1.0 M) was added dropwise. After a further 15 min, Et₃N (20 equiv)

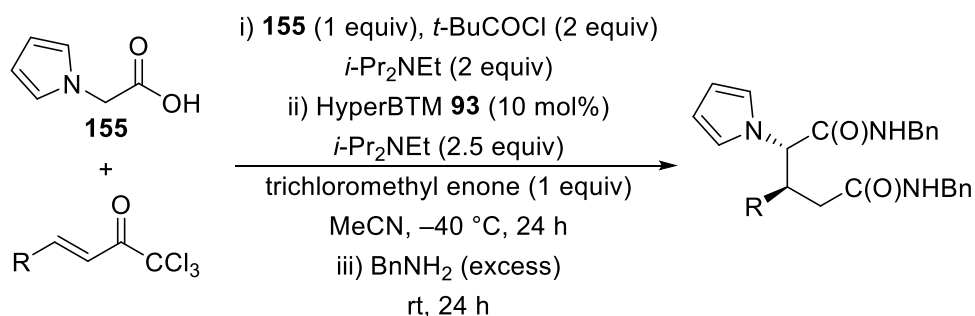
was added dropwise and the reaction stirred for 0.5 h, allowing to warm to rt. The reaction mixture was then quenched with 2 M HCl and extracted with CH₂Cl₂ (×3). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography.

General Procedure D: Michael addition-lactonization with MeOH ring-opening



2-(1*H*-Pyrrol-1-yl)acetic acid **155** (1 equiv.) was dissolved in anhydrous MeCN (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (2 equiv) and pivaloyl chloride (2 equiv) were added. The reaction was stirred at 0 °C for 20 min before cooling to -40 °C. HyperBTM **93** (10 mol%), the required α,β -unsaturated trichloromethyl ketone (1 equiv), and *i*-Pr₂NEt (2.5 equiv) were added sequentially and the reaction stirred at -40 °C for 24 h. Excess MeOH (equal volume) and DMAP (20 mol%) were added before the solution was warmed to rt and stirred for 24 h. The reaction was diluted with CH₂Cl₂ (equal volume) and washed with 1 M HCl (×2) and brine (×2) before being dried over MgSO₄, filtered, and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography.

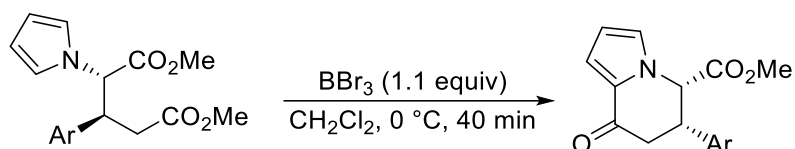
General Procedure E: Michael addition-lactonization with BnNH₂ ring-opening



2-(1*H*-Pyrrol-1-yl)acetic acid **155** (1 equiv.) was dissolved in anhydrous MeCN (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (2 equiv) and pivaloyl chloride (2 equiv) were added. The reaction was stirred at 0 °C for 20 min before cooling to -40 °C. HyperBTM **93** (10 mol%), the required α,β -unsaturated trichloromethyl ketone (1 equiv), and *i*-Pr₂NEt (2.5

equiv) were added sequentially and the reaction stirred at $-40\text{ }^{\circ}\text{C}$ for 24 h. Excess BnNH_2 (equal volumes) was added before the solution was warmed to rt and stirred for 24 h. The reaction was diluted with EtOAc (8 volumes) and washed with 1 M HCl ($\times 3$), NaHCO_3 ($\times 3$), and brine ($\times 3$) before being dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by either trituration with Et_2O or flash silica column chromatography.

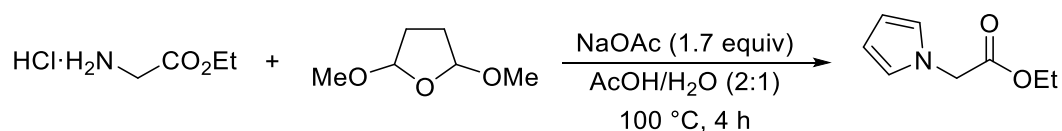
General Procedure F: Intramolecular Friedel-Crafts acylation



The appropriate pyrrole diester (1 equiv) was dissolved in anhydrous CH_2Cl_2 (0.05 M) under an atmosphere of N_2 and cooled to $0\text{ }^{\circ}\text{C}$ before BBr_3 (1.1 equiv) was added dropwise. The reaction was stirred at $0\text{ }^{\circ}\text{C}$ for 40 min before being quenched by the careful addition of water (1 volume) followed by 2 M Na_2CO_3 (1 volume). The solution was extracted with CH_2Cl_2 (2×7 volumes) and the combined organics dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography.

8.3.2. Starting materials synthesis

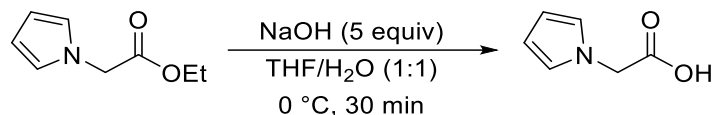
Ethyl 2-(1H-pyrrol-1-yl)acetate (154)



Glycine ethyl ester hydrochloride (2.50 g, 17.9 mmol) and NaOAc (2.45 g, 29.9 mmol) were suspended in H_2O (12.5 mL) and AcOH (25 mL) before 2,5-dimethoxytetrahydrofuran (2.32 mL, 17.9 mmol) was added. The reaction was heated at $100\text{ }^{\circ}\text{C}$ for 4 h before being cooled to rt, poured into water (50 mL) and extracted with EtOAc (30 mL). The aqueous phase was neutralized with solid Na_2CO_3 and further extracted with EtOAc (2×30 mL). The combined organics were washed with water (50 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (Petrol/EtOAc 80:20, R_f 0.56) to give **154** (1.80 g, 66%) as a colourless oil. Spectroscopic data were in accordance with the literature.⁴ ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.31 (3H, t, J 7.2, CH_2CH_3), 4.25

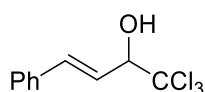
(2H, q, J 7.2, CH_2CH_3), 4.65 (2H, s, CH_2), 6.23 (2H, t, J 2.1, $\text{ArC}(3,4)\text{H}$), 6.69 (2H, t, J 2.1, $\text{ArC}(2,5)\text{H}$).

2-(1*H*-Pyrrol-1-yl)acetic acid (**155**)



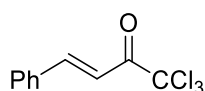
Ester **154** (1.80 g, 11.8 mmol) was dissolved in 1:1 THF/ H_2O (35 mL) and cooled to 0 °C before NaOH pellets (2.36 g, 59.0 mmol) were added. The reaction was stirred at 0 °C for 30 min before being washed with CH_2Cl_2 (40 mL). The aqueous phase was acidified with concentrated 12 M HCl to *ca.* pH 1 and extracted with CH_2Cl_2 (3 \times 40 mL) before being dried over MgSO_4 , filtered, and concentrated under reduced pressure to give **155** (1.43 g, 97%) as a white solid. Spectroscopic data were in accordance with the literature.⁴ mp 90-92 °C [Lit.⁵ 84-87 °C]; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 4.73 (2H, s, CH_2), 6.25 (2H, t, J 2.1, $\text{ArC}(3,4)\text{H}$), 6.69 (2H, t, J 2.1, $\text{ArC}(2,5)\text{H}$).

(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-ol (**157**)



Following General Procedure A, cinnamyl aldehyde (5.03 mL, 40.0 mmol), $\text{Cl}_3\text{CCO}_2\text{H}$ (9.80 g, 60.0 mmol) and $\text{Cl}_3\text{CCO}_2\text{Na}$ (11.1 g, 60 mmol) in DMF (30 mL) gave, after purification by column chromatography (Petrol/ Et_2O 90:10, R_f 0.24), **157** (8.80 g, 87%) as an orange oil. Spectroscopic data were in accordance with the literature.⁶ ^1H NMR (400 MHz, CDCl_3) δ_{H} : 2.95 (1H, d, J 5.6, OH), 4.76–4.81 (1H, m, $\text{C}(2)\text{H}$), 6.38 (1H, dd, J 16.1, 6.1, $\text{C}(3)\text{H}$), 6.93 (1H, d, J 16.0, $\text{C}(4)\text{H}$), 7.28–7.41 (3H, m, $\text{ArC}(3,5)\text{H}$ and $\text{ArC}(4)\text{H}$), 7.45–7.49 (2H, m, $\text{ArC}(2,6)\text{H}$).

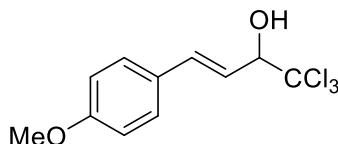
(*E*)-1,1,1-Trichloro-4-phenylbut-3-en-2-one (**158**)



Following General Procedure C, **157** (8.80 g, 35.0 mmol) in CH_2Cl_2 (35 mL), DMSO (19.1 mL, 0.28 mol, 8 equiv) in CH_2Cl_2 (63 mL), oxalyl chloride (12.0 mL, 0.14 mol, 4 equiv) in CH_2Cl_2 (560 mL) and Et_3N (97.6 mL, 0.7 mol, 20 equiv) gave, after purification by column chromatography (Petrol/ EtOAc 95:5, R_f 0.35), **158** (8.30 g, 95%) as a white solid. Spectroscopic data were in

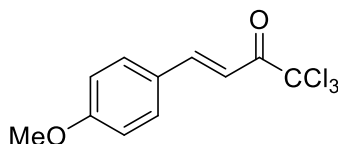
accordance with the literature.⁶ mp 57–58 °C {Lit.⁶ 56–58 °C}; ¹H NMR (500 MHz, CDCl₃) δ_H: 7.37 (1H, d, *J* 15.7, C(3)*H*), 7.44–7.54 (3H, m, ArC(3,5)*H* and ArC(4)*H*), 7.64–7.72 (2H, m, ArC(2,6)*H*), 8.04 (1H, d, *J* 15.7, C(4)*H*).

(*E*)-1,1,1-Trichloro-4-(4-methoxyphenyl)but-3-en-2-ol (452)

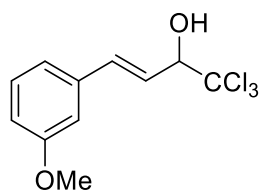


Following General Procedure A, 4-methoxycinnamyl aldehyde (3.24 g, 20.0 mmol), Cl₃CCO₂H (4.90 g, 30.0 mmol) and Cl₃CCO₂Na (5.56 g, 30.0 mmol) in DMF (15 mL) gave, after purification by column chromatography (Petrol/Et₂O 80:20, *R_f* 0.21), **452** (3.94 g, 14.0 mmol, 70%) as a white solid. Spectroscopic data were in accordance with the literature.⁶ mp 66 °C {Lit.⁶ 66–68 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 2.98 (1H, d, *J* 5.8, OH), 3.85 (3H, s, OCH₃), 4.71–4.81 (1H, m, C(2)*H*), 6.24 (1H, dd, *J* 15.8, 6.3, C(3)*H*), 6.86 (1H, d, *J* 16.0, C(4)*H*), 6.88–6.94 (2H, m, ArC(3,5)*H*), 7.38–7.43 (2H, m, ArC(2,6)*H*).

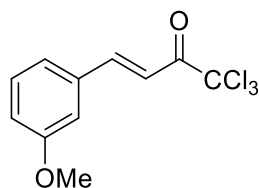
(*E*)-1,1,1-Trichloro-4-(4-methoxyphenyl)but-3-en-2-one (453)



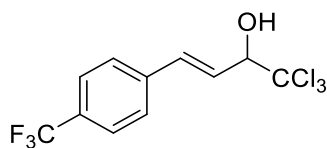
Following General Procedure C, **452** (3.94 g, 14.0 mmol) in CH₂Cl₂ (14 mL), DMSO (7.96 mL, 112 mmol, 8 equiv) in CH₂Cl₂ (25 mL), oxalyl chloride (4.80 mL, 56.0 mmol, 4 equiv) in CH₂Cl₂ (224 mL) and Et₃N (39.0 mL, 0.28 mol, 20 equiv) gave, after purification by column chromatography (Petrol/Et₂O 80:20, *R_f* 0.65), **453** (3.21 g, 82%) as a light yellow solid. Spectroscopic data were in accordance with the literature.⁶ mp 99–101 °C {Lit.⁶ 98–100 °C}; ¹H NMR (500 MHz, CDCl₃) δ_H: 3.90 (3H, s, OCH₃), 6.94–7.01 (2H, m, ArC(3,5)*H*), 7.23 (1H, d, *J* 15.5, C(3)*H*), 7.61–7.67 (2H, m, ArC(2,6)*H*), 7.99 (1H, d, *J* 15.6, C(4)*H*).

(E)-1,1,1-Trichloro-4-(3-methoxyphenyl)but-3-en-2-ol (454)

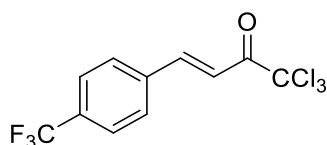
Following General Procedure B, 3-methoxycinnamyl aldehyde (1.64 g, 10.1 mmol), chloroform (1.78 mL, 22.2 mmol, 2.2 equiv) in DMF (8 mL) and KOH (567 mg, 10.1 mmol, 1.0 equiv) in EtOH (4 mL) gave, after purification by column chromatography (Petrol/Et₂O 60:40, *R_f* 0.45), **454** (1.93 g, 68%) as a light yellow oil. ¹H NMR (500 MHz, CDCl₃) δ_H: 2.93 (1H, d, *J* 5.8, OH), 3.83 (3H, s, OCH₃), 4.76 (1H, td, *J* 5.9, 1.3, C(2)H), 6.36 (1H, dd, *J* 15.9, 6.1, C(3)H), 6.85–6.90 (2H, m, C(4)H and ArC(4)H), 6.97–6.98 (1H, m, ArC(2)H), 7.03–7.05 (1H, m, ArC(5)H), 7.27 (1H, t, *J* 7.9, ArC(6)H). The title compound was carried forward immediately without further characterisation due to instability.

(E)-1,1,1-Trichloro-4-(3-methoxyphenyl)but-3-en-2-one (455)

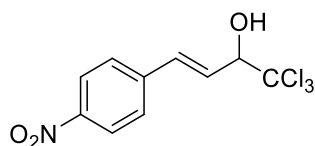
Following General Procedure C, **454** (1.93 g, 6.85 mmol) in CH₂Cl₂ (7 mL), DMSO (3.90 mL, 54.8 mmol, 8 equiv) in CH₂Cl₂ (12 mL), oxalyl chloride (2.35 mL, 27.4 mmol, 4 equiv) in CH₂Cl₂ (110 mL) and Et₃N (19.1 mL, 137 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/Et₂O 90:10, *R_f* 0.31), **455** (1.63 g, 85%) as a white solid. mp 46–47 °C; ν_{max} (film, cm⁻¹) 2968 (C-H), 1709 (C=O), 1603 (C=C), 1580, 1248, 1105, 829; ¹H NMR (500 MHz, CDCl₃) δ_H: 3.89 (3H, s, OCH₃), 7.05 (1H, dd, *J* 8.2, 2.5, ArC(4)H), 7.16 (1H, t, *J* 2.1, ArC(2)H), 7.27–7.28 (1H, m, ArC(5)H), 7.34 (1H, d, *J* 15.6, C(3)H), 7.39 (1H, t, *J* 7.9, ArC(6)H), 8.00 (1H, d, *J* 15.6, C(4)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 55.6 (OCH₃), 96.5 (C(1)), 114.0 (ArC(2)H), 116.2 (C(3)H), 117.7 (ArC(4)H), 121.8 (ArC(5)H), 130.3 (ArC(6)H), 135.2 (ArC(1)), 149.8 (C(4)H), 160.1 (ArC(3)), 180.2 (C(2)); HRMS (ASAP⁺) C₁₁H₁₀O₂³⁵Cl₃ [M+H]⁺ found 278.9745, requires 278.9746 (–0.4 ppm).

(E)-1,1,1-Trichloro-4-(4-(trifluoromethyl)phenyl)but-3-en-2-ol (456)

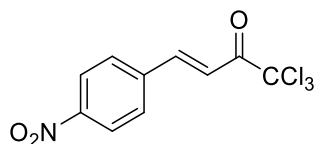
Following General Procedure A, 4-trifluoromethylcinnamyl aldehyde (1.98 g, 9.90 mmol), $\text{Cl}_3\text{CCO}_2\text{H}$ (2.42 g, 14.9 mmol) and $\text{Cl}_3\text{CCO}_2\text{Na}$ (2.75 g, 14.9 mmol) in DMF (20 mL) gave, after purification by column chromatography (Petrol/ Et_2O 60:40, R_f 0.42), **456** (1.74 g, 55%) as a yellow oil. Spectroscopic data were in accordance with the literature.⁷ ^1H NMR (400 MHz, CDCl_3) δ_{H} : 3.03 (1H, d, J 5.6, OH), 4.83 (1H, t, J 5.4, C(2)H), 6.50 (1H, dd, J 15.9, 5.7, C(3)H), 6.98 (1H, d, J 16.0, C(4)H), 7.57 (2H, d, J 8.2, ArC(2,6)H), 7.64 (2H, d, J 8.0, ArC(3,5)H); $^{19}\text{F}\{^1\text{H}\}$ NMR (377 MHz, CDCl_3) δ_{F} : -62.7 (s, CF_3).

(E)-1,1,1-Trichloro-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one (457)

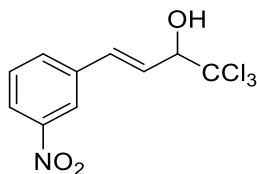
Following General Procedure C, **456** (1.74 g, 5.45 mmol) in CH_2Cl_2 (5 mL), DMSO (3.10 mL, 43.6 mmol, 8 equiv) in CH_2Cl_2 (10 mL), oxalyl chloride (1.87 mL, 21.8 mmol, 4 equiv) in CH_2Cl_2 (87 mL) and Et_3N (15.2 mL, 109 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/ Et_2O 90:10, R_f 0.45), **457** (1.25 g, 72%) as an orange solid. mp 70–72 °C; ν_{max} (film, cm^{-1}) 1709 (C=O), 1614 (C=C), 1319, 1105, 1065; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.40 (1H, d, J 15.7, C(3)H), 7.70 (2H, d, J 8.3, ArC(3,5)H), 7.76 (2H, d, J 8.3, ArC(2,6)H), 8.01 (1H, d, J 15.7, C(4)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 96.2 (C(1)), 118.4 (C(3)H), 123.8 (q, J 272.5, CF_3), 126.2 (q, J 3.8, ArC(3,5)H), 129.2 (ArC(2,6)H), 133.1 (q, J 32.8, ArC(4)), 137.1 (ArC(1)), 147.6 (C(4)H), 179.8 (C(2)); $^{19}\text{F}\{^1\text{H}\}$ NMR (377 MHz, CDCl_3) δ_{F} : -63.0 (s, CF_3); HRMS (ASAP⁺) $\text{C}_{11}\text{H}_7\text{OF}_3^{35}\text{Cl}_3$ [M+H]⁺ found 316.9516, requires 316.9515 (+0.3 ppm).

(E)-1,1,1-Trichloro-4-(4-nitrophenyl)but-3-en-2-ol (458)

Following General Procedure A, 4-nitrocinnamyl aldehyde (1.02 g, 5.76 mmol), $\text{Cl}_3\text{CCO}_2\text{H}$ (1.41 g, 8.64 mmol) and $\text{Cl}_3\text{CCO}_2\text{Na}$ (1.60 g, 8.64 mmol) in DMF (40 mL) gave, after purification by column chromatography (Petrol/ Et_2O 70:30, R_f 0.22), **458** (1.08 g, 63%) as a light red solid. Spectroscopic data were in accordance with the literature.⁸ mp 140–141 °C {Lit.⁸ 143 °C}; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 3.62 (1H, d, J 5.6, OH), 4.85 (1H, td, J 5.5, 1.4, C(2)H), 6.60 (1H, dd, J 15.9, 5.5, C(3)H), 7.03 (1H, dd, J 15.9, 1.4, C(4)H), 7.57–7.65 (2H, m, ArC(2,6)H), 8.20–8.27 (2H, m, ArC(3,5)H).

(E)-1,1,1-Trichloro-4-(4-nitrophenyl)but-3-en-2-one (459)

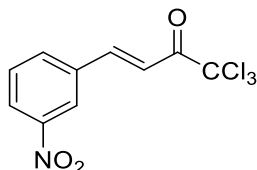
Following General Procedure C, **458** (1.08 g, 3.66 mmol) in CH_2Cl_2 (4 mL), DMSO (2.08 mL, 29.3 mmol, 8 equiv) in CH_2Cl_2 (7 mL), oxalyl chloride (1.26 mL, 14.6 mmol, 4 equiv) in CH_2Cl_2 (58 mL) and Et_3N (10.2 mL, 73.2 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/ Et_2O 80:20, R_f 0.34), **459** (0.80 g, 74%) as a yellow solid. Spectroscopic data were in accordance with the literature.⁸ mp 155–157 °C {Lit.⁸ 158–160 °C}; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.47 (1H, d, J 15.7, C(3)H), 7.80–7.87 (2H, m, ArC(2,6)H), 8.04 (1H, d, J 15.8, C(4)H), 8.30–8.36 (2H, m, ArC(3,5)H).

(E)-1,1,1-Trichloro-4-(3-nitrophenyl)but-3-en-2-ol (460)

Following General Procedure A, 3-nitrocinnamyl aldehyde (2.70 g, 15.3 mmol), $\text{Cl}_3\text{CCO}_2\text{H}$ (3.74 g, 23.0 mmol) and $\text{Cl}_3\text{CCO}_2\text{Na}$ (4.24 g, 23.0 mmol) in DMF (40 mL) gave, after passing through a short pad of silica (eluent: CH_2Cl_2), **460** (2.72 g, 60% crude yield) as a yellow oil which was used directly in the next step. Characterization data: ^1H NMR (500 MHz, CDCl_3) δ_{H} : 3.25 (1H, d,

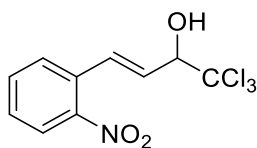
J 5.5, *OH*), 4.83 (1H, td, *J* 5.5, 1.4, C(2)*H*), 6.54 (1H, dd, *J* 15.9, 5.6, C(3)*H*), 7.00 (1H, dd, *J* 15.9, 1.4, C(4)*H*), 7.54 (1H, t, *J* 8.0, ArC(5)*H*), 7.75–7.76 (1H, m, ArC(6)*H*), 8.16 (1H, ddd, *J* 8.2, 2.3, 1.0, ArC(4)*H*), 8.30 (1H, t, *J* 2.0, ArC(2)*H*); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 82.8 (C(2)*H*), 102.5 (C(1)), 121.7 (ArC(2)*H*), 123.3 (ArC(4)*H*), 126.0 (C(3)*H*), 129.9 (ArC(5)*H*), 132.9 (ArC(6)*H*), 134.2 (C(4)*H*), 137.6 (ArC(1)), 149.2 (ArC(3)).

(*E*)-1,1,1-Trichloro-4-(3-nitrophenyl)but-3-en-2-one (461)



Following General Procedure C, **460** (2.72 g, 9.18 mmol) in CH_2Cl_2 (9 mL), DMSO (5.22 mL, 73.4 mmol, 8 equiv) in CH_2Cl_2 (17 mL), oxalyl chloride (3.15 mL, 36.7 mmol, 4 equiv) in CH_2Cl_2 (147 mL) and Et_3N (25.6 mL, 184 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/ Et_2O 80:20, R_f 0.40), **461** (1.68 g, 62%) as a yellow solid. mp 138–139 °C; ν_{max} (film, cm^{-1}) 1715 (C=O), 1609 (C=C), 1531 (N-O), 1344 (N-O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.45 (1H, d, *J* 15.7, C(3)*H*), 7.66 (1H, t, *J* 8.0, ArC(4)*H*), 7.95 (1H, d, *J* 7.7, ArC(6)*H*), 8.03 (1H, d, *J* 15.7, C(4)*H*), 8.32 (1H, ddd, *J* 8.2, 2.2, 1.0, ArC(5)*H*), 8.51 (1H, t, *J* 2.0, ArC(2)*H*); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 96.1 (C(1)), 118.9 (C(3)*H*), 123.1 (ArC(2)*H*), 125.9 (ArC(5)*H*), 130.4 (ArC(4)*H*), 134.7 (ArC(6)*H*), 135.5 (ArC(1)), 146.5 (C(4)*H*), 148.9 (ArC(3)), 179.6 (C(2)); HRMS (ASAP⁺) $\text{C}_{10}\text{H}_7\text{O}_3\text{N}^{35}\text{Cl}_3$ [$\text{M}+\text{H}$]⁺ found 293.9488, requires 293.9492 (–1.4 ppm).

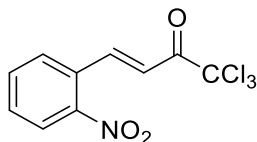
(*E*)-1,1,1-Trichloro-4-(2-nitrophenyl)but-3-en-2-ol (462)



Following General Procedure A, 2-nitrocinnamyl aldehyde (7.09 mL, 40.0 mmol), $\text{Cl}_3\text{CCO}_2\text{H}$ (9.80 g, 60.0 mmol) and $\text{Cl}_3\text{CCO}_2\text{Na}$ (11.1 g, 60.0 mmol) in DMF (100 mL) gave, after purification by column chromatography (Petrol/ Et_2O 70:30, R_f 0.25), **462** (3.56 g, 30%) as a white solid. Spectroscopic data were in accordance with the literature.⁶ mp 113–114 °C {Lit.⁶ 114–116 °C}; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 3.10 (1H, d, *J* 5.7, *OH*), 4.86 (1H, app. t, *J* 5.8, C(2)*H*), 6.35 (1H,

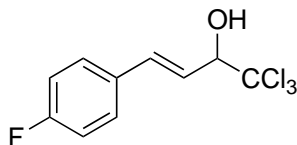
dd, J 15.7, 5.8, C(3) H), 7.45 (1H, dd, J 15.7, 1.3, C(4) H), 7.48–7.54 (1H, m, ArC(4) H), 7.62–7.67 (2H, m, ArC(5,6) H), 8.04 (1H, dt, J 8.2, 1.0, ArC(3) H).

(*E*)-1,1,1-Trichloro-4-(2-nitrophenyl)but-3-en-2-one (463)

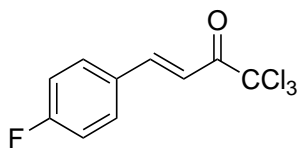


Following General Procedure C, **462** (3.56 g, 12.0 mmol) in CH_2Cl_2 (12 mL), DMSO (6.82 mL, 96.0 mmol, 8 equiv) in CH_2Cl_2 (22 mL), oxalyl chloride (4.12 mL, 48.0 mmol, 4 equiv) in CH_2Cl_2 (192 mL) and Et_3N (33.4 mL, 240 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/ Et_2O 75:25, R_f 0.32), **463** (2.58 g, 73%) as a light yellow solid. Spectroscopic data were in accordance with the literature.⁶ mp 57–59 °C {Lit.⁶ 56–58 °C}; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.27 (1H, d, J 15.5, C(3) H), 7.61–7.70 (1H, m, ArC(4) H), 7.71–7.80 (2H, m, ArC(5,6) H), 8.11–8.19 (1H, m, ArC(3) H), 8.47 (1H, d, J 15.5, C(4) H).

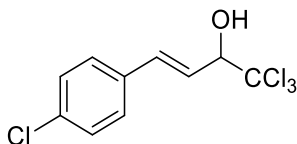
(*E*)-1,1,1-Trichloro-4-(4-fluorophenyl)but-3-en-2-ol (464)



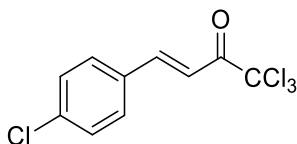
As reported previously following General Procedure A,⁶ 4-fluorocinnamaldehyde (5.00 g, 33.3 mmol), DMF (30 mL), trichloroacetic acid (8.17 g, 50.0 mmol) and sodium trichloroacetate (9.27 g, 50.0 mmol) gave, after purification by column chromatography (Petrol/ Et_2O 85:15, R_f 0.25), **464** (4.31 g, 48%) as an orange solid. Spectroscopic data were in accordance with the literature.⁶ mp 63–62 °C; {Lit.⁶ mp 60–62 °C}; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 2.92 (1H, d, J 5.7, OH), 4.76 (1H, td, J 5.9, 1.3, C(2) H), 6.29 (1H, ddd, J 15.9, 6.1, 0.6, C(3) H), 6.87 (1H, d, J 15.9, C(4) H), 7.01–7.08 (2H, m, ArC(3,5) H), 7.38–7.46 (2H, m, ArC(2,6) H); $^{19}\text{F}\{^1\text{H}\}$ NMR (376 MHz, CDCl_3) δ_{F} : -113.3 (ArC(4) F).

(E)-1,1,1-Trichloro-4-(4-fluorophenyl)but-3-en-2-one (465)

As reported previously following General Procedure C,⁶ **464** (2.52 g, 9.34 mmol) in CH₂Cl₂ (10 mL), DMSO (5.32 mL, 74.7 mmol) in CH₂Cl₂ (20 mL), oxalyl chloride (3.17 mL, 37.4 mmol) in CH₂Cl₂ (150 mL) and Et₃N (26.1 mL, 187 mmol) gave, after purification by column chromatography (Petrol/Et₂O 95:5, R_f 0.25), **465** (2.25 g, 90%) as a white solid. Spectroscopic data were in accordance with the literature.⁶ mp 60–62 °C; {Lit.⁶ mp 58–60 °C}; ¹H NMR (500 MHz, CDCl₃) δ_H: 7.10–7.18 (2H, m, ArC(3,5)H), 7.26 (1H, d, *J* 15.6, C(3)H), 7.62–7.70 (2H, m, ArC(2,6)H), 7.97 (1H, d, *J* 15.6, C(4)H); ¹⁹F{¹H} NMR (471 MHz, CDCl₃) δ_F: –106.8 (ArC(4)F).

(E)-1,1,1-Trichloro-4-(4-chlorophenyl)but-3-en-2-ol (466)

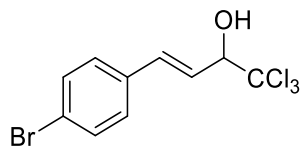
Following General Procedure B, 4-chlorocinnamyl aldehyde (0.87 g, 5.21 mmol), chloroform (0.92 mL, 11.5 mmol, 2.2 equiv) in DMF (4 mL) and KOH (292 mg, 5.21 mmol, 1.0 equiv) in EtOH (4 mL) gave, after purification by column chromatography (Petrol/Et₂O 80:20, R_f 0.41), **466** (0.82 g, 55%) as a light-yellow oil. Spectroscopic data were in accordance with the literature.⁸ ¹H NMR (500 MHz, CDCl₃) δ_H: 3.08 (1H, d, *J* 5.8, OH), 4.73 (1H, app. t, *J* 5.8, C(2)H), 6.34 (1H, dd, *J* 15.8, 5.8, C(3)H), 6.91 (1H, d, *J* 15.8, C(4)H), 7.20–7.35 (2H, m, ArC(2,6)H), 7.38–7.55 (2H, m, ArC(3,5)H).

(E)-1,1,1-Trichloro-4-(4-chlorophenyl)but-3-en-2-one (467)

Following General Procedure C, **466** (0.82 g, 2.87 mmol) in CH₂Cl₂ (3 mL), DMSO (1.63 mL, 23.0 mmol, 8 equiv) in CH₂Cl₂ (5 mL), oxalyl chloride (0.98 mL, 11.5 mmol, 4 equiv) in CH₂Cl₂ (46 mL) and Et₃N (8.0 mL, 57.4 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/Et₂O 90:10, R_f 0.45), **467** (0.63 g, 77%) as a white solid. Spectroscopic data were in

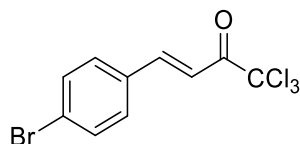
accordance with the literature.⁸ mp 110–111 °C {Lit.⁸ 108–110 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 7.33 (1H, d, *J* 15.7, C(3)*H*), 7.42–7.47 (2H, m, ArC(2,6)*H*), 7.58–7.65 (2H, m, ArC(3,5)*H*), 7.97 (1H, d, *J* 15.7, C(4)*H*).

(*E*)-4-(4-Bromophenyl)-1,1,1-trichlorobut-3-en-2-ol (468)

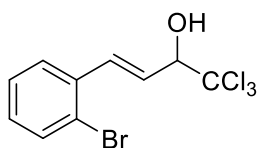


Following General Procedure B, 4-bromocinnamyl aldehyde (0.97 g, 4.61 mmol), chloroform (0.81 mL, 10.1 mmol, 2.2 equiv) in DMF (4 mL) and KOH (259 mg, 4.61 mmol, 1.0 equiv) in EtOH (4 mL) gave, after purification by column chromatography (Petrol/Et₂O 80:20, *R_f* 0.37), **468** (0.94 g, 62%) as a yellow solid. Spectroscopic data were in accordance with the literature.⁸ mp 62–63 °C {Lit.⁸ 63–65 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 4.78 (1H, dd, *J* 6.0, 1.3, C(2)*H*), 6.39 (1H, dd, *J* 15.9, 6.0, C(3)*H*), 6.87 (1H, d, *J* 15.9, C(4)*H*), 7.31–7.35 (2H, m, ArC(2,6)*H*), 7.48–7.52 (2H, m, ArC(3,5)*H*).

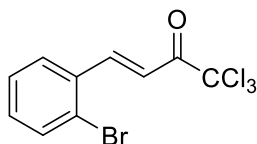
(*E*)-4-(4-Bromophenyl)-1,1,1-trichlorobut-3-en-2-one (469)



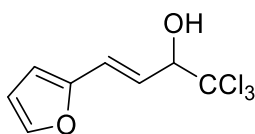
Following General Procedure C, **468** (0.94 g, 2.86 mmol) in CH₂Cl₂ (3 mL), DMSO (1.63 mL, 22.9 mmol, 8 equiv) in CH₂Cl₂ (5 mL), oxalyl chloride (0.98 mL, 11.4 mmol, 4 equiv) in CH₂Cl₂ (46 mL) and Et₃N (8.0 mL, 57.2 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/Et₂O 90:10, *R_f* 0.41), **469** (0.69 g, 73%) as a white solid. Spectroscopic data were in accordance with the literature.⁸ mp 131–132 °C {Lit.⁸ 133–135 °C}; ¹H NMR (500 MHz, CDCl₃) δ_H: 7.35 (1H, d, *J* 15.7, C(3)*H*), 7.51–7.57 (2H, m, ArC(2,6)*H*), 7.58–7.64 (2H, m, ArC(3,5)*H*), 7.96 (1H, d, *J* 15.7, C(4)*H*).

(E)-4-(2-Bromophenyl)-1,1,1-trichlorobut-3-en-2-ol (470)

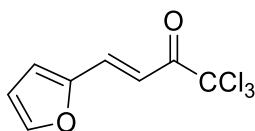
Following General Procedure B, 2-bromocinnamyl aldehyde (1.46 g, 6.92 mmol), chloroform (1.22 mL, 15.2 mmol, 2.2 equiv) in DMF (5 mL) and KOH (299 mg, 6.92 mmol, 1.0 equiv) in EtOH (4 mL) gave, after purification by column chromatography (Petrol/Et₂O 80:20, R_f 0.26), **470** (1.28 g, 56%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ_H: 3.01 (1H, d, *J* 5.8, OH), 4.82 (1H, t, *J* 5.2, C(2)H), 6.31 (1H, dd, *J* 15.8, 6.1, C(3)H), 7.14–7.19 (1H, m, ArC(4)H), 7.24–7.33 (2H, m, ArC(6)H and C(4)H), 7.54–7.59 (2H, m, ArC(3,5)H). The title compound was carried forward immediately without further characterisation due to instability.

(E)-4-(2-Bromophenyl)-1,1,1-trichlorobut-3-en-2-one (471)

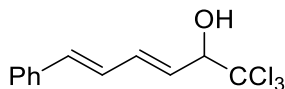
Following General Procedure C, **470** (1.28 g, 3.87 mmol) in CH₂Cl₂ (4 mL), DMSO (2.20 mL, 31.0 mmol, 8 equiv) in CH₂Cl₂ (7 mL), oxalyl chloride (1.33 mL, 15.5 mmol, 4 equiv) in CH₂Cl₂ (62 mL) and Et₃N (10.8 mL, 77.4 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/Et₂O 95:5, R_f 0.33), **471** (1.03 g, 81%) as a light orange solid. mp 60–62 °C; ν_{max} (film, cm⁻¹) 1711 (C=O), 1603 (C=C), 1113; ¹H NMR (500 MHz, CDCl₃) δ_H: 7.28–7.32 (2H, m, ArC(3)H and C(3)H), 7.37–7.40 (1H, m, ArC(6)H), 7.67 (1H, dd, *J* 8.0, 1.3, ArC(4)H), 7.74 (1H, dd, *J* 7.8, 1.7, ArC(5)H), 8.39 (1H, d, *J* 15.6, C(4)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 96.4 (C(1)), 118.6 (C(3)H), 126.6 (ArC(1)), 128.0 (ArC(6)H), 128.4 (ArC(5)H), 132.6 (ArC(3)H), 133.9 (ArC(4)H), 133.9 (ArC(2)), 147.8 (C(4)H), 179.6 (C(2)); HRMS (ASAP⁺) C₁₀H₇O⁷⁹Br³⁵Cl₃ [M+H]⁺ found 326.8750, requires 326.8746 (+1.2 ppm).

(E)-1,1,1-Trichloro-4-(furan-2-yl)but-3-en-2-ol (472)

Following General Procedure A, 3-(furan-2-yl)acrylaldehyde (5.00 g, 40.9 mmol), $\text{Cl}_3\text{CCO}_2\text{H}$ (10.1 g, 61.4 mmol) and $\text{Cl}_3\text{CCO}_2\text{Na}$ (11.4 g, 61.4 mmol) in DMF (30 mL) gave, after purification by column chromatography (Petrol/ Et_2O 85:15, R_f 0.25), **472** (3.65 g, 37%) as a dark yellow oil. Spectroscopic data were in accordance with the literature.⁶ ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.96 (1H, d, J 5.9, OH), 4.77 (1H, td, J 5.8, 1.4, C(2)H), 6.35 (1H, dd, J 15.8, 5.8, C(3)H), 6.40 (1H, d, J 3.3, ArC(3)H), 6.43 (1H, dd, J 3.4, 1.8, ArC(4)H), 6.74 (1H, dd, J 15.7, 1.4, C(4)H), 7.42 (1H, d, J 1.8, ArC(5)H).

(E)-1,1,1-Trichloro-4-(furan-2-yl)but-3-en-2-one (473)

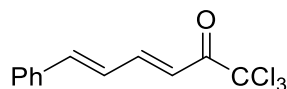
Following General Procedure C, **472** (3.65 g, 15.1 mmol) in CH_2Cl_2 (15 mL), DMSO (8.58 mL, 121 mmol, 8 equiv) in CH_2Cl_2 (28 mL), oxalyl chloride (5.18 mL, 60.4 mmol, 4 equiv) in CH_2Cl_2 (240 mL) and Et_3N (42.1 mL, 302 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/ Et_2O 90:10, R_f 0.35), **473** (1.12 g, 31%) as a light-yellow solid. Spectroscopic data were in accordance with the literature.⁶ mp 39–40 °C {Lit.⁶ 40–42 °C}; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 6.58 (1H, dd, J 3.5, 1.8, ArC(4)H), 6.86 (1H, d, J 3.4, ArC(3)H), 7.24 (1H, d, J 15.3, C(3)H), 7.59–7.63 (1H, m, ArC(5)H), 7.75 (1H, d, J 15.3, C(4)H).

(3E,5E)-1,1,1-Trichloro-6-phenylhexa-3,5-dien-2-ol (474)

Following General Procedure B, (2E,4E)-5-phenylpenta-2,4-dienal (2.52 g, 15.9 mmol), chloroform (2.80 mL, 35.0 mmol, 2.2 equiv) in DMF (12 mL) and KOH (892 mg, 15.9 mmol, 1.0 equiv) in EtOH (4 mL) gave, after purification by column chromatography (Petrol/ EtOAc 90:10, R_f 0.23), **474** (2.47 g, 56%) as a yellow solid. Spectroscopic data were in accordance with the literature.⁸ mp 55–56 °C {Lit.⁸ 57–59 °C}; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 2.93 (1H, d, J 5.9, OH),

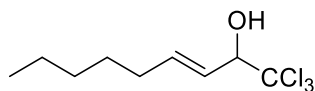
4.72 (1H, td, J 6.0, 1.1, C(2)H), 5.95–6.05 (1H, m, C(3)H), 6.66–6.80 (2H, m, C(4)H and C(5)H), 6.80–6.94 (1H, m, C(6)H), 7.24–7.36 (1H, m, ArC(4)H), 7.32–7.45 (2H, m, ArC(2,6)H), 7.41–7.51 (2H, m, ArC(3,5)H).

(3E,5E)-1,1,1-Trichloro-6-phenylhexa-3,5-dien-2-one (475)



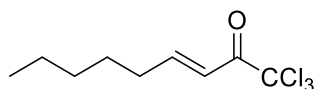
Following General Procedure C, **474** (2.47 g, 8.90 mmol) in CH_2Cl_2 (9 mL), DMSO (5.06 mL, 71.2 mmol, 8 equiv) in CH_2Cl_2 (16 mL), oxalyl chloride (3.05 mL, 35.6 mmol, 4 equiv) in CH_2Cl_2 (142 mL) and Et_3N (24.8 mL, 178 mmol, 20 equiv) gave, after purification by column chromatography (Petrol/ Et_2O 80:20, R_f 0.65), **475** (1.57 g, 64%) as a yellow needle. Spectroscopic data were in accordance with the literature.⁸ mp 36–37 °C {Lit.⁸ 38–40 °C}; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 6.90–6.97 (1H, m, C(3)H), 7.05 (1H, ddd, J 15.5, 10.6, 0.7, C(5)H), 7.14 (1H, d, J 15.5, C(6)H), 7.38–7.45 (3H, m, ArC(4,2,6)H), 7.52–7.56 (2H, m, ArC(3,5)H), 7.80 (1H, dd, J 14.9, 10.6, C(4)H).

(E)-1,1,1-Trichloronon-3-en-2-ol (476)



Following General Procedure A, (*E*)-oct-2-enal (2.50 mL, 19.8 mmol), $\text{Cl}_3\text{CCO}_2\text{H}$ (4.88 g, 29.7 mmol) and $\text{Cl}_3\text{CCO}_2\text{Na}$ (5.55 g, 29.7 mmol) in DMF (15 mL) gave, after purification by column chromatography (Petrol/ Et_2O 95:5, R_f 0.21), **476** (2.04 g, 42%) as a yellow oil. Spectroscopic data were in accordance with the literature.⁶ ^1H NMR (400 MHz, CDCl_3) δ_{H} : 0.86–0.97 (3H, m, CH_3), 1.28–1.57 (6H, m, $3 \times \text{CH}_2$), 2.09–2.21 (2H, m, C(5) H_2), 2.77 (1H, d, J 5.9, OH), 4.54–4.57 (1H, m, C(2)H), 5.67 (1H, ddt, J 15.4, 6.5, 1.5, C(3)H), 6.04 (1H, dtd, J 15.4, 6.8, 1.1, C(4)H).

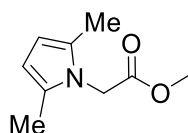
(E)-1,1,1-Trichloronon-3-en-2-one (477)



Following General Procedure C, **476** (2.04 g, 8.32 mmol) in CH_2Cl_2 (8 mL), DMSO (4.73 mL, 66.6 mmol, 8 equiv) in CH_2Cl_2 (15 mL), oxalyl chloride (2.85 mL, 33.3 mmol, 4 equiv) in CH_2Cl_2 (133 mL) and Et_3N (23.2 mL, 166 mmol, 20 equiv) gave, after purification by column

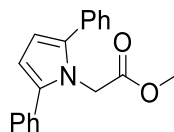
chromatography (Petrol/Et₂O 98:2, R_f 0.40), **477** (1.74 g, 86%) as a colorless oil. Spectroscopic data were in accordance with the literature.⁶ ¹H NMR (400 MHz, CDCl₃) δ_H: 0.90–0.96 (3H, m, CH₃), 1.32–1.40 (4H, m, 2 × CH₂), 1.50–1.57 (2H, m, C(6)H₂), 2.34–2.40 (2H, m, C(5)H₂), 6.76 (1H, dt, *J* 15.3, 1.6, C(3)H), 7.38 (1H, dt, *J* 15.3, 7.0, C(4)H).

Methyl 2-(2,5-dimethyl-1H-pyrrol-1-yl)acetate (**215**)



Following the general procedure by Bard,²⁴ a solution of hexane-2,5-dione (537 mg, 4.70 mmol, 1.0 eq.), glycine methyl ester hydrochloride (886 mg, 7.05 mmol, 1.5 eq.) and *p*-TSA monohydrate (179 mg, 0.94 mmol, 20 mol%) in toluene (24 mL, 0.2 M) was refluxed for 2 days. The mixture was cooled and the toluene was concentrated under reduced pressure. The residue was diluted with EtOAc (20 mL) and H₂O (20 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with 1 M aqueous NaOH (10 mL), H₂O (10 mL) and brine (10 mL), dried with MgSO₄ and concentrated. The crude material was purified by flash column chromatography (10:90 EtOAc:petrol, R_f 0.31) to give the titled compound **215** (550 mg, 70%) as a colourless oil. Spectroscopic data were in accordance with the literature.²⁵ ¹H NMR (400 MHz, CDCl₃) δ_H: 2.17 (6H, s, C(2)ArC(2,5)CH₃), 3.76 (3H, s, C(1)OCH₃), 4.51 (2H, s, C(2)H₂), 5.82 (2H, s, C(2)ArC(3,4)H).

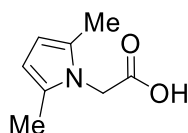
Methyl 2-(2,5-diphenyl-1H-pyrrol-1-yl)acetate (**216**)



Following the general procedure by Bard,²⁴ a solution of 1,4-diphenylbutane-1,4-dione (1.12 g, 4.70 mmol, 1.0 eq.), glycine methyl ester hydrochloride (886 mg, 7.05 mmol, 1.5 eq.) and *p*-TSA monohydrate (179 mg, 0.94 mmol, 20 mol%) in toluene (24 mL, 0.2 M) was refluxed for 2 days. The mixture was cooled and the toluene was concentrated under reduced pressure. The residue was diluted with EtOAc (20 mL) and H₂O (20 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with 1 M aqueous NaOH (10 mL), H₂O (10 mL) and brine (10 mL), dried with MgSO₄

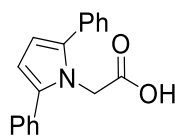
and concentrated. The crude material was purified by flash column chromatography (10:90 EtOAc:petrol) to give the titled compound **216** (753 mg, 55%) as a colourless oil. Spectroscopic data were in accordance with the literature.²⁴ ¹H NMR (400 MHz, DMSO) δ_{H} : 3.50 (3H, s, C(1)OCH₃), 4.65 (2H, s, C(2)H₂), 6.22 (2H, s, C(2)ArC(3,4)H), 7.30–7.46 (10 H, m, ArH).

2-(2,5-Dimethyl-1H-pyrrol-1-yl)acetic acid (**217**)



Following the general procedure by Bard,²⁴ A solution of methyl 2-(2,5-dimethyl-1H-pyrrol-1-yl)acetate (**215**) (970 mg, 5.80 mmol, 1.0 eq.) and LiOH (14 mL, 1 M aqueous) in THF (25 mL) was stirred for 2 days until TLC analysis indicated a complete consumption of **215**. The reaction mixture was quenched with H₂O (20 mL) and acidified with 1 M aq. HCl to pH 2 and extracted with CH₂Cl₂ (10 mL x 3). The combined organic extract was dried with MgSO₄ and concentrated under reduced pressure to afford a crude yellow oil. Acid/base extraction with conc. HCl and 2 M aq. NaOH afforded the titled compound **217** as a red solid (755 mg, 85%). Spectroscopic data were in accordance with the literature.²⁶ mp 134-135 °C {Lit.² 133-134 °C}; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 2.18 (6H, s, C(2)ArC(2,5)CH₃), 4.55 (2H, s, C(2)H₂), 5.84 (2H, s, C(2)ArC(3,4)H), 8.65 (1H, br. s, COOH)

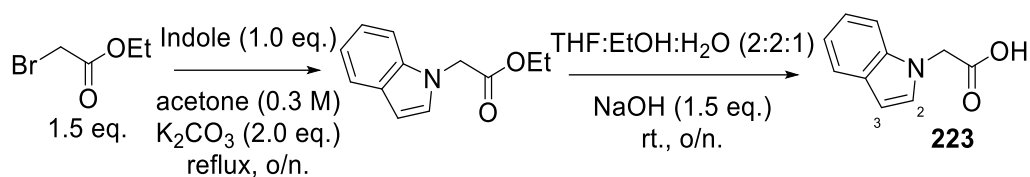
2-(2,5-Diphenyl-1H-pyrrol-1-yl)acetic acid (**218**)



Following the general procedure by Bard,²⁴ A solution of methyl 2-(2,5-diphenyl-1H-pyrrol-1-yl)acetate (**216**) (2.14 g, 7.35 mmol, 1.0 eq.) and LiOH (20 mL, 1 M aqueous) in THF (30 mL) was stirred for 2 days until TLC analysis indicated a complete consumption of **216**. The reaction mixture was quenched with H₂O (50 mL) and acidified with 1 M aq. HCl to pH 2 and extracted with CH₂Cl₂ (10 mL x 3). The combined organic extract was dried with MgSO₄ and concentrated under reduced pressure to afford a crude white solid. Recrystallization in EtOAc/petrol afforded the titled compound **218** as a white solid (1.81 g, 89%). Spectroscopic data were in accordance with the literature.²⁴ mp 195 °C {Lit.²⁴ 194-197 °C}; ¹H NMR (400 MHz, CDCl₃) δ_{H} :

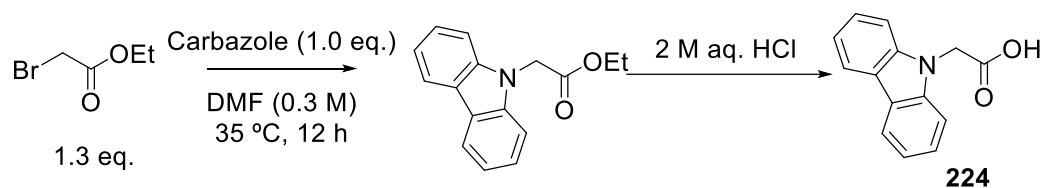
4.66 (2H, s, C(2)H₂), 6.34 (2H, s, C(2)ArC(3,4)H), 7.33–7.43 (10H, m, ArH).

2-(1H-Indol-1-yl)acetic acid (223)

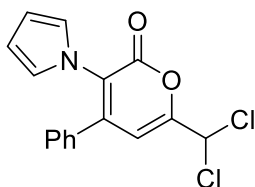


Following the general procedure by Shen,²⁷ to a solution of indole (1.17 g, 10.0 mmol, 1.0 eq.) in acetone (33 mL, 0.3 M) was added potassium carbonate (2.76 g, 20 mmol, 2.0 eq.) and ethyl bromoacetate (1.65 mL, 15 mmol, 1.5 eq.). The mixture was heated to reflux overnight and then the mixture was concentrated under reduced pressure. H₂O (100 mL) was added to the residue and the resulting mixture was extracted with EtOAc (2 x 100 mL) and the combined organic layer was washed with 1 M aq. HCl (50 mL), saturated NaHCO₃ (50 mL) and brine (2 x 100 mL). Then the organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product as light brown oil that was used immediately in the next step.

To a solution of the crude product obtained from next step (assuming quantitative yield, 10.0 mmol) in 50 mL THF:EtOH:H₂O mixed solvent system (2:2:1) was added NaOH (600 mg, 15 mmol). The resulting mixture was stirred at room temperature overnight. Then the mixture was acidified with 1 M aq. HCl to pH 2 and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried with MgSO₄ before concentrated under reduced pressure to give the crude material which was basified with 2 M aq. NaOH to pH 11 and washed with CH₂Cl₂ (2 x 30 mL). The aqueous phase was then extracted with CH₂Cl₂ (3 x 50 mL), dried and concentrated to give the titled compound **223** as a white solid (718 mg, 41% over two-step). Spectroscopic data were in accordance with the literature.²⁸ mp 178 °C {Lit.²⁸ 175 °C}; ¹H NMR (500 MHz, CDCl₃) δ_H: 4.90 (2H, s, CH₂), 6.58 (1H, d, *J* 3.2, indoleC(3)H), 7.08 (1H, d, *J* 3.2, indoleC(2)H), 7.14 (1H, ddd, *J* 8.0, 5.5, 2.5, indoleCH), 7.22–7.25 (2H, m, indoleCH), 7.64 (1H, d, *J* 7.9, indoleCH).

2-(9H-Carbazol-9-yl)acetic acid (224)

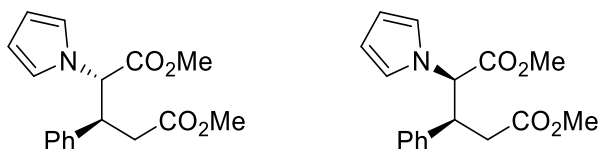
To a solution of carbazole (5.00 g, 30.0 mmol, 1.0 eq.) in DMF (100 mL, 0.3 M) was added ethyl bromoacetate (6.68 g, 40.0 mmol, 1.3 eq.). The mixture was stirred at 35 °C for 12 h, after which the mixture was poured into 200 mL H₂O then filtered. The pH of the filtrate was adjusted to 1.0 with 2 M aq. HCl. Crude product was obtained by filtration of the resulting solid. After drying under vacuum, the crude solid was recrystallized in CH₂Cl₂/ethanol mixture to give the titled compound **224** as a white flake-like crystal (6.05 g, 89%). Spectroscopic data were in accordance with the literature.²⁹ ¹H NMR (400 MHz, CDCl₃) δ_H: 5.06 (2H, s, CH₂), 7.24–7.38 (4H, m, carbazoleCH), 7.46–7.52 (2H, m, carbazoleCH), 8.12 (2H, d, *J* 7.7, carbazoleCH).

8.3.3. Michael Addition-lactonization compound data**6-(Dichloromethyl)-4-phenyl-3-(1H-pyrrol-1-yl)-2H-pyran-2-one (158)**

2-(1*H*-Pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 equiv) was dissolved in anhydrous CH₂Cl₂ (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2 equiv) and pivaloyl chloride (0.062 mL, 0.5 mmol, 2 equiv) were added. The reaction was stirred at 0 °C for 20 min before warming up to rt. BTM **146** (6.3 mg, 10 mol%), **158** (62.4 mg, 0.25 mmol, 1 equiv) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 equiv) were added sequentially and the reaction stirred at rt. for 24 h. Upon completion of the reaction (checked by TLC), it was diluted with CH₂Cl₂ (equal volume) and washed with 1 M HCl (×2) and brine (×2) before being dried over MgSO₄, filtered, and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography (Petrol/EtOAc 90:10, R_f 0.32), to give **159** (40.0 mg, 50%) as a brown oil. ν_{max} (film, cm⁻¹) 3105 (C-H), 3005 (C-H), 1713

(C=O), 1645, 1474, 1364, 903, 771; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 6.18 (2H, t, J 2.2, C(3)Ar(3,4)H), 6.41 (1H, s, CCl_2H), 6.55 (2H, t, J 2.2, C(3)Ar(2,5)H), 6.77 (1H, s, C(5)H), 7.05–7.07 (2H, m, C(4)ArC(2,6)H), 7.32–7.40 (3H, m, C(4)ArC(3,4,5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 64.9 (CCl_2), 106.6 (C(5)H), 110.4 (C(3)ArC(3,4)H), 121.9 (C(3)ArC(2,5)H), 124.1 (C(3)), 127.7 (C(4)ArC(2,6)H), 129.1 (C(4)ArC(3,5)H), 130.4 (C(4)ArC(4)H), 134.0 (C(4)ArC(1)), 146.1 (C(4)), 154.4 (C(6)), 158.7 (C(2)); HRMS (NSI $^+$) $\text{C}_{16}\text{H}_{12}^{35}\text{Cl}_2\text{NO}_2$ [M+H] $^+$ found 320.0243, requires 320.0240 (+1.1 ppm).

Dimethyl (2*S*,3*S*)-3-phenyl-2-(1*H*-pyrrol-1-yl)pentanedioate (167) and dimethyl (2*R*,3*S*)-3-phenyl-2-(1*H*-pyrrol-1-yl)pentanedioate (203)

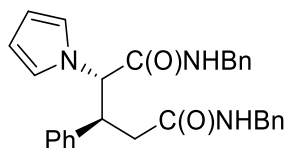


Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl_3 enone **158** (62.4 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (86:14 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*S*)-**167** (58.3 mg, 77%) as a colourless oil. $[\alpha]_{\text{D}}^{20}$ – 35.8 (c 0.6 in CHCl_3); Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin $^{-1}$, 211 nm, 30 °C) t_{R} (major): 8.8 min, t_{R} (minor): 6.6 min, 99:1 er; ν_{max} (film, cm^{-1}) 2957 (C-H), 2918 (C-H), 1746 (C=O), 1720 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.73 (1H, dd, J 16.0, 6.6, C(4)H^AH^B), 2.77 (1H, dd, J 16.0, 8.1, C(4)H^AH^B), 3.58 (3H, s, C(5)COOCH₃), 3.79 (3H, s, C(1)COOCH₃), 3.94–3.99 (1H, m, C(3)H), 4.88 (1H, d, J 9.5, C(2)H), 5.99 (2H, t, J 2.2, C(2)Ar(3,4)H), 6.54 (2H, t, J 2.2, C(2)Ar(2,5)H), 7.03–7.07 (2H, m, C(3)ArC(2,6)H), 7.16–7.22 (3H, m, C(3)ArC(3,4,5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 37.1 (C(4)H₂), 45.2 (C(3)H), 52.0 (C(5)COOCH₃), 52.8 (C(1)COOCH₃), 66.2 (C(2)H), 108.4 (C(2)ArC(3,4)H), 120.8 (C(2)ArC(2,5)H), 127.6 (C(3)ArC(4)H), 127.9 (C(3)ArC(2,6)H), 128.5 (C(3)ArC(3,5)H), 138.4 (C(3)ArC(1)), 170.0 (C(1)), 171.6 (C(5)); HRMS (NSI $^+$) $\text{C}_{17}\text{H}_{20}\text{NO}_4$ [M+H] $^+$ found 302.1388, requires 302.1387 (+0.4 ppm).

(2*R*,3*S*)-**203** (9.5 mg, 13%) as a light-yellow solid. mp 130–132 °C; $[\alpha]_D^{20} - 9.0$ (c 0.1 in CHCl₃); Chiral HPLC analysis, Chiralpak OJ-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 17.5 min, *t*_R (minor): 23.4 min, 85:15 er; *v*_{max} (film, cm⁻¹) 2957 (C-H), 1748 (C=O), 1720 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.28 (1H, dd, *J* 15.9, 4.1, C(4)H^AH^B), 2.53 (1H, dd, *J* 15.9, 10.3, C(4)H^AH^B), 3.43 (3H, s, C(1)COOCH₃), 3.46 (3H, s, C(5)COOCH₃), 3.96 (1H, td, *J* 10.8, 4.1, C(3)H), 4.77 (1H, d, *J* 11.3, C(2)H), 6.21 (2H, t, *J* 2.2, C(2)Ar(3,4)H), 6.89 (2H, t, *J* 2.1, C(2)Ar(2,5)H), 7.24–7.27 (3H, m, C(3)ArC(3,4,5)H), 7.30–7.33 (2H, m, C(3)ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 36.8 (C(4)H₂), 45.7 (C(3)H), 51.8 (C(5)COOCH₃), 52.4 (C(1)COOCH₃), 66.4 (C(2)H), 109.4 (C(2)ArC(3,4)H), 120.5 (C(2)ArC(2,5)H), 127.9 (C(3)ArC(4)H), 128.2 (C(3)ArC(2,6)H), 128.9 (C(3)ArC(3,5)H), 138.4 (C(3)ArC(1)), 169.5 (C(1)), 171.7 (C(5)); HRMS (NSI⁺) C₁₇H₂₀NO₄ [M+H]⁺ found 302.1387, requires 302.1387 (+0.1 ppm).

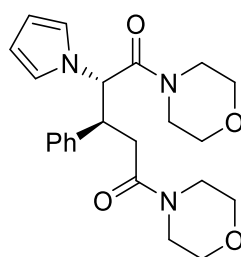
(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-phenyl-2-(1*H*-pyrrol-1-yl)pentanediamide (168)



Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **158** (62.4 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (92:8 dr) that was trituated in ether to give **168** (79.0 mg, 70%) as a light yellow solid. mp 218–220 °C. $[\alpha]_D^{20} + 3.0$ (c 0.19 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90: 10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 28.0 min, *t*_R (minor): 17.3 min, 99.8:0.2 er; *v*_{max} (film, cm⁻¹) 3279 (N-H), 3088 (C-H), 3028 (C-H), 1639 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.62–2.69 (2H, m, C(4)H_AH_B), 4.08 (1H, dt, *J* 9.4, 6.1, C(3)H), 4.27–4.37 (2H, m, C(5)NHCH₂Ph), 4.37–4.45 (2H, m, C(1)NHCH₂Ph), 5.23 (1H, d, *J* 9.4, C(2)H), 5.67 (1H, t, *J* 5.8, C(5)NH), 5.99 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 6.58 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 6.62 (1H, t, *J* 5.9, C(1)NH), 7.03–7.05 (2H, m, C(5)NHCH₂ArC(2,6)H), 7.11–7.19 (7H, m, C(1)NHCH₂ArC(3,4,5,6)H + C(5)NHCH₂ArC(3,4,5)H), 7.23–7.30 (6H, m, C(3)ArC(2,3,4,5,6)H + C(1)NHCH₂ArC(2)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 40.0 (C(4)H₂), 43.7 (C(1)NHCH₂ +

C(5)NHCH₂), 45.0 (C(3)H), 66.0 (C(2)H), 108.9 (C(2)ArC(3,4)H), 120.9 (C(2)ArC(2,5)H), 127.4 (C(3)ArC(2,6)H), 127.6 (C(3)ArC(3,5)H), 127.7 (C(3)ArC(4)H), 127.8 (C(1)NHCH₂ArC(2,6)H + C(5)NHCH₂ArC(2,6)H), 128.2 (C(1)NHCH₂ArC(3,5)H + C(5)NHCH₂ArC(3,5)H), 128.6 (C(1)NHCH₂ArC(4)H), 128.8 (C(5)NHCH₂ArC(4)H), 137.8 (C(1)NHCH₂ArC(1) + C(5)NHCH₂ArC(1)), 139.3 (C(3)ArC(1)), 169.8 (C(1)), 170.9 (C(5)); HRMS (NSI⁺) C₂₉H₃₀N₃O₂ [M+H]⁺ found 452.2330, requires 452.2333 (-0.6 ppm).

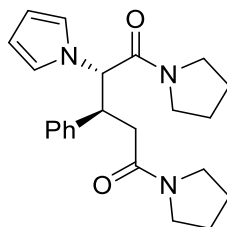
(2S,3S)-1,5-Dimorpholino-3-phenyl-2-(1H-pyrrol-1-yl)pentane-1,5-dione (169)



Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **158** (62.4 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2.5 mL) at rt for 24 h gave crude product (87:13 dr) that was purified by column chromatography (60:40 hexane/EtOAc) to give **169** (56.6 mg, 55%) as a white solid. mp 186–188 °C; [α]_D²⁰ - 51.3 (c 0.32 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 50.8 min, t_R (minor): 23.4 min, 99:1 er; ν_{max} (film, cm⁻¹) 2955 (C-H), 2851 (C-H), 1634 (C=O), 1614 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.72 (1H, dd, *J* 14.8, 6.8, C(4)H^AH^B), 2.85 (1H, dd, *J* 14.8, 5.7, C(4)H^AH^B), 3.13–3.18 (1H, m, C(1)NC(2)H), 3.24–3.28 (1H, m, C(1)NC(2)H), 3.34–3.39 (2H, m, C(1)NC(6)H), 3.43–3.69 (11H, m, C(1)NC(6)H + C(1)NC(3,5)H₂ + C(5)NC(2,3,5,6)H₂), 3.76–3.80 (1H, m, C(5)NC(2)H), 3.98 (1H, dt, *J* 9.4, 6.2, C(3)H), 5.46 (1H, d, *J* 9.5, C(2)H), 5.92 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 6.48 (2H, t, *J* 2.1, C(2)Ar(2,5)H), 7.08–7.10 (2H, m, C(3)ArC(2,6)H), 7.14–7.20 (3H, m, C(3)ArC(3,4,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 35.7 (C(4)H₂), 42.0 (C(1)NC(2)H₂), 43.0 (C(5)NC(2)H₂), 45.9 (C(3)H), 46.4 (C(1)NC(6)H₂), 46.6 (C(1)NC(6)H₂), 61.0 (C(2)H), 66.5 (C(1)NC(3)H₂), 66.6 (C(5)NC(3)H₂), 66.8 (C(1)NC(5)H₂), 66.8 (C(5)NC(5)H₂), 108.6 (C(2)ArC(3,4)H), 120.2 (C(2)ArC(2,5)H), 127.4

(C(3)ArC(4)H), 128.4 (C(3)ArC(2,6)H + C(3)ArC(3,5)H), 138.9 (C(3)ArC(1)), 167.4 (C(1)), 169.9 (C(5)); HRMS (NSI⁺) C₂₃H₃₀N₃O₄ [M+H]⁺ found 412.2232, requires 412.2231 (+0.3 ppm).

(2S,3S)-3-Phenyl-2-(1*H*-pyrrol-1-yl)-1,5-di(pyrrolidin-1-yl)pentane-1,5-dione (170)

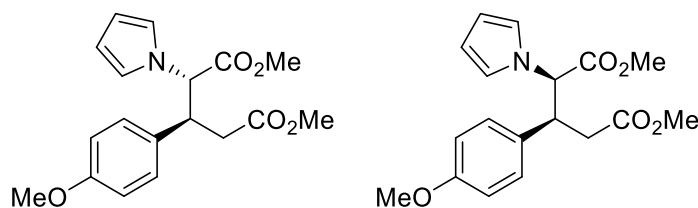


Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **158** (62.4 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with pyrrolidine (2.5 mL) at rt for 24 h gave crude product (88:12 dr) that was purified by column chromatography (EtOAc, R_f 0.21) to give **170** (47.4 mg, 50%) as a white solid. mp 174–177 °C; [α]_D²⁰ - 79.5 (c 0.41 in CHCl₃); Chiral HPLC analysis, Chiralpak AS-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 20.6 min, t_R (minor): 15.5 min, 99:1 er; ν_{max} (film, cm⁻¹) 2976 (C-H), 2870 (C-H), 1637 (C=O), 1624 (C=O), 1443 (Ar); ¹H NMR (500 MHz, CDCl₃) δ_H: 1.64–1.91 (7H, m, C(1)NC(3,4)H₂ + C(5)NC(3,4)H₂), 1.92–2.00 (1H, m, C(1)NC(3)H), 2.69–2.74 (2H, m, C(4)H₂), 2.76–2.79 (1H, m, C(1)NC(2)H), 3.19–3.24 (1H, m, C(1)NC(2)H), 3.32–3.40 (3H, m, C(1)NC(5)H₂ + C(5)NC(2)H), 3.41–3.46 (1H, m, C(5)NC(2)H), 3.50–3.55 (1H, m, C(5)NC(5)H), 3.89–3.94 (1H, m, C(5)NC(5)H), 4.01–4.05 (1H, m, C(3)H), 5.60 (1H, d, *J* 10.0, C(2)H), 5.89–5.90 (2H, m, C(2)Ar(3,4)H), 6.62–6.63 (2H, m, C(2)Ar(2,5)H), 7.11–7.17 (5H, m, C(3)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 24.3 (C(5)NC(3)H₂), 24.5 (C(1)NC(3)H₂), 26.1 (C(5)NC(4)H₂), 26.1 (C(1)NC(4)H₂), 37.6 (C(4)H₂), 45.7 (C(3)H), 46.3 (C(5)NC(5)H₂), 46.4 (C(1)NC(5)H₂), 47.0 (C(5)NC(1)H₂ + C(1)NC(1)H₂), 62.4 (C(2)H), 107.9 (C(2)ArC(3,4)H), 120.5 (C(2)ArC(2,5)H), 127.1 (C(3)ArC(4)H), 128.2 (C(3)ArC(2,6)H), 128.4 (C(3)ArC(3,5)H), 139.7 (C(3)ArC(1)), 167.5 (C(1)), 170.1 (C(5)); HRMS (NSI⁺) C₂₃H₃₀N₃O₂ [M+H]⁺ found 380.2328, requires 380.2333 (-1.2 ppm).

Selected data for minor diastereoisomer: Chiral HPLC analysis, Chiralpak OD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 20.5 min, t_R (minor): 25.4 min,

81:19 er; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 1.51–1.60 (1H, m, C(1)NC(3)H), 1.66–1.79 (7H, m, C(1)NC(3,4)H₂ + C(5)NC(3,4)H₂), 2.26–2.34 (2H, m, C(4)H₂), 2.94–2.99 (1H, m, C(5)NC(5)H), 3.06–3.15 (2H, m, C(1)NC(2)H + C(1)NC(2)H), 3.20–3.34 (5H, m, C(5)NC(5)H + C(1)NC(5)H₂ + C(5)NC(2)H + C(5)NC(2)H), 4.10 (1H, ddd, *J* 11.4, 7.3, 4.8, C(3)H), 5.32 (1H, d, *J* 10.9, C(2)H), 6.16 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 7.01 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 7.18–7.21 (1H, m, C(3)ArC(4)H), 7.25–7.28 (2H, m, C(3)ArC(2,6)H), 7.35–7.37 (2H, m, C(3)ArC(3,4)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 24.1 (C(5)NC(3)H₂), 24.4 (C(1)NC(3)H₂), 26.0 (C(5)NC(4)H₂), 26.1 (C(1)NC(4)H₂), 35.7 (C(4)H₂), 45.6 (C(1)NC(5)H₂), 45.8 (C(5)NC(5)H₂), 46.0 (C(3)H), 46.5 (C(5)NC(1)H₂), 46.7 (C(1)NC(1)H₂), 63.1 (C(2)H), 108.5 (C(2)ArC(3,4)H), 120.9 (C(2)ArC(2,5)H), 127.2 (C(3)ArC(4)H), 128.5 (C(3)ArC(2,6)H), 128.5 (C(3)ArC(3,5)H), 140.3 (C(3)ArC(1)), 167.1 (C(1)), 169.6 (C(5)).

Dimethyl (2*S*,3*S*)-3-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (173) and dimethyl (2*R*,3*S*)-3-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (478)



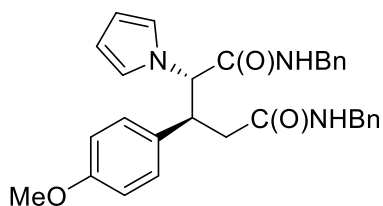
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **453** (69.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (88:11 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*S*)-**173** (65.4 mg, 79%) as a yellow oil. $[\alpha]_{\text{D}}^{20}$ – 20.0 (*c* 0.15 in CHCl_3); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin^{–1}, 211 nm, 30 °C) *t*_R (major): 15.3 min, *t*_R (minor): 13.7 min, 99.7:0.3 er; ν_{max} (film, cm^{–1}) 2999 (C-H), 2953 (C-H), 1740 (C=O), 1514 (Ar C=C); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.66–2.74 (2H, m, C(4)H^AH^B), 3.58 (3H, s, C(5)COOCH₃), 3.74 (3H, s, OCH₃), 3.76 (3H, s, C(1)COOCH₃), 3.89–3.94 (1H, m, C(3)H), 4.84 (1H, d, *J* 9.2, C(2)H), 6.00 (2H, t, *J* 2.2, C(2)Ar(3,4)H), 6.53 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 6.71–6.74 (2H, m, C(3)ArC(3,5)H), 6.93–6.96 (2H, m, C(3)ArC(2,6)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 37.2

(C(4)H₂), 44.4 (C(3)H), 52.0 (C(5)COOCH₃), 52.7 (C(1)COOCH₃), 55.2 (OCH₃), 66.3 (C(2)H), 108.4 (C(2)ArC(3,4)H), 113.9 (C(3)ArC(3,5)H), 120.9 (C(2)ArC(2,5)H), 129.0 (C(3)ArC(2,6)H), 130.3 (C(3)ArC(1)), 158.9 (C(3)ArC(4)), 170.1 (C(1)), 171.7 (C(5)); HRMS (ASAP⁺) C₁₈H₂₂NO₅ [M+H]⁺ found 332.1496, requires 332.1498 (-0.6 ppm).

(2*R*,3*S*)-**478** (8.9 mg, 11%) as a white solid. mp 90–92 °C; $[\alpha]_{\text{D}}^{20} - 5.0$ (c 0.15 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major,2*R*,3*S*): 23.1 min, t_R (minor,2*S*,3*R*): 20.6 min, 85.5:14.5 er; v_{max} (film, cm⁻¹) 2953 (C-H), 1744 (C-H), 1516 (Ar); ¹H NMR (400 MHz, CDCl₃) δ_H: 2.25 (1H, dd, *J* 15.8, 4.1, C(4)H^AH^B), 2.48 (1H, dd, *J* 15.8, 10.4, C(4)H^AH^B), 3.46 (3H, s, C(1)COOCH₃), 3.47 (3H, s, C(5)COOCH₃), 3.79 (3H, s, OCH₃), 3.88–3.93 (1H, m, C(3)H), 4.72 (1H, d, *J* 11.3, C(2)H), 6.20 (2H, t, *J* 2.2, C(2)Ar(3,4)H), 6.83–6.86 (2H, m, C(3)ArC(3,5)H), 6.88 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 7.16–7.19 (2H, m, C(3)ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 36.9 (C(4)H₂), 44.9 (C(3)H), 51.8 (C(5)COOCH₃), 52.4 (C(1)COOCH₃), 55.3 (O-CH₃), 66.5 (C(2)H), 109.3 (C(2)ArC(3,4)H), 114.2 (C(3)ArC(3,5)H), 120.5 (C(2)ArC(2,5)H), 129.3 (C(3)ArC(2,6)H), 130.2 (C(3)ArC(1)), 159.1 (C(3)ArC(4)), 169.6 (C(1)), 171.8 (C(5)); HRMS (NSI⁺) C₁₈H₂₂NO₅ [M+H]⁺ found 332.1495, requires 332.1492 (+0.8 ppm).

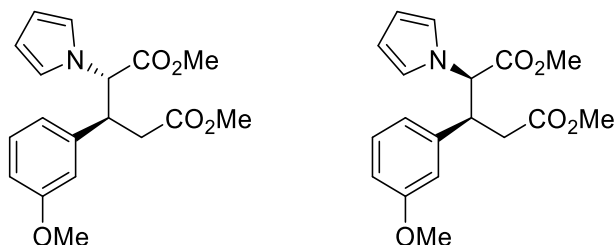
(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(4-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)pentanediamide (174**)**



Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **453** (69.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95 : 5 dr_{anti:syn}) that was triturated in ether to give **174** (80.0 mg, 67%) as a white solid. mp 194–195 °C. $[\alpha]_{\text{D}}^{20} + 3.2$ (c 0.16 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90: 10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 40.7 min, t_R (minor): 28.4 min, >99.5:0.5 er; v_{max} (film, cm⁻¹) 3289 (N-H), 3088 (C-H), 1639 (C=O); ¹H NMR

(500 MHz, CDCl₃) δ_H: 2.57–2.65 (2H, m, C(4)H_AH_B), 3.74 (3H, s, C(3)ArC(4)OCH₃), 4.05 (1H, dt, *J* 9.1, 6.3, C(3)H), 4.28–4.37 (2H, m, C(5)NHCH₂Ph), 4.40 (2H, app. d, *J* 5.8, C(1)NHCH₂Ph), 5.17 (1H, d, *J* 9.1, C(2)H), 5.69 (1H, t, *J* 5.8, C(5)NH), 6.00 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 6.56–6.58 (3H, m, C(2)Ar(2,5)H + C(1)NH), 6.68–6.71 (2H, m, C(3)ArC(3,5)H), 7.02–7.06 (4H, m, C(3)ArC(2,6)H + C(1)NHCH₂ArC(2,6)H), 7.13–7.16 (2H, m, C(5)NHCH₂ArC(2,6)H), 7.22–7.30 (6H, m, C(1)NHCH₂ArC(3,4,5)H + C(5)NHCH₂ArC(3,4,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 40.1 (C(4)H₂), 43.7 (C(1)NHCH₂ + C(5)NHCH₂), 44.1 (C(3)H), 55.2 (C(3)ArC(4)OCH₃), 66.2 (C(2)H), 108.9 (C(2)ArC(3,4)H), 113.9 (C(3)ArC(3,5)H), 121.0 (C(2)ArC(2,5)H), 127.6 (C(1)NHCH₂ArC(2,6)H), 127.7 (C(5)NHCH₂ArC(2,6)H), 127.8 (C(1)NHCH₂ArC(3,4,5)H), 128.8 (C(5)NHCH₂ArC(3,4,5)H), 129.3 (C(3)ArC(2,6)H), 131.1 (C(3)ArC(1)), 137.8 (C(1)NHCH₂ArC(1)), 137.9 (C(5)NHCH₂ArC(1)), 158.8 (C(3)ArC(4)), 169.9 (C(1)), 171.0 (C(5)); HRMS (NSI⁺) C₃₀H₃₂N₃O₃ [M+H]⁺ found 482.2430, requires 482.2438 (-1.7 ppm).

Dimethyl (2*S*,3*S*)-3-(3-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (175) and dimethyl (2*R*,3*S*)-3-(3-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (479)

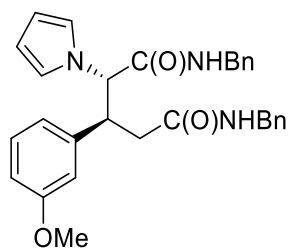


Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **455** (69.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (77:23 dr) that was purified by column chromatography (Petrol/EtOAc 80:20) to give:

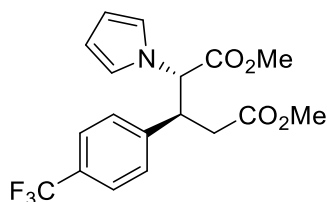
(2*S*,3*S*)-**175** (43.0 mg, 52%) as a colourless oil. $[\alpha]_D^{20} - 30.5$ (c 0.2 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) *t*_R (major): 13.4 min, *t*_R (minor): 11.4 min, 98.5:1.5 er; *v*_{max} (film, cm⁻¹) 2951 (C-H), 1728 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.71 (1H, dd, *J* 16.0, 6.3, C(4)H^AH^B), 2.77 (1H, dd, *J* 16.0, 8.4, C(4)H^AH^B),

3.60 (3H, s, C(5)COOCH₃), 3.70 (3H, s, OCH₃), 3.76 (3H, s, C(1)COOCH₃), 3.91–3.96 (1H, m, C(3)H), 4.84 (1H, d, *J* 9.4, C(2)H), 6.00 (2H, t, *J* 2.2, C(2)Ar(3,4)H), 6.52–6.53 (1H, m, C(3)ArC(2)H), 6.55 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 6.65 (1H, app. d, *J* 7.7, C(3)ArC(4)H), 6.71 (1H, ddd, *J* 8.3, 2.6, 0.9, C(3)ArC(6)H), 7.11 (1H, t, *J* 7.9, C(3)ArC(5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_c: 36.9 (C(4)H₂), 45.1 (C(3)H), 52.0 (C(5)COOCH₃), 52.7 (C(1)COOCH₃), 55.3 (OCH₃), 66.2 (C(2)H), 108.5 (C(2)ArC(3,4)H), 113.1 (C(3)ArC(6)H), 113.8 (C(3)ArC(2)H), 120.0 (C(3)ArC(4)H), 120.9 (C(2)ArC(2,5)H), 129.4 (C(3)ArC(5)H), 140.1 (C(3)ArC(1)), 159.5 (C(3)ArC(3)), 170.0 (C(1)), 171.6 (C(5)); HRMS (NSI⁺) C₁₈H₂₂NO₅ [M+H]⁺ found 332.1493, requires 332.1492 (+0.2 ppm).

(2*R*,3*S*)-**479** (12.8 mg, 15%) as a white solid. mp 76–78 °C; [α]_D²⁰ – 6.0 (c 0.3 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) t_R (major): 12.7 min, t_R (minor): 11.6 min, 82:18 er; ν_{max} (film, cm⁻¹) 2953 (C-H), 1740 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.27 (1H, dd, *J* 15.9, 4.2, C(4)H^AH^B), 2.52 (1H, dd, *J* 15.9, 10.2, C(4)H^AH^B), 3.47 (3H, s, C(1)COOCH₃), 3.48 (3H, s, C(5)COOCH₃), 3.79 (3H, s, OCH₃), 3.91–3.96 (1H, m, C(3)H), 4.76 (1H, d, *J* 11.2, C(2)H), 6.21 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 6.77–6.81 (2H, m, C(3)ArC(2,4)H), 6.85 (1H, app. d, *J* 7.7, C(3)ArC(6)H), 6.87 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 7.23 (1H, t, *J* 7.8, C(3)ArC(5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_c: 36.7 (C(4)H₂), 45.7 (C(3)H), 51.8 (C(5)COOCH₃), 52.5 (C(1)COOCH₃), 55.4 (OCH₃), 66.3 (C(2)H), 109.4 (C(2)ArC(3,4)H), 113.2 (C(3)ArC(4)H), 114.0 (C(3)ArC(2)H), 120.4 (C(3)ArC(6)H), 120.6 (C(2)ArC(2,5)H), 129.9 (C(3)ArC(5)H), 140.1 (C(3)ArC(1)), 159.8 (C(3)ArC(3)), 169.5 (C(1)), 171.7 (C(5)); HRMS (NSI⁺) C₁₈H₂₂NO₅ [M+H]⁺ found 332.1493, requires 332.1492 (+0.2 ppm).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(3-methoxyphenyl)-2-(1*H*-pyrrol-1-yl)pentanediamide (176)

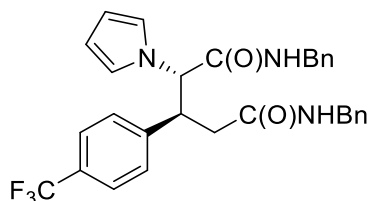
Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **455** (69.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (hexane/EtOAc 50:50 to 40:60) to give **176** (69.8 mg, 58%) as a white solid. mp 158–160 °C; $[\alpha]_D^{20} + 4.2$ (c 0.12 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 23.5 min, *t*_R (minor): 20.2 min, 99.5:0.5 er; *v*_{max} (film, cm⁻¹) 3279 (N-H), 3088 (C-H), 2922 (C-H), 1639 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.64–2.71 (2H, m, C(4)*H*^A*H*^B), 3.70 (3H, s, C(3)ArC(4)OCH₃), 4.10 (1H, dt, *J* 9.3, 6.2, C(3)*H*), 4.32 (1H, dd, *J* 14.8, 5.6, C(5)NHCH_AH_BPh), 4.37 (1H, dd, *J* 14.8, 5.8, C(5)NHCH_AH_BPh), 4.43 (2H, app d, *J* 5.9, C(1)NHCH₂Ph), 5.22 (1H, d, *J* 9.3, C(2)*H*), 5.74 (1H, t, *J* 5.7, C(5)NH), 6.03 (2H, t, *J* 2.1, C(2)Ar(3,4)*H*), 6.61–6.64 (3H, m, C(2)Ar(2,5)*H* + C(1)NH), 6.70 (1H, t, *J* 2.1, C(3)ArC(2)*H*), 6.73–6.75 (2H, m, C(3)ArC(4,6)*H*), 7.06–7.08 (2H, m, C(1)NHCH₂ArC(2,6)*H*), 7.12 (1H, t, *J* 7.9, C(3)ArC(5)*H*), 7.17–7.18 (2H, m, C(5)NHCH₂ArC(2,6)*H*), 7.25–7.32 (6H, m, C(1)NHCH₂ArC(3,4,5)*H* + C(5)NHCH₂ArC(3,4,5)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 39.9 (C(4)H₂), 43.7 (C(1)NHCH₂), 43.7 (C(5)NHCH₂), 44.8 (C(3)H), 55.2 (C(3)ArC(3)OCH₃), 66.0 (C(2)H), 108.9 (C(2)ArC(3,4)H), 112.9 (C(3)ArC(4)H), 114.0 (C(3)ArC(2)H), 120.4 (C(3)ArC(6)H), 120.9 (C(2)ArC(2,5)H), 127.6 (C(5)NHCH₂ArC(2,6)H), 127.6 (C(1)NHCH₂ArC(2,6)H), 127.7 (C(1)NHCH₂ArC(3,4,5)H), 128.8 (C(5)NHCH₂ArC(3,4,5)H), 129.5 (C(3)ArC(5)H), 137.8 (C(5)NHCH₂ArC(1)), 137.8 (C(1)NHCH₂ArC(1)), 140.9 (C(3)ArC(1)), 159.6 (C(3)ArC(3)), 169.8 (C(1)), 170.9 (C(5)); HRMS (NSI⁺) C₃₀H₃₂N₃O₃ [M+H]⁺ found 482.2430, requires 482.2438 (-1.7 ppm).

Dimethyl (2*S*,3*S*)-2-(1*H*-pyrrol-1-yl)-3-(4-(trifluoromethyl)phenyl)pentanedioate (177)

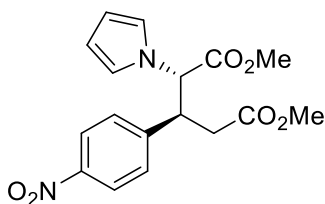
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **457** (79.4 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (91:9 dr) that was purified by column chromatography (Petrol/EtOAc 90:10) to give:

(2*S*,3*S*)-**177** (60.9 mg, 66%) as a light yellow oil. $[\alpha]_D^{20} - 25.2$ (*c* 0.29 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 13.7 min, *t*_R (minor): 11.0 min, 97:3 er; *v*_{max} (film, cm⁻¹) 2957 (C-H), 1740 (C=O), 1325; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.77 (2H, d, *J* 7.2, C(4)*H*^A*H*^B), 3.59 (3H, s, C(5)COOCH₃), 3.77 (3H, s, C(1)COOCH₃), 4.04 (1H, dt, *J* 9.5, 7.3, C(3)*H*), 4.86 (1H, d, *J* 9.6, C(2)*H*), 5.99 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.52 (2H, t, *J* 2.1, C(2)Ar(2,5)*H*), 7.16 (2H, d, *J* 8.1, C(3)ArC(2,6)*H*), 7.45 (2H, d, *J* 8.1, C(3)ArC(3,5)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 36.9 (C(4)H₂), 45.0 (C(3)H), 52.1 (C(5)COOCH₃), 52.9 (C(1)COOCH₃), 65.8 (C(2)H), 108.9 (C(2)ArC(3,4)H), 120.7 (C(2)ArC(2,5)H), 124.1 (q, *J* 272.1, CF₃), 125.4 (q, *J* 3.8, C(3)ArC(3,5)H), 128.4 (C(3)ArC(2,6)H), 129.8 (q, *J* 32.5, C(3)ArC(4)), 142.6 (C(3)ArC(1)), 169.6 (C(1)), 171.2 (C(5)); ¹⁹F NMR (471 MHz, CDCl₃) δ_F: –62.6 (s, CF₃); HRMS (ASAP⁺) C₁₈H₁₉NO₄F₃ [M+H]⁺ found 370.1267, requires 370.1266 (+0.3 ppm); Selected data for minor diastereoisomer (2*R*,3*S*): ¹H NMR (500 MHz, CDCl₃) δ_H: 2.34 (1H, dd, *J* 16.2, 4.0, C(4)*H*^A*H*^B), 2.55 (1H, dd, *J* 16.2, 10.3, C(4)*H*^A*H*^B), 3.49 (3H, s, C(1)COOCH₃), 3.51 (3H, s, C(5)COOCH₃), 4.06 (1H, td, *J* 10.7, 4.0, C(3)*H*), 4.82 (1H, d, *J* 11.2, C(2)*H*), 6.25 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.89 (2H, t, *J* 2.2, C(2)Ar(2,5)*H*), 7.39–7.45 (2H, m, C(3)ArC(2,6)*H*), 7.58–7.65 (2H, m, C(3)ArC(3,5)*H*).

**(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-2-(1*H*-pyrrol-1-yl)-3-(4-(trifluoromethyl)phenyl)pentanediamide
(178)**



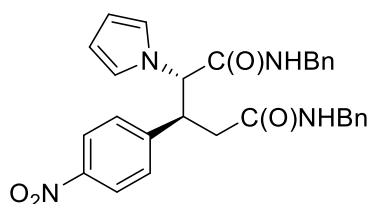
Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **457** (79.4 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (> 95 : 5 *dr*_{anti:syn}) that was triturated in ether to give **178** (77.9 mg, 60%) as a white solid. mp 204–205 °C; [α]_D²⁰ - 1.5 (c 0.24 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) *t*_R (major): 17.5 min, *t*_R (minor): 14.3 min, 99.5:0.5 *er*; *v*_{max} (film, cm⁻¹) 3294 (N-H), 3088 (C-H), 1639 (C=O), 1557; ¹H NMR (500 MHz, DMSO) δ_H: 2.42 (1H, dd, *J* 14.1, 3.7, C(4)*H*^A*H*^B), 2.65 (1H, dd, *J* 14.1, 11.4, C(4)*H*^A*H*^B), 3.91 (1H, dd, *J* 15.5, 5.1, C(5)NHCH^A*H*^BPh), 4.03–4.08 (1H, m, C(3)*H*), 4.22–4.29 (2H, m, C(5)NHCH^A*H*^BPh + C(1)NHCH^A*H*^BPh), 4.40 (1H, dd, *J* 15.0, 5.9, C(1)NHCH^A*H*^BPh), 5.01 (1H, d, *J* 11.3, C(2)*H*), 5.78 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.67–6.69 (4H, m, C(2)Ar(2,5)*H* + C(1)NHCH₂ArC(2,6)*H*), 7.06–7.09 (2H, m, C(5)NHCH₂ArC(2,6)*H*), 7.11–7.14 (1H, m, C(1)NHCH₂ArC(4)*H*), 7.21–7.22 (2H, m, C(5)NHCH₂ArC(3,5)*H*), 7.23–7.27 (1H, m, C(5)NHCH₂ArC(4)*H*), 7.29–7.32 (2H, m, C(1)NHCH₂ArC(3,5)*H*), 7.35 (2H, app. d, *J* 8.0, C(3)ArC(2,6)*H*), 7.52 (2H, app. d, *J* 8.1, C(3)ArC(3,5)*H*), 8.28–8.30 (1H, m, C(5)NH), 8.91 (1H, t, *J* 5.8, C(1)NH); ¹³C{¹H} NMR (126 MHz, DMSO) δ_C: 38.9 (C(4)H₂), 42.1 (C(5)NHCH₂), 42.8 (C(1)NHCH₂), 45.1 (C(3)H), 65.8 (C(2)H), 108.0 (C(2)ArC(3,4)H), 120.3 (C(2)ArC(2,5)H), 124.8 (q, *J* 271.9, C(3)ArC(4)CF₃), 125.1 (d, *J* 4.2, C(3)ArC(3,5)H), 126.9 (C(1)NHCH₂ArC(2,6)H), 127.0 (C(1)NHCH₂ArC(4)H), 127.5 (C(5)NHCH₂ArC(4)H), 127.9 (C(5)NHCH₂ArC(3,5)H), 128.3 (C(5)NHCH₂ArC(2,6)H), 128.9 (C(1)NHCH₂ArC(3,5)H), 129.5 (C(3)ArC(2,6)H), 139.1 (C(1)NHCH₂ArC(1)), 139.6 (C(5)NHCH₂ArC(1)), 145.0 (C(3)ArC(1)), 168.9 (C(1)), 169.6 (C(5)); ¹⁹F NMR (471 MHz, DMSO) δ_F: -60.7; HRMS (NSI⁺) C₃₀H₂₉N₃O₂F₃ [M+H]⁺ found 520.2199, requires 520.2206 (-1.4 ppm).

Dimethyl (2*S*,3*S*)-3-(4-nitrophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (179)

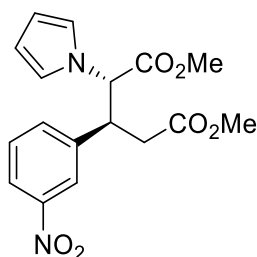
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **459** (73.6 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (89:11 dr) that was purified by column chromatography (Petrol/EtOAc 85:15 to 75:25) to give:

(2*S*,3*S*)-**179** (70.1 mg, 81%) as a light yellow oil. $[\alpha]_D^{20} - 40.0$ (*c* 0.11 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) *t*_R (major): 40.3 min, *t*_R (minor): 37.5 min, 98.5:1.5 er; *v*_{max} (film, cm⁻¹) 2957 (C-H), 1736 (C=O), 1700 (C=O), 1520 (N-O), 1344 (N-O); ¹H NMR (500 MHz, CDCl₃) δ _H: 2.75–2.84 (2H, m, C(4)*H*^A*H*^B), 3.58 (3H, s, C(5)COOCH₃), 3.78 (3H, s, C(1)COOCH₃), 4.07–4.12 (1H, m, C(3)*H*), 4.84 (1H, d, *J* 10.0, C(2)*H*), 5.98 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.51 (2H, t, *J* 2.2, C(2)Ar(2,5)*H*), 7.22–7.23 (2H, m, C(3)ArC(2,6)*H*), 8.04–8.05 (2H, m, C(3)ArC(3,5)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ _C: 36.9 (C(4)H₂), 45.1 (C(3)H), 52.2 (C(5)COOCH₃), 53.1 (C(1)COOCH₃), 65.6 (C(2)H), 109.2 (C(2)ArC(3,4)H), 120.5 (C(2)ArC(2,5)H), 123.7 (C(3)ArC(3,5)H), 128.9 (C(3)ArC(2,6)H), 146.1 (C(3)ArC(1)), 147.3 (C(3)ArC(4)), 169.4 (C(1)), 170.9 (C(5)); HRMS (NSI⁺) C₁₇H₁₉N₂O₆ [M+H]⁺ found 347.1242, requires 347.1238 (+1.3 ppm).

Selected data for minor diastereoisomer (2*R*,3*S*): ¹H NMR (500 MHz, CDCl₃) δ _H: 2.36 (1H, dd, *J* 16.4, 3.9, C(4)*H*^A*H*^B), 2.57 (1H, dd, *J* 16.4, 10.4, C(4)*H*^A*H*^B), 3.51 (3H, s, C(1)COOCH₃), 3.52 (3H, s, C(5)COOCH₃), 4.08–4.13 (1H, m, C(3)*H*), 4.85 (1H, d, *J* 11.0, C(2)*H*).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(4-nitrophenyl)-2-(1*H*-pyrrol-1-yl)pentanediamide (180)

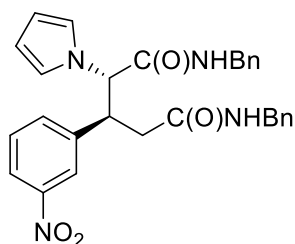
Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **459** (73.6 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (petrol/EtOAc 50:50 to 30:70) to give **180** (68.3 mg, 55%) as a light-brown solid. mp 182–184 °C; $[\alpha]_{\text{D}}^{20}$ – 9.5 (c 0.21 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 59.9 min, *t*_R (minor): 33.6 min, 98:2 er; *v*_{max} (film, cm⁻¹) 3327 (N-H), 3281 (N-H), 3088 (C-H), 1639 (C=O), 1522 (N-O), 1358 (N-O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.67 (1H, dd, *J* 14.9, 6.5, C(4)*H*^A*H*^B), 2.70 (1H, dd, *J* 15.1, 5.9, C(4)*H*^A*H*^B), 4.21 (1H, dt, *J* 9.3, 6.1, C(3)*H*), 4.33 (2H, app d, *J* 5.8, C(5)NHCH₂Ph), 4.36–4.45 (2H, m, C(1)NHCH₂Ph), 5.25 (1H, d, *J* 9.4, C(2)*H*), 5.76 (1H, t, *J* 6.0, C(5)NH), 6.00 (2H, t, *J* 2.1, C(2)Ar(3,4)*H*), 6.46 (1H, t, *J* 6.0, C(1)NH), 6.53 (2H, t, *J* 2.2, C(2)Ar(2,5)*H*), 7.08–7.10 (2H, m, C(1)NHCH₂ArC(2,6)*H*), 7.15–7.16 (2H, m, C(5)NHCH₂ArC(2,6)*H*), 7.26–7.31 (8H, m, C(3)ArC(2,6)*H* + C(1)NHCH₂ArC(3,4,5)*H* + C(5)NHCH₂ArC(3,4,5)*H*), 7.96–7.99 (2H, m, C(3)ArC(3,5)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 39.2 (C(4)H₂), 43.7 (C(1)NHCH₂), 43.7 (C(5)NHCH₂), 44.8 (C(3)H), 65.2 (C(2)H), 109.5 (C(2)ArC(3,4)H), 120.6 (C(2)ArC(2,5)H), 123.5 (C(3)ArC(3,5)H), 127.5 (C(5)NHCH₂ArC(2,6)H), 127.7 (C(1)NHCH₂ArC(2,6)H), 127.8 (C(5)NHCH₂ArC(3,5)H), 127.8 (C(1)NHCH₂ArC(3,5)H), 128.8 (C(3)ArC(2,6)H), 129.2 (C(5)NHCH₂ArC(4)H + C(1)NHCH₂ArC(4)H), 137.4 (C(1)NHCH₂ArC(1)), 137.6 (C(5)NHCH₂ArC(1)), 146.9 (C(3)ArC(4)), 147.0 (C(3)ArC(1)), 168.9 (C(1)), 169.9 (C(5)); HRMS (NSI⁺) C₂₉H₂₉N₄O₄ [M+H]⁺ found 497.2172, requires 497.2183 (–2.3 ppm).

Dimethyl (2*S*,3*S*)-3-(3-nitrophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (181)

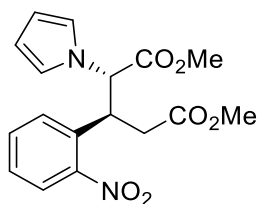
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **461** (73.6 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (87:13 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 80:20) to give:

(2*S*,3*S*)-**181** (69.3 mg, 80%) as a yellow oil. $[\alpha]_{\text{D}}^{20} - 30.0$ (c 0.05 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) *t*_R (major): 34.7 min, *t*_R (minor): 31.3 min, 96:4 er; *v*_{max} (film, cm⁻¹) 2955 (C-H), 1732 (C=O), 1528; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.76–2.84 (2H, m, C(4)*H*^A*H*^B), 3.59 (3H, s, C(5)COOCH₃), 3.80 (3H, s, C(1)COOCH₃), 4.06–4.11 (1H, m, C(3)*H*), 4.84 (1H, d, *J* 9.9, C(2)*H*), 5.97 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.51 (2H, t, *J* 2.1, C(2)Ar(2,5)*H*), 7.33–7.37 (2H, m, C(3)ArC(5,6)*H*), 7.95 (1H, app. s, C(3)ArC(2)*H*), 8.04 (1H, dt, *J* 7.4, 2.1, C(3)ArC(4)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 36.8 (C(4)H₂), 45.0 (C(3)*H*), 52.2 (C(5)COOCH₃), 53.1 (C(1)COOCH₃), 65.7 (C(2)), 109.2 (C(2)ArC(3,4)*H*), 120.5 (C(2)ArC(2,5)*H*), 122.6 (C(3)ArC(2)*H*), 122.8 (C(3)ArC(4)*H*), 129.4 (C(3)ArC(5)*H*), 134.6 (C(3)ArC(6)*H*), 140.6 (C(3)ArC(1)), 148.1 (C(3)ArC(3)), 169.4 (C(1)), 171.0 (C(5)); HRMS (ASAP⁺) C₁₇H₁₉N₂O₆ [M+H]⁺ found 347.1244, requires 347.1243 (+0.3 ppm).

Selected data for minor diastereoisomer (2*R*,3*S*): ¹H NMR (500 MHz, CDCl₃) δ_H: 2.37 (1H, dd, *J* 16.4, 3.9, C(4)*H*^A*H*^B), 2.59 (1H, dd, *J* 16.4, 10.4, C(4)*H*^A*H*^B), 3.52 (6H, s, C(1)COOCH₃ + C(5)COOCH₃), 4.11 (1H, td, *J* 10.7, 3.8, C(3)*H*), 4.85 (1H, d, *J* 11.1, C(2)*H*), 6.26 (2H, t, *J* 2.1, C(2)Ar(3,4)*H*), 6.87 (1H, t, *J* 2.3, C(3)ArC(2)*H*), 6.88 (2H, t, *J* 2.1, C(2)Ar(2,5)*H*), 7.46–7.57 (1H, m, C(3)Ar*H*), 7.62–7.68 (1H, m, C(3)Ar*H*), 8.17 (1H, dt, *J* 5.3, 1.8, C(3)Ar*H*).

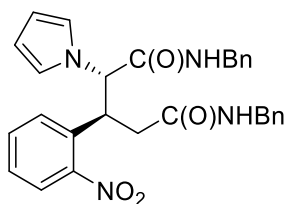
(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(3-nitrophenyl)-2-(1*H*-pyrrol-1-yl)pentanediamide (182**)**

Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **461** (73.6 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (hexane/EtOAc 50:50) to give **182** (74.4 mg, 60%) as a brown solid. mp 181–182 °C; $[\alpha]_{\text{D}}^{20} + 23.0$ (c 0.10 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) *t*_R (major): 27.1 min, *t*_R (minor): 21.7 min, 96.5:3.5 er; ν_{max} (film, cm⁻¹) 3285 (N-H), 3090 (C-H), 1639 (C=O), 1525 (N-O), 1348 (N-O); ¹H NMR (500 MHz, DMSO) δ_{H} : 2.46–2.49 (1H, m, C(4)*H*^A*H*^B), 2.71 (1H, dd, *J* 14.2, 11.4, C(4)*H*^A*H*^B), 3.94 (1H, dd, *J* 15.4, 5.1, C(5)NHCH^A*H*^BPh), 4.12 (1H, td, *J* 11.4, 3.8, C(3)*H*), 4.23 (1H, dd, *J* 15.4, 6.9, C(5)NHCH^A*H*^BPh), 4.30 (1H, dd, *J* 15.0, 5.5, C(1)NHCH^A*H*^BPh), 4.42 (1H, dd, *J* 15.0, 5.9, C(1)NHCH^A*H*^BPh), 5.08 (1H, d, *J* 11.2, C(2)*H*), 5.79 (2H, t, *J* 2.1, C(2)Ar(3,4)*H*), 6.70–6.71 (4H, m, C(2)Ar(2,5)*H* + C(1)NHCH₂ArC(2,6)*H*), 7.08–7.14 (3H, m, C(1)NHCH₂ArC(3,4,5)*H*), 7.23–7.25 (2H, m, C(5)NHCH₂ArC(2,6)*H*), 7.26–7.28 (1H, m, C(5)NHCH₂ArC(4)*H*), 7.31–7.34 (2H, m, C(5)NHCH₂ArC(3,5)*H*), 7.43 (1H, t, *J* 7.8, C(3)ArC(5)*H*), 7.56–7.58 (1H, m, C(3)ArC(6)*H*), 8.02–8.04 (2H, m, C(3)ArC(2,4)*H*), 8.36 (1H, t, *J* 6.1, C(5)NH), 8.90 (1H, t, *J* 5.8, C(1)NH); ¹³C{¹H} NMR (126 MHz, DMSO) δ_{C} : 38.3 (C(4)H₂), 41.6 (C(5)NHCH₂), 42.4 (C(1)NHCH₂), 44.6 (C(3)H), 65.2 (C(2)H), 107.7 (C(2)ArC(3,4)H), 119.9 (C(2)ArC(2,5)H), 121.8 (C(3)ArC(2)H), 122.5 (C(3)ArC(4)H), 126.5 (C(1)NHCH₂ArC(2,6)H), 126.6 (C(1)NHCH₂ArC(3,5)H), 127.1 (C(5)NHCH₂ArC(4)H), 127.4 (C(5)NHCH₂ArC(2,6)H), 128.0 (C(1)NHCH₂ArC(4)H), 128.4 (C(5)NHCH₂ArC(3,5)H), 129.3 (C(3)ArC(5)H), 135.5 (C(3)ArC(6)H), 138.6 (C(1)NHCH₂ArC(1)), 139.1 (C(5)NHCH₂ArC(1)), 142.1 (C(3)ArC(1)), 147.3 (C(3)ArC(3)), 168.3 (C(1)), 169.1 (C(5)); HRMS (NSI⁺) C₂₉H₂₉N₄O₄ [M+H]⁺ found 497.2175, requires 497.2183 (-1.7 ppm).

Dimethyl (2*S*,3*S*)-3-(2-nitrophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (183)

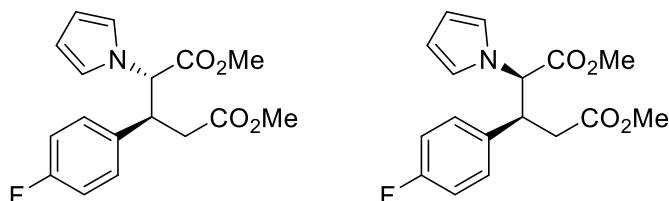
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **463** (73.6 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (88:12 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*S*)-**183** (73.6 mg, 85%) as a light brown oil. $[\alpha]_{\text{D}}^{20} - 11.0$ (*c* 0.4 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 12.2 min, *t*_R (minor): 9.8 min, 97.5:2.5 er; *v*_{max} (film, cm⁻¹) 3013 (C-H), 2959 (C-H), 1742 (C=O), 1728 (C=O), 1524, 1354; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.87 (1H, dd, *J* 16.4, 6.0, C(4)*H*^A*H*^B), 2.90 (1H, dd, *J* 16.4, 8.0, C(4)*H*^A*H*^B), 3.57 (3H, s, C(5)COOCH₃), 3.74 (3H, s, C(1)COOCH₃), 4.69 (1H, app. s, C(3)*H*), 5.18 (1H, d, *J* 9.1, C(2)*H*), 5.99 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.66 (2H, t, *J* 2.2, C(2)Ar(2,5)*H*), 7.28–7.29 (1H, m, C(3)ArC(6)*H*), 7.31–7.34 (1H, m, C(3)ArC(4)*H*), 7.46 (1H, t, *J* 7.6, C(3)ArC(5)*H*), 7.75 (1H, dd, *J* 8.2, 1.4, C(3)ArC(3)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 36.8 (C(4)H₂), 39.1 (C(3)H, broad), 52.1 (C(5)COOCH₃), 53.0 (C(1)COOCH₃), 64.4 (C(2)H), 109.1 (C(2)ArC(3,4)H), 120.6 (C(2)ArC(2,5)H), 125.0 (C(3)ArC(3)H), 128.4 (C(3)ArC(4)H+C(3)ArC(6)H), 132.7 (C(3)ArC(5)H), 132.9 (C(3)ArC(1)), 150.4 (C(3)ArC(2)), 169.4 (C(1)), 171.1 (C(5)); HRMS (ASAP⁺) C₁₇H₁₉N₂O₆ [M+H]⁺ found 347.1243, requires 347.1243 (0.0 ppm).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(2-nitrophenyl)-2-(1*H*-pyrrol-1-yl)pentanediamide (184**)**

Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **463** (73.6 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95:5 dr) that was triturated in ether to give **184** (65.7 mg, 53%) as a white solid. mp 219–220 °C (dec); $[\alpha]_D^{20} - 60.5$ (c 0.22 in DMSO); Chiral HPLC analysis, Chiralpak IB (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 34.1 min, *t*_R (minor): 21.6 min, >99.5:0.5 er; *v*_{max} (film, cm⁻¹) 3289 (N-H), 3088 (C-H), 1645 (C=O), 1528 (N-O), 1352 (N-O); ¹H NMR (500 MHz, DMSO) δ_H : 2.51 (1H, overlapped with solvent signals, C(4)*H*^A*H*^B), 2.65–2.71 (1H, m, C(4)*H*^A*H*^B), 3.97 (1H, dd, *J* 15.5, 5.3, C(5)NHCH^A*H*^BPh), 4.16 (1H, dd, *J* 15.6, 6.3, C(5)NHCH^A*H*^BPh), 4.26 (1H, dd, *J* 15.3, 5.4, C(1)NHCH^A*H*^BPh), 4.38 (1H, dd, *J* 15.0, 5.8, C(1)NHCH^A*H*^BPh), 4.71–4.76 (1H, m, C(3)*H*), 5.28 (1H, d, *J* 10.4, C(2)*H*), 5.80 (2H, app. s, C(2)Ar(3,4)*H*), 6.73 (2H, app. s, C(2)Ar(2,5)*H*), 6.82–6.83 (2H, m, C(1)NHCH₂ArC(2,6)*H*), 7.18–7.19 (5H, m, C(5)NHCH₂ArC(2,6)*H* + C(1)NHCH₂ArC(3,4,5)*H*), 7.23–7.31 (3H, m, C(5)NHCH₂ArC(3,4,5)*H*), 7.38–7.41 (1H, m, C(3)ArC(4)*H*), 7.56 (2H, app. s, C(3)ArC(3,5)*H*), 7.74 (1H, d, *J* 8.1, C(3)ArC(6)*H*), 8.28 (1H, app. s, C(5)NH), 8.92 (1H, app. s, C(1)NH); ¹³C{¹H} NMR (126 MHz, DMSO) δ_C : 38.0 (C(3)*H*), 38.6 (C(4)*H*₂), 41.7 (C(5)NHCH₂), 42.4 (C(1)NHCH₂), 64.1 (C(2)*H*), 107.6 (C(2)ArC(3,4)*H*), 120.0 (C(2)ArC(2,5)*H*), 124.5 (C(3)ArC(6)*H*), 126.6 (C(5)NHCH₂ArC(2,6)*H*), 126.8 (C(1)NHCH₂ArC(2,6)*H*), 127.0 (C(1)NHCH₂ArC(3,5)*H*), 127.4 (C(5)NHCH₂ArC(3,5)*H*), 127.8 (C(3)ArC(4)*H*), 128.1 (C(1)NHCH₂ArC(4)*H*), 128.4 (C(5)NHCH₂ArC(4)*H*), 128.7 (C(3)ArC(5)*H*), 132.7 (C(3)ArC(3)*H*), 133.9 (C(3)ArC(1)), 138.6 (C(1)NHCH₂ArC(1)), 139.1 (C(5)NHCH₂ArC(1)), 150.4 (C(3)ArC(2)), 168.3 (C(1)), 169.1 (C(5)); HRMS (NSI⁺) C₂₉H₂₉N₄O₄ [M+H]⁺ found 497.2174, requires 497.2183 (–1.9 ppm).

Dimethyl (2*S*,3*S*)-3-(4-fluorophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (185) and dimethyl (2*R*,3*S*)-3-(4-fluorophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (200) and



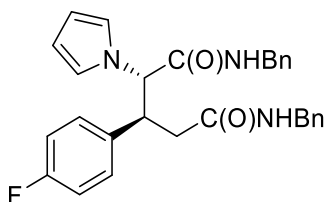
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **465** (66.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (80:20 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*S*)-**185** (58.7 mg, 74%) as a light yellow oil. $[\alpha]_{\text{D}}^{20} - 35.9$ (*c* 1.65 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 7.4 min, *t*_R (minor): 6.7 min, 99:1 er; *v*_{max} (film, cm⁻¹) 2955 (C-H), 1734 (C=O), 1510, 725; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.68–2.75 (2H, m, C(4)*H^AH^B*), 3.58 (3H, s, C(5)COOCH₃), 3.77 (3H, s, C(1)COOCH₃), 3.95 (1H, dt, *J* 9.5, 7.4, C(3)*H*), 4.81 (1H, d, *J* 9.5, C(2)*H*), 5.99 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.52 (2H, t, *J* 2.2, C(2)Ar(2,5)*H*), 6.86–6.90 (2H, m, C(3)ArC(2,6)*H*), 6.99–7.02 (2H, m, C(3)ArC(3,5)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 37.2 (C(4)H₂), 44.6 (C(3)H), 52.0 (C(5)COOCH₃), 52.9 (C(1)COOCH₃), 66.2 (C(2)H), 108.7 (C(2)ArC(3,4)H), 115.4 (d, ²*J*_{CF} 21.4, C(3)ArC(3)H + C(3)ArC(5)H), 120.7 (C(2)ArC(2,5)H), 129.5 (d, ³*J*_{CF} 8.1, C(3)ArC(2)H + C(3)ArC(6)H), 134.1 (d, ⁴*J*_{CF} 3.2, C(3)ArC(1)), 162.1 (d, ¹*J*_{CF} 246.1, C(3)ArC(4)), 169.9 (C(1)), 171.5 (C(5)); ¹⁹F{¹H} NMR (377 MHz, CDCl₃) δ_F: -114.7; HRMS (ASAP⁺) C₁₇H₁₉NO₄F [M+H]⁺ found 320.1298, requires 320.1298 (0.0 ppm).

(2*R*,3*S*)-**200** (14.7 mg, 18%) as a white solid. mp. 96–97 °C; $[\alpha]_{\text{D}}^{20} - 10.0$ (*c* 0.2 in CHCl₃); Chiral HPLC analysis, Chiralpak OJ-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major,2*R*,3*S*): 15.4 min, *t*_R (minor,2*S*,3*R*): 23.2 min, 90:10 er; *v*_{max} (film, cm⁻¹) 2949 (C-H), 1728 (C=O), 727, 700; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.27 (1H, dd, *J* 15.9, 4.1, C(4)*H^AH^B*), 2.48 (1H, dd, *J* 16.0, 10.4, C(4)*H^AH^B*), 3.46 (3H, s, C(1)COOCH₃), 3.47 (3H, s, C(5)COOCH₃), 3.95 (1H, td, *J* 10.8, 4.1, C(3)*H*), 4.73 (1H, d, *J* 11.3, C(2)*H*), 6.21 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.87 (2H,

t, J 2.2, C(2)Ar(2,5)H), 6.99–7.03 (2H, m, C(3)ArC(2,6)H), 7.22–7.26 (2H, m, C(3)ArC(3,5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 36.8 (C(4)H₂), 45.0 (C(3)H), 51.8 (C(5)COOCH₃), 52.5 (C(1)COOCH₃), 66.3 (C(2)H), 109.5 (C(2)ArC(3,4)H), 115.8 (d, $^2J_{\text{CF}}$ 21.6, C(3)ArC(3)H + C(3)ArC(5)H), 120.5 (C(2)ArC(2,5)H), 129.9 (d, $^3J_{\text{CF}}$ 8.1, C(3)ArC(2)H + C(3)ArC(6)H), 134.2 (d, $^4J_{\text{CF}}$ 3.5, C(3)ArC(1)), 162.3 (d, $^1J_{\text{CF}}$ 246.2, C(3)ArC(4)), 169.4 (C(1)), 171.5 (C(5)); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -114.3; HRMS (NSI⁺) C₁₇H₁₉NO₄F [M+H]⁺ found 320.1295, requires 320.1293 (+0.7 ppm).

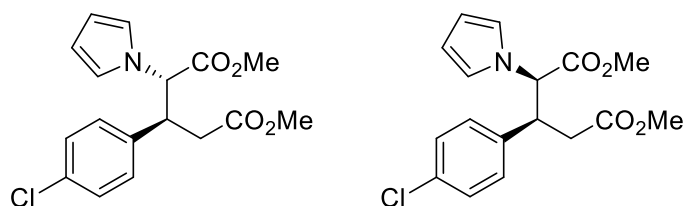
(2S,3S)-N¹,N⁵-Dibenzyl-3-(4-fluorophenyl)-2-(1H-pyrrol-1-yl)pentanediamide (186)



Following General Procedure E, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **467** (66.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (95:5 dr) that was triturated in ether to give **186** (70.4 mg, 60%) as a white solid. mp 224–225 °C (dec); $[\alpha]_{\text{D}}^{20}$ + 3.6 (c 0.11 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 28.9 min, t_{R} (minor): 14.5 min, 99.9:0.1 er; ν_{max} (film, cm⁻¹) 3275 (N-H), 3034 (C-H), 1641 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.62 (2H, d, J 6.2, C(4)H^AH^B), 4.08 (1H, dt, J 9.3, 6.2, C(3)H), 4.29–4.37 (2H, m, C(5)NHCH₂Ph), 4.38–4.44 (2H, m, C(1)NHCH₂Ph), 5.18 (1H, d, J 9.2, C(2)H), 5.70 (1H, t, J 5.9, C(5)NH), 6.00 (2H, t, J 2.2, C(2)Ar(3,4)H), 6.51–6.55 (3H, m, C(2)Ar(3,4)H + C(1)NH), 6.82–6.87 (2H, m, C(3)ArC(2,6)H), 7.05–7.10 (4H, m, C(3)ArC(3,5)H + C(1)NHCH₂ArC(2,6)H), 7.14–7.16 (2H, m, C(5)NHCH₂ArC(2,6)H), 7.23–7.30 (6H, m, C(1)NHCH₂ArC(3,4,5)H + C(5)NHCH₂ArC(3,4,5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 39.9 (C(4)H₂), 43.7 (C(5)NHCH₂ + C(1)NHCH₂), 44.2 (C(3)H), 66.0 (C(2)H), 109.1 (C(2)ArC(3,4)H), 115.4 (d, $^2J_{\text{CF}}$ 21.6, C(3)ArC(3)H + C(3)ArC(5)H), 120.9 (C(2)ArC(2,5)H), 127.7 (C(5)NHCH₂ArC(2,6)H), 127.8 (C(5)NHCH₂ArC(3,4,5)H), 127.8 (C(1)NHCH₂ArC(2,6)H), 128.8 (C(1)NHCH₂ArC(3,4,5)H), 129.9

(d, $^3J_{CF}$ 8.0, C(3)ArC(2)H + C(3)ArC(6)H), 135.0 (d, $^4J_{CF}$ 3.5, C(3)ArC(1)), 137.7 (C(1)NHCH₂ArC(1)), 137.8 (C(5)NHCH₂ArC(1)), 162.0 (d, $^1J_{CF}$ 246.0, C(3)ArC(4)), 169.6 (C(1)), 170.7 (C(5)); ^{19}F NMR (471 MHz, CDCl₃) δ_{F} : -115.0 (s, C(3)ArC(4)F); HRMS (NSI⁺) C₂₉H₂₉N₃O₂F [M+H]⁺ found 470.2235, requires 470.2238 (-0.7 ppm).

Dimethyl (2*S*,3*S*)-3-(4-chlorophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (187) and dimethyl (2*R*,3*S*)-3-(4-chlorophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (480)



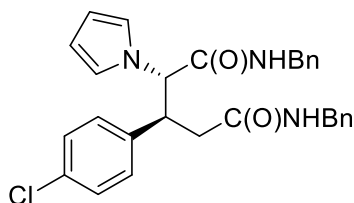
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **467** (71.0 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (87:13 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*S*)-**187** (58.8 mg, 70%) as a colourless oil. $[\alpha]_{\text{D}}^{20}$ - 30.0 (c 0.25 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (99:1 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 36.9 min, *t*_R (minor): 32.2 min, 99:1 er; *v*_{max} (film, cm⁻¹) 2999 (C-H), 2953 (C-H), 1732 (C=O); ^1H NMR (500 MHz, CDCl₃) δ_{H} : 2.68–2.74 (2H, m, C(4)*H*^A*H*^B), 3.58 (3H, s, C(5)COOCH₃), 3.76 (3H, s, C(1)COOCH₃), 3.94 (1H, dt, *J* 9.6, 7.4, C(3)*H*), 4.81 (1H, d, *J* 9.5, C(2)*H*), 6.00 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.52 (2H, t, *J* 2.2, C(2)Ar(2,5)*H*), 6.96–6.98 (2H, m, C(3)ArC(2,6)*H*), 7.15–7.17 (2H, m, C(3)ArC(3,5)*H*); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl₃) δ_{C} : 37.0 (C(4)H₂), 44.6 (C(3)H), 52.1 (C(5)COOCH₃), 52.9 (C(1)COOCH₃), 66.0 (C(2)H), 108.7 (C(2)ArC(3,4)H), 120.7 (C(2)ArC(2,5)H), 128.7 (C(3)ArC(3,5)H), 129.3 (C(3)ArC(2,6)H), 133.4 (C(3)ArC(4)), 136.9 (C(3)ArC(1)), 169.8 (C(1)), 171.4 (C(5)); HRMS (NSI⁺) C₁₇H₁₉NO₄³⁵Cl [M+H]⁺ found 336.1001, requires 336.0997 (+1.2 ppm).

(2*R*,3*S*)-**480** (8.9 mg, 11%) as a white solid. mp. 118–120 °C; $[\alpha]_{\text{D}}^{20}$ + 6.0 (c 0.1 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) *t*_R

(major): 20.8 min, t_R (minor): 18.8 min, 95:5 er; ν_{\max} (film, cm^{-1}) 2953 (C-H), 1740 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.27 (1H, dd, J 16.0, 4.0, C(4) $H^A H^B$), 2.48 (1H, dd, J 16.0, 10.4, C(4) $H^A H^B$), 3.48 (6H, s, 2CH_3), 3.94 (1H, td, J 10.8, 4.1, C(3) H), 4.74 (1H, d, J 11.2, C(2) H), 6.21 (2H, t, J 2.1, C(2)Ar(3,4) H), 6.86 (2H, t, J 2.2, C(2)Ar(2,5) H), 7.19–7.21 (2H, m, C(3)ArC(2,6) H), 7.27–7.31 (2H, m, C(3)ArC(3,5) H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 36.6 (C(4) H_2), 45.1 (C(3) H), 51.9 (C(5)COOCH₃), 52.6 (C(1)COOCH₃), 66.1 (C(2) H), 109.6 (C(2)ArC(3,4) H), 120.5 (C(2)ArC(2,5) H), 129.1 (C(3)ArC(3,5) H), 129.7 (C(3)ArC(2,4) H), 133.7 (C(3)ArC(4)), 137.0 (C(3)ArC(1)), 169.3 (C(1)), 171.5 (C(5)); HRMS (ASAP⁺) $\text{C}_{17}\text{H}_{19}\text{NO}_4^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$ found 336.1005, requires 336.1003 (+0.6 ppm).

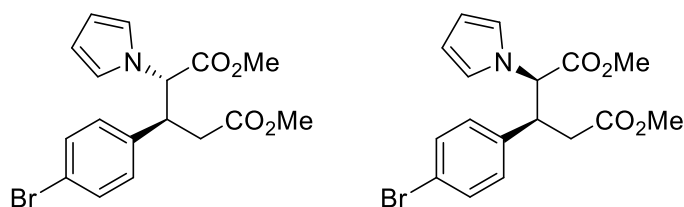
(2*S*,3*S*)- N^1,N^5 -Dibenzyl-3-(4-chlorophenyl)-2-(1*H*-pyrrol-1-yl)pentanediamide (188)



Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **467** (71.0 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95:5 dr) that was triturated in ether to give **188** (85.1 mg, 70%) as a white solid. mp 232–234 °C; $[\alpha]_{\text{D}}^{20} + 15.0$ (c 0.10 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 27.9 min, t_R (minor): 20.1 min, 98.5:1.5 er; ν_{\max} (film, cm^{-1}) 3273 (N-H), 3030 (C-H), 1639 (C=O); ^1H NMR (500 MHz, DMSO) δ_{H} : 2.39 (1H, dd, J 13.9, 3.7, C(4) $H^A H^B$), 2.59 (1H, dd, J 13.9, 11.5, C(4) $H^A H^B$), 3.89–3.97 (2H, m, C(3) H + C(5)NHCH $H^A H^B$ Ph), 4.25–4.30 (2H, m, C(5)NHCH $H^A H^B$ Ph + C(1)NHCH $H^A H^B$ Ph), 4.40 (1H, dd, J 15.0, 5.9, C(1)NHCH $H^A H^B$ Ph), 4.93 (1H, d, J 11.3, C(2) H), 5.79 (2H, t, J 2.1, C(2)Ar(3,4) H), 6.65–6.67 (4H, m, C(2)Ar(2,5) H + C(1)NHCH₂ArC(2,6) H), 7.11–7.16 (5H, m, C(1)NHCH₂ArC(3,5) H + C(5)NHCH₂ArC(3,4,5) H), 7.20–7.23 (4H, m, C(3)ArC(2,6) H + C(5)NHCH₂ArC(2,6) H), 7.24–7.27 (1H, m, C(1)NHCH₂ArC(4) H), 7.30–7.33 (2H, m, C(3)ArC(3,5) H), 8.26–8.28 (1H, m, C(5)NH), 8.90 (1H, t, J 5.8, C(1)NH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz,

DMSO δ_c : 38.7 (C(4)H₂), 41.6 (C(5)NHCH₂), 42.3 (C(1)NHCH₂), 44.3 (C(3)H), 65.6 (C(2)H), 107.5 (C(2)ArC(3,4)H), 119.9 (C(2)ArC(2,5)H), 126.5 (C(5)NHCH₂ArC(2,6)H), 126.5 (C(1)NHCH₂ArC(2,6)H), 127.1 (C(5)NHCH₂ArC(3,5)H), 127.4 (C(3)ArC(2,6)H), 127.8 (C(1)NHCH₂ArC(3,5)H), 127.9 (C(5)NHCH₂ArC(4)H), 128.4 (C(3)ArC(3,5)H), 130.1 (C(1)NHCH₂ArC(4)H), 131.2 (C(3)ArC(4)), 138.7 (C(1)NHCH₂ArC(1)), 138.7 (C(3)ArC(1)), 139.2 (C(5)NHCH₂ArC(1)), 168.7 (C(1)), 169.3 (C(5)); HRMS (NSI⁺) C₂₉H₂₉N₃O₂³⁵Cl [M+H]⁺ found 486.1938, requires 486.1943 (−1.0 ppm).

Dimethyl (2*S*,3*S*)-3-(4-bromophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (189) and dimethyl (2*R*,3*S*)-3-(4-bromophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (481)



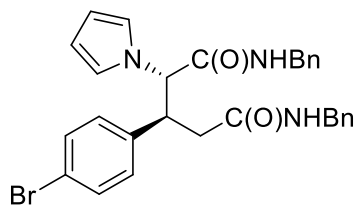
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **469** (82.1 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at −40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (89:11 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*S*)-**189** (62.6 mg, 66%) as a yellow oil. $[\alpha]_D^{20} - 27.7$ (c 1.1 in CHCl₃); Chiral HPLC analysis, Chiralpak OJ-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin^{−1}, 211 nm, 30 °C) t_R (major): 28.8 min, t_R (minor): 51.9 min, 99.5:0.5 er; ν_{\max} (film, cm^{−1}) 2953 (C-H), 1736 (C=O), 1489; ¹H NMR (500 MHz, CDCl₃) δ_H : 2.71–2.72 (2H, m, C(4)H^AH^B), 3.59 (3H, s, C(5)COOCH₃), 3.76 (3H, s, C(1)COOCH₃), 3.94 (1H, dt, *J* 9.5, 7.3, C(3)H), 4.82 (1H, d, *J* 9.5, C(2)H), 6.00 (2H, t, *J* 2.2, C(2)Ar(3,4)H), 6.52 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 6.90–6.93 (2H, m, C(3)ArC(2,6)H), 7.30–7.33 (2H, m, C(3)ArC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_c : 36.9 (C(4)H₂), 44.7 (C(3)H), 52.1 (C(5)COOCH₃), 52.9 (C(1)COOCH₃), 65.9 (C(2)H), 108.7 (C(2)ArC(3,4)H), 120.7 (C(2)ArC(2,5)H), 121.6 (C(3)ArC(4)), 129.6 (C(3)ArC(2,6)H), 131.6 (C(3)ArC(3,5)H), 137.5 (C(3)ArC(1)), 169.7

(C(1)), 171.3 (C(5)); HRMS (ASAP⁺) C₁₇H₁₉⁷⁹BrNO₄ [M+H]⁺ found 380.0496, requires 380.0497 (-0.3 ppm);

(2*R*,3*S*)-**481** (7.7 mg, 8%) as a light-yellow solid. mp 106–108 °C; [α]_D²⁰ – 11.1 (c 0.15 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 24.2 min, t_R (minor): 21.5 min, 92:8 er; v_{max} (film, cm⁻¹) 2953 (C-H), 1732 (C=O), 1487, 1435; ¹H NMR (400 MHz, CDCl₃) δ _H: 2.26 (1H, dd, *J* 16.0, 4.1, C(4)H^AH^B), 2.48 (1H, dd, *J* 16.0, 10.4, C(4)H^AH^B), 3.48 (3H, s, C(1)OOCH₃), 3.48 (3H, s, C(5)OOCH₃), 3.93 (1H, td, *J* 10.8, 4.1, C(3)H), 4.74 (1H, d, *J* 11.2, C(2)H), 6.21 (2H, t, *J* 2.2, C(2)Ar(3,4)H), 6.85 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 7.13–7.16 (2H, m, C(3)ArC(2,6)H), 7.43–7.46 (2H, m, C(3)ArC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ _C: 36.5 (C(4)H₂), 45.1 (C(3)H), 51.9 (C(5)COOCH₃), 52.6 (C(1)COOCH₃), 66.0 (C(2)H), 109.6 (C(2)ArC(3,4)H), 120.5 (C(2)ArC(2,5)H), 121.9 (C(3)ArC(4)), 130.0 (C(3)ArC(2,6)H), 132.0 (C(3)ArC(3,5)H), 137.6 (C(3)ArC(1)), 169.3 (C(1)), 171.5 (C(5)); HRMS (NSI⁺) C₁₇H₁₉⁷⁹BrNO₄ [M+H]⁺ found 380.0495, requires 380.0492 (+0.8 ppm).

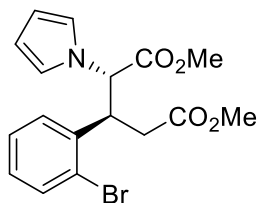
(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-3-(4-bromophenyl)-2-(1*H*-pyrrol-1-yl)pentanediamide (190)



Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **469** (82.1 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95:5 dr) that was triturated in Et₂O to give **190** (99.5 mg, 75%) as a white solid. mp 243–244 °C (dec); [α]_D²⁰ – 5.2 (c 0.27 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 28.3 min, t_R (minor): 24.7 min, 99.5:0.5 er; v_{max} (film, cm⁻¹) 3279 (N-H), 3090 (C-H), 1637 (C=O); ¹H NMR (500 MHz, DMSO) δ _H: 2.38 (1H, dd, *J* 13.9, 3.7, C(4)H^AH^B), 2.58 (1H, dd, *J* 13.9, 11.6, C(4)H^AH^B), 3.89–3.96 (2H, m, C(3)H + C(5)NHCH^AH^BPh), 4.25–4.31 (2H, m, C(5)NHCH^AH^BPh + C(1)NHCH^AH^BPh), 4.40 (1H, dd, *J* 15.0, 5.9, C(1)NHCH^AH^BPh), 4.94 (1H, d, *J* 11.3, C(2)H), 5.79

(2H, t, J 2.2, C(2)Ar(3,4)H), 6.65–6.68 (4H, m, C(2)Ar(2,5)H + C(1)NHCH₂ArC(2,6)H), 7.07–7.10 (2H, m, C(3)ArC(2,6)H), 7.14–7.16 (3H, m, C(1)NHCH₂ArC(3,4,5)H), 7.21–7.23 (2H, m, C(5)NHCH₂ArC(2,6)H), 7.24–7.27 (1H, m, C(5)NHCH₂ArC(4)H), 7.30–7.33 (2H, m, C(5)NHCH₂ArC(3,5)H), 7.34–7.36 (2H, m, C(3)ArC(3,5)H), 8.26–8.28 (1H, m, C(5)NH), 8.90 (1H, t, J 5.8, C(1)NH); ¹³C{¹H} NMR (126 MHz, DMSO): 38.6 (C(4)H₂), 41.6 (C(5)NHCH₂), 42.3 (C(1)NHCH₂), 44.4 (C(3)H), 65.5 (C(2)H), 107.5 (C(2)ArC(3,4)H), 119.8 (C(2)ArC(2)H), 119.9 (C(2)ArC(5)H), 126.5 (C(1)NHCH₂ArC(4)H), 126.5 (C(1)NHCH₂ArC(2,6)H), 127.1 (C(5)NHCH₂ArC(4)H), 127.4 (C(5)NHCH₂ArC(2,6)H), 128.0 (C(1)NHCH₂ArC(3,5)H), 128.4 (C(5)NHCH₂ArC(3,5)H), 130.5 (C(3)ArC(2,6)H), 130.8 (C(3)ArC(3,5)H), 138.7 (C(5)NHCH₂ArC(1)), 139.1 (C(1)NHCH₂ArC(1) + C(3)ArC(1)), 139.2 (C(3)ArC(4)), 168.6 (C(1)), 169.3 (C(5)); HRMS (NSI⁺) C₂₉H₂₉N₃O₂⁷⁹Br [M+H]⁺ found 530.1435, requires 530.1438 (–0.5 ppm).

Dimethyl (2*S*,3*S*)-3-(2-bromophenyl)-2-(1*H*-pyrrol-1-yl)pentanedioate (**191**)

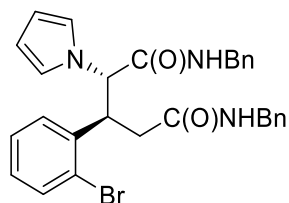


Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **471** (82.1 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (91:9 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 80:20) to give:

(2*S*,3*S*)-**191** (61.8 mg, 65%) as a light-yellow oil. $[\alpha]_{\text{D}}^{20}$ – 23.2 (c 0.44 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin^{–1}, 211 nm, 30 °C) t_{R} (major): 16.5 min, t_{R} (minor): 8.5 min, 98.5:1.5 er; ν_{max} (film, cm^{–1}) 2951 (C–H), 1734 (C=O), 1435; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.79–2.86 (2H, m, C(4)H^AH^B), 3.57 (3H, s, C(5)COOCH₃), 3.73 (3H, s, C(1)COOCH₃), 4.54 (1H, app. s, C(3)H), 5.12 (1H, app. s, C(2)H), 6.00 (2H, app. s, C(2)Ar(3,4)H), 6.71 (2H, t, J 2.2, C(2)Ar(2,5)H), 7.01–7.05 (1H, m, C(3)ArC(4)H), 7.12–7.18 (2H, m, C(3)ArC(5,6)H), 7.46–7.48 (1H, m, C(3)ArC(3)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 36.4 (C(4)H₂),

43.2 (C(3)H), 51.8 (C(5)COOCH₃), 52.7 (C(1)COOCH₃), 64.2 (C(2)H), 108.6 (C(2)ArC(3,4)H), 120.5 (C(2)ArC(2,5)H), 127.4 (C(3)ArC(5,6)H), 127.7 (C(3)ArC(2)), 128.9 (C(3)ArC(4)H), 133.4 (C(3)ArC(3)H), 137.4 (C(3)ArC(1)), 169.6 (C(1)), 171.2 (C(5)); HRMS (ASAP⁺) C₁₇H₁₉NO₄⁷⁹Br [M+H]⁺ found 380.0497, requires 380.0497 (0.0 ppm).

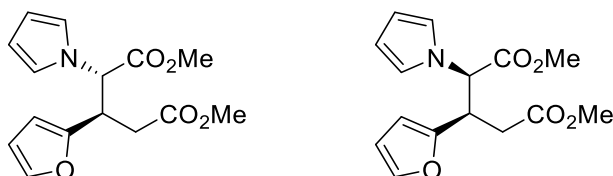
(2S,3S)-N¹,N⁵-Dibenzyl-3-(2-bromophenyl)-2-(1H-pyrrol-1-yl)pentanediamide (192)



Following General Procedure E, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **471** (82.1 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95:5 dr) that was triturated in ether to give **192** (99.5 mg, 75%) as a white solid. mp 196–197 °C; [α]_D²⁰ + 3.6 (c 0.28 in DMSO); Chiral HPLC analysis, Chiralpak AS-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 17.6 min, t_R (minor): 8.1 min, >99.5:0.5 er; ν_{max} (film, cm⁻¹) 3289 (N-H), 3061 (C-H), 1641 (C=O), 1557; ¹H NMR (500 MHz, DMSO) δ_H: 2.43–2.46 (1H, m, C(4)H^AH^B), 2.66–2.70 (1H, m, C(4)H^AH^B), 3.99 (1H, dd, *J* 15.4, 5.4, C(5)NHCH^AH^BPh), 4.17–4.25 (2H, m, C(5)NHCH^AH^BPh + C(1)NHCH^AH^BPh), 4.38 (1H, dd, *J* 15.1, 6.1, C(1)NHCH^AH^BPh), 4.44–4.47 (1H, m, C(3)H), 5.21 (1H, d, *J* 10.4, C(2)H), 5.80 (2H, app. s, C(2)Ar(3,4)H), 6.70 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 6.77–6.79 (2H, m, C(1)NHCH₂ArC(2,6)H), 7.07–7.10 (1H, m, C(3)ArC(4)H), 7.13–7.17 (5H, m, C(5)NHCH₂ArC(2,3,4,5,6)H), 7.22–7.29 (4H, m, C(3)ArC(5,6)H + C(1)NHCH₂ArC(3,5)H), 7.40 (1H, d, *J* 7.7, C(1)NHCH₂ArC(4)H), 7.44 (1H, dd, *J* 8.0, 1.3, C(3)ArC(3)H), 8.25 (1H, t, *J* 6.0, C(5)NH), 8.92 (1H, app. s, C(1)NH); ¹³C{¹H} NMR (126 MHz, DMSO) δ_C: 37.9 (C(4)H₂), 41.8 (C(5)NHCH₂), 42.4 (C(1)NHCH₂), 43.1 (C(3)H), 64.6 (C(2)H), 107.5 (C(2)ArC(3,4)H), 120.0 (C(2)ArC(2,5)H), 125.8 (C(1)NHCH₂ArC(2,6)H), 126.6 (C(3)ArC(3)H), 126.8 (C(1)NHCH₂ArC(3,5)H), 127.1 (C(3)ArC(4)H), 127.4 (C(3)ArC(5)H), 127.5 (C(3)ArC(6)H), 128.2 (C(5)NHCH₂ArC(2,6)H), 128.5 (C(5)NHCH₂ArC(3,5)H), 128.5 (C(5)NHCH₂ArC(4)H + C(1)NHCH₂ArC(4)H), 128.7 (C(3)ArC(1)), 132.8 (C(3)ArC(2)), 138.8

(C(1)NHCH₂ArC(1)), 139.2 (C(5)NHCH₂ArC(1)), 168.6 (C(1)), 169.3 (C(5)); HRMS (NSI⁺) C₂₉H₂₉N₃O₂⁷⁹Br [M+H]⁺ found 530.1431, requires 530.1438 (−1.3 ppm).

Dimethyl (2*S*,3*R*)-3-(furan-2-yl)-2-(1*H*-pyrrol-1-yl)pentanedioate (193) and dimethyl (2*R*,3*R*)-3-(furan-2-yl)-2-(1*H*-pyrrol-1-yl)pentanedioate (482)



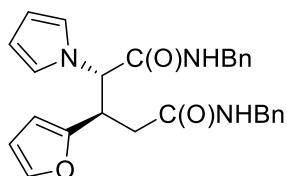
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **473** (60.0 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at −40 °C for 40 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (83:17 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*R*)-**193** (59.2 mg, 81%) as a yellow solid. mp. 65–66 °C; [α]_D²⁰ + 13.0 (c 0.1 in CHCl₃); Chiral HPLC analysis, Chiralpak OJ-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin^{−1}, 211 nm, 30 °C) t_R (major): 33.6 min, t_R (minor): 46.9 min, 99:1 er; ν_{max} (film, cm^{−1}) 2953 (C-H), 1734 (C=O), 1437; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.53 (1H, dd, *J* 16.4, 7.0, C(4)*H*^A*H*^B), 2.74 (1H, dd, *J* 16.4, 7.6, C(4)*H*^A*H*^B), 3.67 (3H, s, C(5)COOCH₃), 3.79 (3H, s, C(1)COOCH₃), 4.16 (1H, q, *J* 7.3, C(3)*H*), 5.05 (1H, d, *J* 7.3, C(2)*H*), 5.94 (1H, dt, *J* 3.3, 0.8, C(3)ArC(3)*H*), 6.07 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.23 (1H, dd, *J* 3.3, 1.8, C(3)ArC(4)*H*), 6.44 (2H, t, *J* 2.2, C(2)Ar(2,5)*H*), 7.31 (1H, dd, *J* 1.9, 0.8, C(3)ArC(5)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 34.3 (C(4)H₂), 39.0 (C(3)*H*), 52.1 (C(5)COOCH₃), 52.8 (C(1)COOCH₃), 63.9 (C(2)*H*), 108.3 (C(3)ArC(3)*H*), 108.6 (C(2)ArC(3,4)*H*), 110.6 (C(3)ArC(4)*H*), 121.1 (C(2)ArC(2,5)*H*), 142.1 (C(3)ArC(5)*H*), 151.7 (C(3)ArC(2)), 169.8 (C(1)), 171.7 (C(5)); HRMS (NSI⁺) C₁₅H₁₈NO₅ [M+H]⁺ found 292.1181, requires 292.1179 (+0.5 ppm).

(2*R*,3*R*)-**482** (12.1 mg, 17%) as a yellow oil. [α]_D²⁰ − 5.0 (c 0.2 in CHCl₃); Chiral HPLC analysis, Chiralpak OJ-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin^{−1}, 211 nm, 30 °C) t_R (major): 21.7 min, t_R (minor): 40.6 min, 85:15 er; ν_{max} (film, cm^{−1}) 2953 (C-H), 1740 (C=O); ¹H NMR (400 MHz, CDCl₃) δ_H: 2.24 (1H, dd, *J* 16.0, 4.1, C(4)*H*^A*H*^B), 2.53 (1H, dd, *J* 16.0, 9.7, C(4)*H*^A*H*^B), 3.55 (3H, s,

C(5)COOCH₃), 3.60 (3H, s, C(1)COOCH₃), 4.06–4.11 (1H, m, C(3)H), 4.89 (1H, d, *J* 10.9, C(2)H), 6.18 (1H, d, *J* 3.3, C(3)ArC(3)H), 6.19 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 6.29 (1H, dd, *J* 3.2, 1.9, C(3)ArC(4)H), 6.82 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 7.35–7.36 (1H, m, C(3)ArC(5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_c: 34.4 (C(4)H₂), 39.5 (C(3)H), 51.9 (C(5)COOCH₃), 52.7 (C(1)COOCH₃), 64.2 (C(2)H), 108.1 (C(3)ArC(3)H), 109.5 (C(2)ArC(3,4)H), 110.6 (C(3)ArC(4)H), 120.5 (C(2)ArC(2,5)H), 142.5 (C(3)ArC(5)H), 151.6 (C(3)ArC(2)), 169.7 (C(1)), 171.6 (C(5)); HRMS (NSI⁺) C₁₅H₁₈NO₅ [M+H]⁺ found 292.1183, requires 292.1179 (+1.2 ppm).

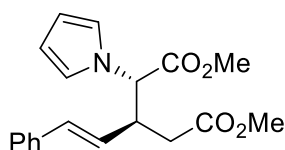
(2*S*,3*R*)-N¹,N⁵-Dibenzyl-3-(furan-2-yl)-2-(1*H*-pyrrol-1-yl)pentanediamide (194)



Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **473** (60.0 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 40 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (90:10 dr) that was purified by column chromatography (hexane/EtOAc 50:50) to give **194** (60.0 mg, 64%) as a white solid. mp 186–188 °C; [α]_D²⁰ –12.5 (c 0.16 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 23.2 min, t_R (minor): 19.0 min, 99.5:0.5 er; ν_{max} (film, cm⁻¹) 3327 (N-H), 3275 (N-H), 3088 (C-H), 1643 (C=O), 1553; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.48 (1H, dd, *J* 14.8, 6.9, C(4)H^AH^B), 2.65 (1H, dd, *J* 14.8, 6.8, C(4)H^AH^B), 4.30 (1H, dd, *J* 14.9, 5.3, C(1)NHCH^AH^BPh), 4.35 (2H, d, *J* 5.7, C(5)NHCH₂Ph), 4.38–4.48 (2H, m, C(1)NHCH^AH^BPh + C(3)H), 5.13 (1H, d, *J* 7.1, C(2)H), 5.91–5.95 (1H, m, C(5)NH), 5.99 (1H, d, *J* 3.2, C(3)ArC(3)H), 6.07 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 6.23 (1H, dd, *J* 3.2, 1.8, C(3)ArC(4)H), 6.37–6.41 (3H, m, C(2)Ar(2,5)H + C(1)NH), 7.14–7.16 (4H, m, C(1)NHCH₂ArC(2,6)H + C(5)NHCH₂ArC(2,6)H), 7.21 (1H, dd, *J* 1.8, 0.8, C(3)ArC(5)H), 7.22–7.32 (6H, m, C(1)NHCH₂ArC(3,4,5)H + C(5)NHCH₂ArC(3,4,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_c: 36.6 (C(4)H₂), 38.4 (C(3)H), 43.6 (C(1)NHCH₂), 43.7 (C(5)NHCH₂), 65.4 (C(2)H), 108.5 (C(3)ArC(3)H), 109.2 (C(2)ArC(3,4)H), 110.9 (C(3)ArC(4)H), 121.1

(C(2)ArC(2,5)H), 127.5 (C(1)NHCH₂ArC(2,6)H), 127.6 (C(5)NHCH₂ArC(2,6)H), 127.8 (C(1)NHCH₂ArC(4)H + C(5)NHCH₂ArC(4)H), 128.7 (C(1)NHCH₂ArC(3,5)H), 128.8 (C(5)NHCH₂ArC(3,5)H), 137.8 (C(1)NHCH₂ArC(1)), 138.0 (C(5)NHCH₂ArC(1)), 141.5 (C(3)ArC(5)H), 152.4 (C(3)ArC(1)), 169.3 (C(1)), 170.5 (C(5)); HRMS (NSI⁺) C₂₇H₂₈N₃O₃ [M+H]⁺ found 442.2123, requires 442.2125 (−0.5 ppm).

Dimethyl (2*S*,3*S*)-2-(1*H*-pyrrol-1-yl)-3-((*E*-styryl)pentanedioate (195)



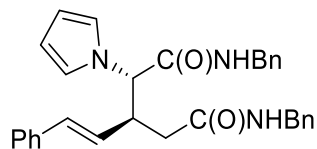
Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **475** (68.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at −40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (85:15 dr) that was purified by column chromatography (Petrol/EtOAc 85:15) to give:

(2*S*,3*S*)-**195** (50.0 mg, 61%) as a yellow oil. $[\alpha]_{\text{D}}^{20} + 11.1$ (c 0.67 in CHCl₃); Chiral HPLC analysis, Chiralpak OJ-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin^{−1}, 220 nm, 30 °C) *t*_R (major): 27.5 min, *t*_R (minor): 47.4 min, 99.5:0.5 er; *v*_{max} (film, cm^{−1}) 2953 (C-H), 1732 (C=O), 1487 (C=C); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.41 (1H, dd, *J* 16.2, 6.8, C(4)*H*^A*H*^B), 2.48 (1H, dd, *J* 16.1, 7.0, C(4)*H*^A*H*^B), 3.56–3.63 (1H, m, C(3)*H*), 3.71 (3H, s, C(5)COOCH₃), 3.79 (3H, s, C(1)COOCH₃), 4.97 (1H, d, *J* 7.2, C(2)*H*), 5.97 (1H, dd, *J* 15.8, 8.8, ArCH=CH), 6.18 (2H, t, *J* 2.2, C(2)Ar(3,4)*H*), 6.41 (1H, d, *J* 15.9, ArCH=CH), 6.77 (2H, t, *J* 2.2, C(2)Ar(2,5)*H*), 7.24–7.33 (5H, m, Ar*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 35.9 (C(4)H₂), 42.7 (C(3)*H*), 52.0 (C(5)COOCH₃), 52.7 (C(1)COOCH₃), 64.7 (C(2)*H*), 108.8 (C(2)ArC(3,4)*H*), 121.4 (C(2)ArC(2,5)*H*), 126.3 (ArCH=CH), 126.5 (ArC(2,6)*H*), 127.9 (ArC(3,5)*H*), 128.6 (ArC(4)*H*), 133.5 (ArCH=CH), 136.8 (ArC(1)), 169.9 (C(1)), 172.0 (C(5)); HRMS (NSI⁺) C₁₉H₂₁NO₄ [M+H]⁺ found 328.1548, requires 328.1543 (+1.4 ppm).

Selected data for minor diastereoisomer (2*R*,3*S*): ¹H NMR (500 MHz, CDCl₃) δ_H: 2.22 (2H, dd, *J* 6.3, 3.5, C(4)*H*^A*H*^B), 3.44–3.55 (1H, m, C(3)*H*), 3.62 (3H, s, C(5)COOCH₃), 3.66 (3H, s, C(1)COOCH₃), 4.75 (1H, d, *J* 10.8, C(2)*H*), 6.07 (1H, dd, *J* 15.8, 9.2, ArCH=CH), 6.22 (2H, t, *J* 2.1,

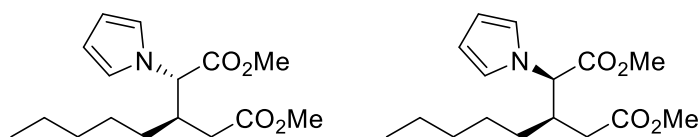
C(2)Ar(3,4)H), 6.61 (1H, d, *J* 15.9, ArCH=CH), 6.87 (2H, t, *J* 2.1, C(2)Ar(2,5)H), 7.31–7.44 (5H, m, ArH).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-2-(1*H*-pyrrol-1-yl)-3-((*E*)-styryl)pentanediamide (196)



Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **475** (68.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (hexane/EtOAc 40:60) to give **196** (71.6 mg, 60%) as a white solid. mp 168–170 °C; [α]_D²⁰ –24.8 (c 0.21 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin^{–1}, 254 nm, 30 °C) t_R (major): 15.5 min, t_R (minor): 19.7 min, >99.5:0.5 er; ν_{max} (film, cm^{–1}) 3277 (N-H), 3059 (C-H), 3028 (C-H), 1672 (C=C), 1637 (C=O), 1541; ¹H NMR (400 MHz, CDCl₃) δ_H: 2.30 (1H, dd, *J* 14.7, 6.8, C(4)H^AH^B), 2.46 (1H, dd, *J* 14.7, 6.0, C(4)H^AH^B), 3.78–3.83 (1H, m, C(3)H), 4.34 (1H, dd, *J* 14.9, 5.7, C(1)NHCH^AH^BPh), 4.39–4.48 (2H, m, C(5)NHCH₂Ph), 4.51 (1H, dd, *J* 14.9, 6.3, C(1)NHCH^AH^BPh), 5.07 (1H, d, *J* 7.0, C(2)H), 5.87 (1H, t, *J* 5.8, C(5)NH), 6.09 (1H, dd, *J* 16.0, 8.3, C(3)CH=CHPh), 6.16 (2H, t, *J* 2.2, C(2)Ar(3,4)H), 6.34 (1H, t, *J* 6.0, C(1)NH), 6.46 (1H, d, *J* 15.9, C(3)CH=CHPh), 6.75 (2H, t, *J* 2.1, C(2)Ar(2,5)H), 7.16–7.19 (2H, m, C(3)CH=CHArC(2,6)H), 7.20–7.32 (13H, m, C(3)CH=CHArC(3,4,5)H + C(1)NHCH₂ArCH + C(5)NHCH₂ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 38.3 (C(4)H₂), 42.1 (C(3)H), 43.6 (C(1)NHCH₂), 43.7 (C(5)NHCH₂), 65.8 (C(2)H), 109.5 (C(2)ArC(3,4)H), 121.4 (C(2)ArC(2,5)H), 126.5 (ArCH), 127.2 (C(3)CH=CHPh), 127.6 (C(3)CH=CHArC(2,6)H), 127.7 (ArCH), 127.8 (ArCH), 127.9 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 128.9 (ArCH), 133.4 (C(3)CH=CHPh), 136.9 (C(3)CH=CHArC(1)), 137.9 (C(1)NHCH₂ArC(1)), 138.1 (C(5)NHCH₂ArC(1)), 169.5 (C(1)), 170.7 (C(5)); HRMS (NSI⁺) C₃₁H₃₂N₃O₂ [M+H]⁺ found 478.2482, requires 478.2489 (–1.5 ppm).

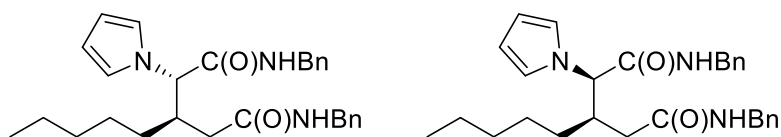
Dimethyl (2*S*,3*R*)-3-pentyl-2-(1*H*-pyrrol-1-yl)pentanedioate (197) and dimethyl (2*R*,3*R*)-3-pentyl-2-(1*H*-pyrrol-1-yl)pentanedioate (483)



Following General Procedure D, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (33.4 mg, 0.267 mmol), *i*-Pr₂NEt (0.092 mL, 0.534 mmol), pivaloyl chloride (0.066 mL, 0.534 mmol) in MeCN (2.7 mL) at 0 °C for 20 min followed by HyperBTM **93** (8.2 mg, 10 mol%), CCl₃ enone **477** (65.0 mg, 0.267 mmol) and *i*-Pr₂NEt (0.12 mL, 0.668 mmol) at -40 °C for 40 h. Ring-opening with MeOH (2.7 mL) and DMAP (6.5 mg, 20 mol%) at rt for 24 h gave crude product (51:49 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*R*)-**197** (37 mg, 47%) as a yellow oil. $[\alpha]_D^{20} - 6.4$ (c 0.5 in CHCl₃); ν_{\max} (film, cm⁻¹) 2953 (C-H), 2932 (C-H), 2859 (C-H), 1736 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H : 0.84 (3H, t, *J* 7.0, CH₃), 1.10–1.38 (8H, m, 4 × CH₂), 2.26 (1H, dd, *J* 16.4, 6.9, C(4)H^AH^B), 2.39 (1H, dd, *J* 16.4, 5.4, C(4)H^AH^B), 2.62–2.69 (1H, m, C(3)H), 3.69 (3H, s, C(5)COOCH₃), 3.73 (3H, s, C(1)COOCH₃), 4.77 (1H, d, *J* 8.7, C(2)H), 6.16 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 6.73 (2H, t, *J* 2.2, C(2)Ar(2,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 14.1 (CH₃), 22.5 (CH₂), 26.1 (CH₂), 29.8 (CH₂), 31.7 (CH₂), 34.6 (C(4)H₂), 38.4 (C(3)H), 51.9 (C(5)COOCH₃), 52.6 (C(1)COOCH₃), 64.6 (C(2)H), 108.7 (C(2)ArC(3,4)H), 121.0 (C(2)ArC(2,5)H), 170.7 (C(1)), 172.7 (C(5)); HRMS (NSI⁺) C₁₆H₂₆NO₄ [M+H]⁺ found 296.1859, requires 296.1856 (+0.9 ppm).

(2*R*,3*R*)-**483** (37 mg, 47%) as a yellow oil. $[\alpha]_D^{20} + 2.3$ (c 0.13 in CHCl₃); ν_{\max} (film, cm⁻¹) 2953 (C-H), 2930 (C-H), 2860 (C-H), 1736 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H : 0.88 (3H, t, *J* 6.9, CH₃), 1.20–1.39 (8H, m, 4 × CH₂), 1.97 (1H, dd, *J* 16.2, 6.7, C(4)H^AH^B), 2.19 (1H, dd, *J* 16.2, 4.5, C(4)H^AH^B), 2.64–2.71 (1H, m, C(3)H), 3.61 (3H, s, C(5)COOCH₃), 3.73 (3H, s, C(1)COOCH₃), 4.67 (1H, d, *J* 10.4, C(2)H), 6.15 (2H, t, *J* 2.1, C(2)Ar(3,4)H), 6.77 (2H, t, *J* 2.2, C(2)Ar(2,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 14.1 (CH₃), 22.6 (CH₂), 26.1 (CH₂), 30.5 (CH₂), 31.9 (CH₂), 33.4 (C(4)H₂), 38.9 (C(3)H), 51.7 (C(5)COOCH₃), 52.6 (C(1)COOCH₃), 64.7 (C(2)H), 108.9 (C(2)ArC(3,4)H), 120.7 (C(2)ArC(2,5)H), 170.8 (C(1)), 172.6 (C(5)); HRMS (ASAP⁺) C₁₆H₂₆NO₄ [M+H]⁺ found 296.1859, requires 296.1862 (-1.0 ppm).

(2*S*,3*R*)-*N*¹,*N*⁵-Dibenzyl-3-pentyl-2-(1*H*-pyrrol-1-yl)pentanediamide (198) and (2*R*,3*R*)-*N*¹,*N*⁵-dibenzyl-3-pentyl-2-(1*H*-pyrrol-1-yl)pentanediamide (484)

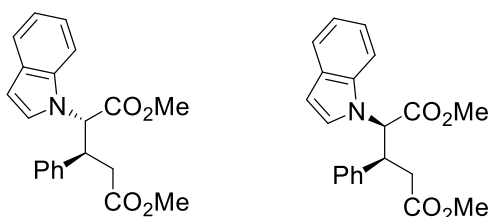
Following General Procedure E, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **477** (60.9 mg, 0.25 mmol) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 40 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product (57:43 dr) that was triturated in ether to give the combined *syn* and *anti* diastereoisomers (70:30 dr) (40.1 mg, 36%) as a yellow solid. mp 133–134 °C; Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (2*S*,3*R*-major): 75.5 min, t_R (2*R*,3*S*-minor): 59.8 min, 99.5:0.5 er; t_R (2*R*,3*R*-major): 107.3 min, t_R (2*S*,3*S*-minor): 125.6 min, 66:34 er; v_{max} (film, cm⁻¹) 3281 (N-H), 3088 (C-H), 2957 (C-H), 2932 (C-H), 2859 (C-H), 1638 (C=O), 1553.

(2*S*,3*R*)-**198**: ¹H NMR (500 MHz, CDCl₃) δ_H: 0.82 (3H, t, *J* 7.0, CH₃), 1.09–1.47 (8H, m, 4 × CH₂), 2.19 (1H, dd, *J* 15.1, 6.3, C(4)H^AH^B), 2.36 (1H, dd, *J* 15.0, 4.2, C(4)H^AH^B), 2.61–2.67 (1H, m, C(3)H), 4.31–4.47 (4H, m, C(5)NHCH₂Ph + C(1)NHCH₂Ph), 4.84 (1H, d, *J* 9.2, C(2)H), 6.09–6.13 (1H, m, C(1)NH), 6.16–6.17 (2H, t, *J* 1.9, C(2)Ar(3,4)H), 6.56 (1H, t, *J* 6.1, C(5)NH), 6.76 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 7.16–7.36 (10H, m, C(1)NHCH₂ArCH + C(5)NHCH₂ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 14.0 (CH₃), 22.5 (CH₂), 26.9 (CH₂), 29.9 (CH₂), 31.7 (CH₂), 36.2 (C(4)H₂), 38.8 (C(3)H), 43.5 (C(1)NHCH₂), 43.6 (C(5)NHCH₂), 65.8 (C(2)H), 109.0 (C(2)ArC(3,4)H), 120.8 (C(2)ArC(2,5)H), 127.5 (ArCH), 127.6 (ArCH), 127.8 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 137.9 (C(1)NHCH₂ArC(1)), 138.1 (C(5)NHCH₂ArC(1)), 170.4 (C(1)), 171.5 (C(5)).

(2*R*,3*R*)-**484**: ¹H NMR (500 MHz, CDCl₃) δ_H: 0.86 (1H, t, *J* 6.9, CH₃), 1.09–1.47 (8H, m, 4 × CH₂), 1.95 (1H, dd, *J* 14.7, 6.4, C(4)H^AH^B), 2.30 (1H, dd, *J* 14.7, 4.3, C(4)H^AH^B), 2.70–2.76 (1H, m, C(3)H), 4.31–4.47 (4H, m, C(5)NHCH₂Ph + C(1)NHCH₂Ph), 4.74 (1H, d, *J* 8.0, C(2)H), 5.97 (1H, t, *J* 5.8, C(1)NH), 6.09–6.13 (1H, m, C(5)NH), 6.16–6.17 (2H, t, *J* 1.9, C(2)Ar(3,4)H), 6.74 (2H, t, *J* 2.2, C(2)Ar(2,5)H), 7.16–7.36 (10H, m, C(1)NHCH₂ArCH + C(5)NHCH₂ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 14.1 (CH₃), 26.9 (CH₂), 27.6 (CH₂), 30.7 (CH₂), 31.8 (CH₂), 36.7 (C(4)H₂), 39.2

(C(3)H), 43.5 (C(1)NHCH₂), 43.6 (C(5)NHCH₂), 65.7 (C(2)H), 109.2 (C(2)ArC(3,4)H), 120.9 (C(2)ArC(2,5)H), 127.5 (ArCH), 127.6 (ArCH), 128.7 (ArCH), 128.8 (ArCH), 137.6 (C(1)NHCH₂ArC(1)), 138.3 (C(5)NHCH₂ArC(1)), 170.0 (C(1)), 171.7 (C(5)); HRMS (NSI⁺) C₂₈H₃₆N₃O₂ [M+H]⁺ found 446.2798, requires 446.2802 (−0.9 ppm).

Dimethyl (2*S*,3*S*)-2-(1*H*-indol-1-yl)-3-phenylpentanedioate (226) and dimethyl (2*R*,3*S*)-2-(1*H*-indol-1-yl)-3-phenylpentanedioate (227)

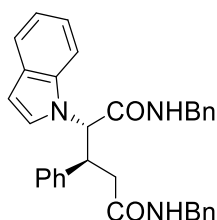


Following General Procedure **D**, 2-(1*H*-indol-1-yl)acetic acid **155** (43.8 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **158** (74.9 mg, 0.3 mmol, 1.2 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at −40 °C for 24 h. Ring-opening with MeOH (2.5 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (80:20 dr) that was purified by column chromatography (Petrol/EtOAc 90:10 to 85:15) to give:

(2*S*,3*S*)-**226** (59.7 mg, 68%) as a light-yellow solid. mp 80–82 °C; [α]_D²⁰ + 36.2 (c 0.6 in CHCl₃); Chiralpak AD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin^{−1}, 211 nm, 30 °C) t_R (major): 16.2 min, t_R (minor): 12.1 min, 95:5 er; ν_{max} (film, cm^{−1}) 3030 (C-H), 3007 (C-H), 2953 (C-H), 1732 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.78–2.86 (2H, m, C(4)H₂), 3.60 (3H, s, C(5)COOCH₃), 3.73 (3H, s, C(1)COOCH₃), 4.20–4.24 (1H, m, C(3)H), 5.42 (1H, d, *J* 9.1, C(2)H), 6.39 (1H, d, *J* 3.2, C(2)Ar(3)H), 7.02–7.15 (8H, m, C(2)Ar(2,5,6)H + C(3)ArCH), 7.26–7.28 (1H, m, C(2)Ar(7)H), 7.50 (1H, dt, *J* 7.8, 1.0, C(2)Ar(4)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 37.4 (C(4)H₂), 44.1 (C(3)H), 52.0 (C(5)COOCH₃), 52.8 (C(1)COOCH₃), 61.8 (C(2)H), 102.6 (C(2)ArC(3)H), 109.1 (C(2)ArC(7)H), 119.9 (C(3)ArCH), 121.0 (C(2)ArC(4)H), 121.8 (C(3)ArCH), 126.9 (C(3)ArCH), 127.7 (C(2)ArC(2)H), 128.0 (C(2)ArC(5)H), 128.3 (C(2)ArC(6)H), 128.5 (C(3)ArCH), 136.6 (C(2)ArC), 138.4 (C(3)ArC(1)), 170.1 (C(1)), 171.8 (C(5)); HRMS (NSI⁺) C₂₁H₂₂NO₄ [M+H]⁺ found 352.1543, requires 352.1543 (−0.1 ppm).

(2*R*,3*S*)-**227** (13.2 mg, 15%) as a colourless oil. $[\alpha]_D^{20} + 8.2$ (c 0.2 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 23.4 min, *t*_R (minor): 15.2 min, 74:26 er; ν_{\max} (film, cm⁻¹) 2988 (C-H), 1731 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.29 (1H, dd, *J* 16.0, 4.4, C(4)*H*^A*H*^B), 2.55 (1H, dd, *J* 16.0, 10.3, C(4)*H*^A*H*^B), 3.39 (3H, s, C(1)COOCH₃), 3.41 (3H, s, C(5)COOCH₃), 4.13–4.18 (1H, m, C(3)*H*), 5.24 (1H, d, *J* 11.3, C(2)*H*), 6.64 (1H, d, *J* 3.3, C(2)Ar(3)*H*), 7.14–7.17 (1H, m, C(2)Ar(2)*H*), 7.25–7.31 (2H, m, C(2)Ar(5)*H* + C(3)ArCH), 7.35–7.37 (4H, m, C(3)ArCH), 7.48 (1H, d, *J* 8.3, C(2)Ar(6)*H*), 7.51 (1H, d, *J* 3.4, C(2)Ar(7)*H*), 7.64 (1H, dt, *J* 7.8, 0.9, C(2)Ar(4)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 36.8 (C(4)*H*₂), 45.0 (C(3)*H*), 51.6 (C(5)COOCH₃), 52.3 (C(1)COOCH₃), 62.2 (C(2)*H*), 103.8 (C(2)ArC(3)*H*), 109.2 (C(2)ArC(7)*H*), 120.3 (C(3)ArCH), 121.2 (C(2)ArC(4)*H*), 122.24 (C(3)ArCH), 125.3 (C(3)ArCH), 127.9 (C(2)ArC(2)*H*), 128.3 (C(2)ArC(5)*H*), 128.8 (C(2)ArC(6)*H*), 136.7 (C(2)ArC), 138.3 (C(3)ArC(1)), 169.4 (C(1)), 171.5 (C(5)).

(2*S*,3*S*)-*N*¹,*N*⁵-Dibenzyl-2-(1*H*-indol-1-yl)-3-phenylpentanediamide (228**)**

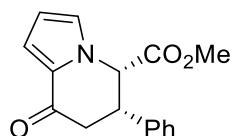


Following General Procedure E, 2-(1*H*-indol-1-yl)acetic acid **155** (43.8 mg, 0.25 mmol), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), CCl₃ enone **158** (74.9 mg, 0.3 mmol, 1.2 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with BnNH₂ (2.5 mL) at rt for 24 h gave crude product that was triturated in ether to give **228** (80.3 mg, 64%) as a white solid. mp 189–190 °C. $[\alpha]_D^{20} + 7.9$ (c 0.2 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) *t*_R (major): 17.7 min, *t*_R (minor): 8.5 min, 97:3 er; ν_{\max} (film, cm⁻¹) 3277 (N-H), 3086 (C-H), 3063 (C-H), 1672 (C=O), 1636 (C=O), 1557 (Ar C=C), 1454 (Ar C=C); ¹H NMR (500 MHz, DMSO) δ_{H} : 2.49 (1H, d, *J* 12.1, C(4)*H*^A*H*^B), 2.71 (1H, dd, *J* 13.8, 11.6, C(4)*H*^A*H*^B), 3.93 (1H, dd, *J* 15.6, 5.0, C(5)NHCH^A*H*^BPh), 4.16 (1H, td, *J* 11.4, 3.5, C(3)*H*), 4.24 (2H, td, *J* 15.4, 14.7, 6.1, C(1)NHCH^A*H*^BPh + C(5)NHCH^A*H*^BPh), 4.41 (1H, dd, *J* 15.0, 6.0, C(1)NHCH^A*H*^BPh), 5.49 (1H, d, *J* 11.3, C(2)*H*), 6.29 (1H, d, *J* 3.3, C(2)Ar(3)*H*), 6.65–6.67 (2H,

m, C(1)NHCH₂ArC(2,6)H), 6.90 (1H, t, *J* 7.4, C(2)Ar(2)H), 7.00–7.12 (7H, m, C(1)NHCH₂ArC(3,4,5)H + C(2)Ar(4,5)H + C(5)NHCH₂ArC(2,6)H), 7.19–7.30 (7H, m, C(5)NHCH₂ArC(3,4,5)H + C(3)ArC(2,6,3,5)H), 7.36 (1H, d, *J* 7.8, C(3)ArC(4)H), 7.55 (1H, d, *J* 8.4, C(2)Ar(6)H), 7.59 (1H, d, *J* 3.4, C(2)Ar(7)H), 8.25–8.27 (1H, m, C(5)NH), 9.05 (1H, t, *J* 5.7, C(1)NH); ¹³C{¹H} NMR (126 MHz, DMSO) δ_C: 40.0 (C(4)H₂), 41.6 (C(5)NHCH₂), 42.5 (C(1)NHCH₂), 44.2 (C(3)H), 61.9 (C(2)H), 101.3 (C(2)ArC(3)H), 109.7 (C(2)ArC(6)H), 119.0 (C(2)ArC(2)H), 120.1 (C(2)ArC(5)H), 120.8 (C(2)ArC(7)H), 126.4 (C(2)ArC(4)H), 126.6 (C(3)ArC(4)H), 126.6 (C(3)ArC(3,5)H), 126.7 (C(3)ArC(2,6)H), 127.1 (C(1)NHCH₂ArC(2,6)H), 127.5 (C(1)NHCH₂ArC(4)H), 127.6 (C(1)NHCH₂ArC(3,5)H), 127.8 (C(5)NHCH₂ArC(4)H), 128.0 (C(5)NHCH₂ArC(3,5)H), 128.2 (C(5)NHCH₂ArC(2)H), 128.4 (C(5)NHCH₂ArC(6)H), 136.1 (C(3)ArC(1)), 138.6 (C(2)ArC), 139.1 (C(1)NHCH₂ArC(1)), 139.6 (C(5)NHCH₂ArC(1)), 168.7 (C(1)), 169.4 (C(5)); HRMS (NSI⁺) C₃₃H₃₂N₃O₂ [M+H]⁺ found 502.2484, requires 502.2489 (−1.0 ppm).

8.3.4. Friedel-Crafts Acylation Compound Data

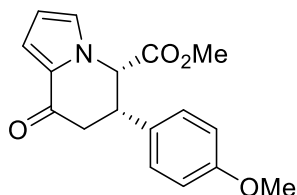
Methyl (5*S*,6*S*)-8-oxo-6-phenyl-5,6,7,8-tetrahydroindolizine-5-carboxylate (**206**)



Following General Procedure F, **167** (50.0 mg, 0.166 mmol), anhydrous CH₂Cl₂ (3.5 mL) and BBr₃ (0.18 mL, 1.1 equiv, 1 M in CH₂Cl₂) gave, after flash column chromatography (petrol/EtOAc 60:40, R_f 0.55), **206** (33.5 mg, 0.125 mmol, 75%) as a yellow solid. mp 109–110 °C. [α]_D²⁰ + 347.7 (c 0.55 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 13.8 min, t_R (minor): 29.8 min, >99.5 :0.5 er; ν_{max} (film, cm⁻¹) 3111 (C-H), 3057 (C-H), 2953 (C-H), 1736 (C=O), 1655 (C=O), 1533 (Ar); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.80 (1H, dd, *J* 17.1, 4.0, C(7)H^AH^B), 3.45–3.48 (1H, m, C(7)H^AH^B), 3.51 (3H, s, OCH₃), 4.03 (1H, dt, *J* 13.7, 4.7, C(6)H), 5.11 (1H, d, *J* 5.4, C(5)H), 6.39 (1H, dd, *J* 4.1, 2.5, C(2)H), 6.91 (1H, dd, *J* 2.5, 1.5, C(3)H), 7.15 (1H, dd, *J* 4.1, 1.5, C(1)H), 7.26–7.29 (2H, m, C(6)ArC(2,6)H), 7.34–7.38 (1H, m, C(6)ArC(4)H), 7.40–7.43 (2H, m, C(6)ArC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 37.2 (C(7)H₂), 42.8 (C(6)H), 52.4 (OCH₃), 62.0 (C(5)H), 111.7 (C(2)H), 114.7 (C(1)H),

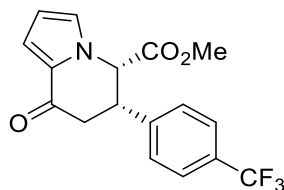
125.4 (C(3)H), 127.5 (C(6)ArC(2,6)H), 128.2 (C(6)ArC(4)H), 129.0 (C(6)ArC(3,5)H), 130.3 (C(1)CN(4)), 137.1 (C(6)ArC(1)), 168.6 (C(5)C=OOMe), 186.3 (C(8)); HRMS (ASAP⁺) C₁₆H₁₆NO₃ [M+H]⁺ found 270.1136, requires 270.1130 (+2.2 ppm).

Methyl (5S,6S)-6-(4-methoxyphenyl)-8-oxo-5,6,7,8-tetrahydroindolizine-5-carboxylate (207)



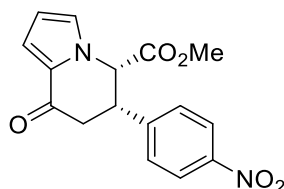
Following General Procedure F, **173** (55.0 mg, 0.166 mmol), anhydrous CH₂Cl₂ (3.5 mL) and BBr₃ (0.18 mL, 1.1 equiv, 1 M in CH₂Cl₂) gave, after flash column chromatography (petrol/EtOAc 60:40, R_f 0.4), **207** (34.8 mg, 0.116 mmol, 70%) as a white solid. mp 121–122 °C. [α]_D²⁰ + 295.0 (c 0.42 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_R (major): 16.2 min, t_R (minor): 26.7 min, 98:2 er; ν_{max} (film, cm⁻¹) 3109 (C-H), 2953 (C-H), 1738 (C=O), 1655 (C=O), 1514 (Ar); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.74 (1H, dd, *J* 17.1, 4.0, C(7)H^AH^B), 3.40 (1H, dd, *J* 17.1, 13.7, C(7)H^AH^B), 3.50 (3H, s, C(5)C=OOCH₃), 3.81 (3H, s, C(6)ArC(4)OCH₃), 3.95 (1H, dt, *J* 13.6, 4.7, C(6)H), 5.04 (1H, d, *J* 5.4, C(5)H), 6.35 (1H, dd, *J* 4.1, 2.5, C(2)H), 6.87 (1H, dd, *J* 2.6, 1.5, C(3)H), 6.89–6.92 (2H, m, C(6)ArC(3,5)H), 7.11 (1H, dd, *J* 4.1, 1.6, C(1)H), 7.15–7.18 (2H, m, C(6)ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 37.6 (C(7)H₂), 42.2 (C(6)H), 52.5 (C(5)C=OOCH₃), 55.4 (C(6)ArC(4)OCH₃), 62.2 (C(5)H), 111.8 (C(2)H), 114.4 (C(6)ArC(3,5)H), 114.7 (C(1)H), 125.5 (C(3)H), 128.6 (C(6)ArC(2,6)H), 129.1 (C(6)ArC(1)), 130.4 (C(1)CN(4)), 159.4 (C(6)ArC(4)), 168.8 (C(5)C=OOMe), 186.5 (C(8)); HRMS (ASAP⁺) C₁₇H₁₈NO₄ [M+H]⁺ found 300.1240, requires 300.1236 (+1.3 ppm).

Methyl (5S,6S)-8-oxo-6-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (208)



Following General Procedure F, **177** (52.1 mg, 0.141 mmol), anhydrous CH_2Cl_2 (2.8 mL) and BBr_3 (0.16 mL, 1.1 equiv, 1 M in CH_2Cl_2) gave, after flash column chromatography (petrol/EtOAc 60:40, R_f 0.51), **208** (41.8 mg, 0.124 mmol, 88%) as a white crystalline solid. mp 136–138 °C. $[\alpha]_{\text{D}}^{20} + 257.2$ (c 0.47 in CHCl_3); Chiral HPLC analysis, Chiralpak OD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_{R} (major): 29.7 min, t_{R} (minor): 49.6 min, 97.5:2.5 er; ν_{max} (film, cm⁻¹) 3117 (C-H), 2957 (C-H), 1742 (C=O), 1661 (C=O), 1325; ¹H NMR (500 MHz, CDCl_3) δ_{H} : 2.79 (1H, ddd, J 17.0, 4.1, 0.7, C(7) $H^A H^B$), 3.44 (1H, dd, J 17.0, 13.5, C(7) $H^A H^B$), 3.50 (3H, s, C(5)C=OOC H_3), 4.07 (1H, dt, J 13.5, 4.7, C(6) H), 5.11 (1H, d, J 5.2, C(5) H), 6.38 (1H, dd, J 4.1, 2.5, C(2) H), 6.91 (1H, dd, J 2.5, 1.5, C(3) H), 7.14 (1H, dd, J 4.1, 1.5, C(1) H), 7.38–7.40 (2H, m, C(6)ArC(2,6) H), 7.65–7.66 (2H, m, C(6)ArC(3,5) H); ¹³C{¹H} NMR (126 MHz, CDCl_3) δ_{C} : 37.2 (C(7) H_2), 42.7 (C(6) H), 52.7 (C(5)C=OOC H_3), 61.7 (C(5) H), 112.0 (C(2) H), 115.2 (C(1) H), 124.0 (q, J 272.1, C(6)ArC(4)CF₃), 125.8 (C(3) H), 126.0 (q, J 3.7, C(6)ArC(3,5) H), 128.1 (C(6)ArC(2,6) H), 130.3 (C(6)ArC(1)), 130.6 (q, J 32.7, C(6)ArC(4)), 141.2 (C(1)CN(4)), 168.3 (C(5)C=OOC H_3), 185.5 (C(8)); ¹⁹F NMR (471 MHz, CDCl_3) δ_{F} : -62.7 (CF₃); HRMS (ASAP⁺) C₁₇H₁₅NO₃F₃ [M+H]⁺ found 338.1006, requires 338.1004 (+0.6 ppm).

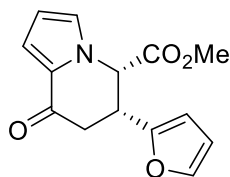
Methyl (5S,6S)-6-(4-nitrophenyl)-8-oxo-5,6,7,8-tetrahydroindolizine-5-carboxylate (209)



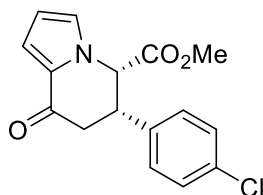
Following General Procedure F, **179** (65.3 mg, 0.189 mmol), anhydrous CH_2Cl_2 (3.8 mL) and BBr_3 (0.21 mL, 1.1 equiv, 1 M in CH_2Cl_2) gave, after flash column chromatography (petrol/EtOAc 60:40, R_f 0.34), **209** (47.4 mg, 0.151 mmol, 80%) as a white crystalline solid. mp 184–186 °C. $[\alpha]_{\text{D}}^{20} + 289.8$ (c 0.44 in CHCl_3); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane/*i*-PrOH,

flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_R (major): 24.9 min, t_R (minor): 22.2 min, 98:2 er; ν_{\max} (film, cm⁻¹) 3113 (C-H), 2955 (C-H), 1742 (C=O), 1661 (C=O), 1520 (N-O), 1348 (N-O); ¹H NMR (500 MHz, CDCl₃) δ_H : 2.82 (1H, dd, J 16.9, 4.1, C(7)H^AH^B), 3.43 (1H, dd, J 16.9, 13.4, C(7)H^AH^B), 3.52 (3H, s, C(5)C=OOCH₃), 4.13 (1H, dt, J 13.4, 4.6, C(6)H), 5.13 (1H, d, J 5.2, C(5)H), 6.39 (1H, dd, J 4.1, 2.5, C(2)H), 6.93 (1H, dd, J 2.6, 1.6, C(3)H), 7.15 (1H, dd, J 4.1, 1.5, C(1)H), 7.44–7.47 (2H, m, C(6)ArC(2,6)H), 8.25–8.27 (2H, m, C(6)ArC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 37.2 (C(7)H₂), 42.7 (C(6)H), 52.8 (C(5)C=OOCH₃), 61.4 (C(5)H), 112.1 (C(2)H), 115.4 (C(1)H), 124.3 (C(6)ArC(3,5)H), 125.9 (C(3)H), 128.8 (C(6)ArC(2,6)H), 130.2 (C(1)CN(4)), 144.5 (C(6)ArC(1)), 147.8 (C(6)ArC(4)), 168.1 (C(5)C=OOMe), 184.9 (C(8)); HRMS (ASAP⁺) C₁₆H₁₅N₂O₅ [M+H]⁺ found 315.0982, requires 315.0981 (+1.3 ppm).

Methyl (5S,6R)-6-(furan-2-yl)-8-oxo-5,6,7,8-tetrahydroindolizine-5-carboxylate (**210**)



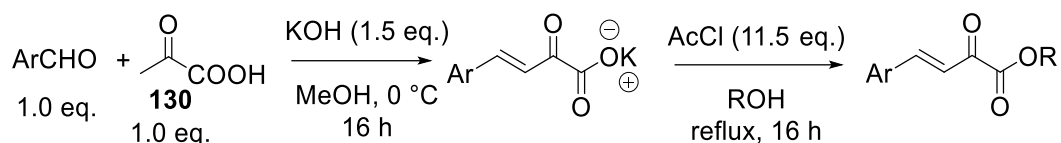
Following General Procedure F, **193** (50.5 mg, 0.173 mmol), anhydrous CH₂Cl₂ (3.5 mL) and BBr₃ (0.19 mL, 1.1 equiv, 1 M in CH₂Cl₂) gave, after flash column chromatography (petrol/EtOAc 60:40, R_f 0.55), **210** (33.6 mg, 0.130 mmol, 75%) as a yellow oil. $[\alpha]_D^{20} + 135.4$ (c 0.13 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 33.3 min, t_R (minor): 27.9 min, 98:2 er; ν_{\max} (film, cm⁻¹) 3121 (C-H), 2955 (C-H), 1744 (C=O), 1655 (C=O), 1535 (Ar); ¹H NMR (500 MHz, CDCl₃) δ_H : 2.84 (1H, dd, J 17.4, 4.4, C(7)H^AH^B), 3.16 (1H, dd, J 17.4, 13.3, C(7)H^AH^B), 3.56 (3H, s, C(5)C=OOCH₃), 4.07 (1H, dt, J 13.3, 4.7, C(6)H), 5.28 (1H, d, J 5.3, C(5)H), 6.17–6.18 (1H, m, C(6)ArC(3)H), 6.35–6.36 (2H, m, C(6)ArC(4)H + C(2)H), 6.90 (1H, dd, J 2.5, 1.5, C(3)H), 7.12 (1H, dd, J 4.1, 1.5, C(1)H), 7.42–7.43 (1H, m, C(6)ArC(5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 36.2 (C(7)H₂), 37.1 (C(6)H), 52.8 (C(5)C=OOCH₃), 59.8 (C(5)H), 107.2 (C(6)ArC(3)H), 110.6 (C(2)H), 111.9 (C(6)ArC(4)H), 115.1 (C(1)H), 126.0 (C(3)H), 130.4 (C(1)CN(4)), 142.8 (C(6)ArC(5)H), 151.2 (C(6)ArC(2)), 168.5 (C(5)C=OOMe), 185.2 (C(8)); HRMS (ASAP⁺) C₁₄H₁₄NO₄ [M+H]⁺ found 260.0926, requires 260.0923 (+1.2 ppm).

Methyl (5S,6S)-6-(4-chlorophenyl)-8-oxo-5,6,7,8-tetrahydroindolizine-5-carboxylate (211)

Following General Procedure F, **187** (53.9 mg, 0.161 mmol), anhydrous CH_2Cl_2 (3.2 mL) and BBr_3 (0.18 mL, 1.1 equiv, 1 M in CH_2Cl_2) gave, after flash column chromatography (petrol/EtOAc 70:30, R_f 0.39), **211** (44.0 mg, 0.145 mmol, 90%) as a white solid. mp 150–152 °C. $[\alpha]_{\text{D}}^{20} + 332.0$ (c 0.2 in CHCl_3); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 15.6 min, t_{R} (minor): 26.9 min, 99:1 er; ν_{max} (film, cm⁻¹) 3121 (C-H), 2955 (C-H), 1736 (C=O), 1655 (C=O), 1535 (Ar); ¹H NMR (500 MHz, CDCl_3) δ_{H} : 2.76 (1H, dd, J 17.0, 3.9, C(7) $H^A H^B$), 3.39 (1H, dd, J 17.0, 13.5, C(7) $H^A H^B$), 3.52 (3H, s, C(5)C=OOC H_3), 3.98 (1H, dt, J 13.6, 4.7, C(6) H), 5.06 (1H, d, J 5.3, C(5) H), 6.37 (1H, dd, J 4.1, 2.5, C(2) H), 6.89 (1H, dd, J 2.6, 1.5, C(3) H), 7.13 (1H, dd, J 4.1, 1.5, C(1) H), 7.18–7.21 (2H, m, C(6)ArC(2,6) H), 7.35–7.38 (2H, m, C(6)ArC(3,5) H); ¹³C{¹H} NMR (126 MHz, CDCl_3) δ_{C} : 37.4 (C(7) H_2), 42.3 (C(6) H), 52.6 (C(5)C=OOC H_3), 61.8 (C(5) H), 111.9 (C(2) H), 115.0 (C(1) H), 125.6 (C(3) H), 129.0 (C(6)ArC(2,6) H), 129.3 (C(6)ArC(3,5) H), 130.3 (C(1)CN(4)), 134.2 (C(6)ArC(4)), 135.7 (C(6)ArC(1)), 168.5 (C(5)C=OOMe), 185.8 (C(8)); HRMS (NSI⁺) $\text{C}_{16}\text{H}_{15}\text{NO}_3^{35}\text{Cl}$ $[\text{M}+\text{H}]^+$ found 304.0738, requires 304.0735 (+1.0 ppm).

8.4. Experimentals for Chapter 4

General Procedure A: Synthesis of α -keto- β,γ -unsaturated ester

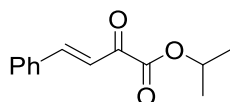


Following literature procedures,¹ to a solution of pyruvic acid **130** (50 mmol, 1.0 eq.) and aromatic aldehyde (50 mmol, 1.0 eq.) in MeOH (5 mL) at 0 °C was added a solution of KOH (75 mmol, 1.5 eq.) in MeOH (15 mL). The first 1 eq. of the KOH solution was added dropwise over 30 minutes. The last 0.5 eq. was added as one portion and the reaction mixture was stirred at 40 °C for 1 h followed by 0 °C for 16 h. The precipitate was collected by filtration, washed twice with cold MeOH, once with Et₂O and dried under vacuum to furnish the potassium salt that was used directly in the next step.

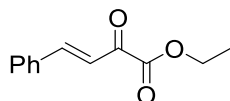
Acetyl chloride (400 mmol, 11.5 eq.) was added to MeOH (200 mL) at 0 °C to generate HCl. Potassium salt obtained from last step was added and the mixture stirred at 0 °C for 30 min then warmed to rt for 2 h before heating at reflux for 16 h. Concentration *in vacuo* gave a sticky solid which was dissolved in H₂O (50 mL) and extracted with CH₂Cl₂ (50 mL x 3). The combined organics were washed with saturated aq. NaHCO₃ (25 mL), H₂O (25 mL) and brine (25 mL) before being dried with MgSO₄. Concentration *in vacuo* afforded the crude reaction mixture which was purified by flash column chromatography (EtOAc/petrol).

All the rest of CF₃ enone starting materials were kindly provided by colleague from Smith group and used as received.

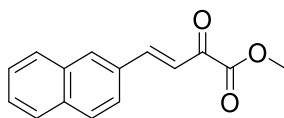
Isopropyl (*E*)-2-oxo-4-phenylbut-3-enoate (**485**)



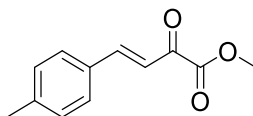
Following **General Procedure A**, the titled compound was obtained as a yellow oil (21% yield over two-step). Spectroscopy data were in accordance with the literature.¹ ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.41 (6H, d, *J* 6.1, CH₃), 5.22 (1H, septet, *J* 6.1, CH), 7.34 (1H, d, *J* 16.2, C(3)*H*), 7.40–7.52 (3H, m, ArCH), 7.62–7.69 (2H, m, ArCH), 7.82 (1H, d, *J* 16.1, C(4)*H*).

Ethyl (E)-2-oxo-4-phenylbut-3-enoate (486)

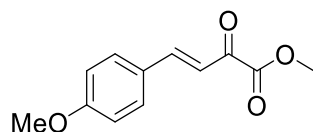
Following **General Procedure A**, the titled compound was obtained as a yellow oil (25% yield over two-step). Spectroscopy data were in accordance with the literature.¹ ¹H NMR (400 MHz, CDCl₃) δ_H: 1.43 (3H, t, *J* 7.2, CH₃), 4.42 (2H, q, *J* 7.1, CH₂), 7.30 (1H, d, *J* 16.1, C(3)*H*), 7.38–7.46 (3H, m, Ar*H*), 7.62–7.69 (2H, m, Ar*H*), 7.83 (1H, d, *J* 16.1, C(4)*H*).

Methyl (E)-4-(naphthalen-2-yl)-2-oxobut-3-enoate (487)

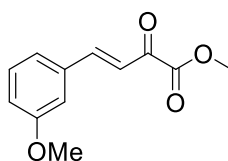
Following **General Procedure A**, the titled compound was obtained as a yellow solid (40% yield over two-step). Spectroscopy data were in accordance with the literature.¹ mp 67-69 °C {Lit.¹ 70-72 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 4.01 (3H, s, CH₃), 7.51 (1H, d, *J* 16.0, C(3)*H*), 7.52–7.61 (2H, m, Ar*CH*), 7.75–7.84 (1H, m, Ar*CH*), 7.87–7.95 (3H, m, Ar*CH*), 8.03–8.12 (2H, m, C(4)*H* and Ar*CH*).

Methyl (E)-2-oxo-4-(*p*-tolyl)but-3-enoate (488)

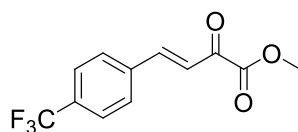
Following **General Procedure A**, the titled compound was obtained as a yellow solid (41% yield over two-step). Spectroscopy data were in accordance with the literature.⁹ mp 80-81 °C {Lit.¹⁰ 70-72 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 2.41 (3H, s, CH₃), 3.94 (3H, s, OCH₃), 7.22 (2H, d, *J* 7.8, Ar*CH*), 7.32 (1H, d, *J* 16.1, C(3)*H*), 7.55 (2H, d, *J* 7.9, Ar*CH*), 7.88 (1H, d, *J* 16.2, C(4)*H*).

Methyl (E)-4-(4-methoxyphenyl)-2-oxobut-3-enoate (489)

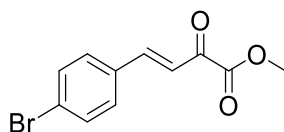
Following **General Procedure A**, the titled compound was obtained as a yellow solid (25% yield over two-step). Spectroscopy data were in accordance with the literature.¹ mp 84-86 °C {Lit.¹ 86-88 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.87 (3H, s, OCH₃), 3.96 (3H, s, OCH₃), 6.92–7.00 (2H, m, ArCH), 7.28 (1H, d, *J* 16.0, C(3)H), 7.58–7.64 (2H, m, ArCH), 7.88 (1H, d, *J* 16.0, C(4)H).

Methyl (E)-4-(3-methoxyphenyl)-2-oxobut-3-enoate (490)

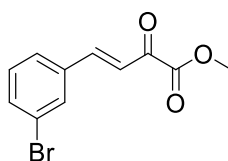
Following **General Procedure A**, the titled compound was obtained as a yellow solid (25% yield over two-step). Spectroscopy data were in accordance with the literature.⁹ mp 83-84 °C {Lit.¹⁰ 100-102 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.85 (3H, s, CH₃), 3.93 (3H, s, CH₃), 6.92–7.06 (1H, m, ArCH), 7.11–7.12 (1H, m, C(3)H), 7.19–7.23 (1H, m, ArCH), 7.26–7.36 (2H, m, ArCH), 7.82 (1H, d, *J* 16.1, C(4)H).

Methyl (E)-2-oxo-4-(4-(trifluoromethyl)phenyl)but-3-enoate (491)

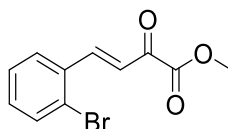
Following **General Procedure A**, the titled compound was obtained as a yellow solid (30% yield over two-step). Spectroscopy data were in accordance with the literature.¹¹ mp 116-117 °C {Lit.¹¹ 122-123 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.95 (3H, s, CH₃), 7.37 (1H, d, *J* 16.2, C(3)H), 7.71 (2H, d, *J* 8.1, C(4)ArC(2,6)H), 7.76 (2H, d, *J* 8.2, C(4)ArC(3,5)H), 7.89 (1H, d, *J* 16.2, C(4)H).

Methyl (E)-4-(4-bromophenyl)-2-oxobut-3-enoate (492)

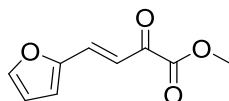
Following **General Procedure A**, the titled compound was obtained as a yellow solid (28% yield over two-step). Spectroscopy data were in accordance with the literature.¹ mp 115-116 °C {Lit.¹ 116-118 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.98 (3H, s, CH₃), 7.42 (1H, d, *J* 15.9, C(3)*H*), 7.48–7.54 (2H, m, ArCH), 7.55–7.64 (2H, m, ArCH), 7.81 (1H, d, *J* 15.9, C(4)*H*).

Methyl (E)-4-(3-bromophenyl)-2-oxobut-3-enoate (493)

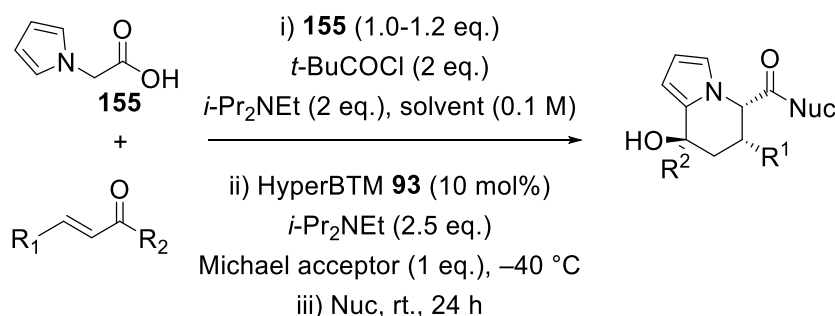
Following **General Procedure A**, the titled compound was obtained as a yellow solid (34% yield over two-step). Spectroscopy data were in accordance with the literature.¹ mp 103-104 °C {Lit.¹ 96-98 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.86 (3H, s, CH₃), 7.22 (1H, t, *J* 8.0, ArCH), 7.29 (1H, d, *J* 16.1, C(3)*H*), 7.43–7.54 (2H, m, ArCH), 7.66–7.73 (2H, m, C(4)*H* and ArCH).

Methyl (E)-4-(2-bromophenyl)-2-oxobut-3-enoate (494)

Following **General Procedure A**, the titled compound was obtained as a yellow solid (26% yield over two-step). Spectroscopy data were in accordance with the literature.¹¹ mp 50-52 °C {Lit.¹¹ 54-57 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.94 (3H, s, CH₃), 7.28–7.40 (3H, m, C(3)*H* + ArCH), 7.62–7.79 (2H, m, ArCH), 8.25 (1H, d, *J* 16.1, C(4)*H*).

Methyl (E)-4-(furan-2-yl)-2-oxobut-3-enoate (495)

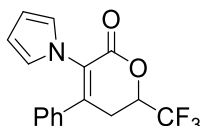
Following literature procedures,¹ to a solution of pyruvic acid **130** (3.52 g, 50 mmol, 1.0 eq.) and furan-2-carbaldehyde (4.14 mL, 50 mmol, 1.0 eq.) in MeOH (5 mL) at 0 °C was added a solution of KOH (4.21 g, 75 mmol, 1.5 eq.) in MeOH (15 mL). The first 1 eq. of the KOH solution was added dropwise over 30 minutes. The last 0.5 eq. was added as one portion and the reaction mixture was stirred at 40 °C for 1 h followed by 0 °C for 16 h. The precipitate was collected by filtration, washed twice with cold MeOH, once with Et₂O and dried under vacuum to furnish the crude potassium salt, which was then all dissolved in DMF (40 mL). Methyl iodide (3.4 mL, 55 mmol, 1.1 eq.) was added and the reaction mixture was heated at 75 °C for 4 h. Once the reaction mixture was cooled to room temperature, H₂O (40 mL) was added and the organic layer was extracted with DCM (3 x 40 mL). The combined organic extracts were washed with H₂O (3 x 30 mL) and brine (3 x 30 mL), dried, filtered and concentrated under reduced pressure. Chromatographic purification (15:85 EtOAc/petrol) gave the titled compound as a dark yellow solid (1.62 g, 18% over two-step). Spectroscopy data were in accordance with the literature.¹ mp 51-53 °C; {Lit.¹ 56-58 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.84 (3H, s, CH₃), 6.47 (1H, dd, *J* 3.5, 1.8, ArCH), 6.76 (1H, d, *J* 3.4, ArCH), 7.17 (1H, d, *J* 15.9, C(3)H), 7.48–7.53 (1H, m, ArCH), 7.58 (1H, d, *J* 16.0, C(4)H).

General Procedure B: Enantioselective synthesis of tetrahydroindolizine

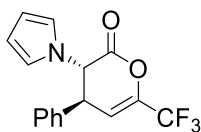
2-(1*H*-Pyrrol-1-yl)acetic acid **155** (1.0-1.2 eq.) was dissolved in the solvent stated (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (2 eq.) and pivaloyl chloride (2 eq.) were added. The reaction was stirred at 0 °C for 20 min before cooling down to -40 °C. HyperBTM **93** (10 mol%), the required Michael acceptor (1 eq.), and *i*-Pr₂NEt (2.5 eq.) were

added sequentially and the reaction stirred at $-40\text{ }^{\circ}\text{C}$ for the time stated. After that, the reaction was quenched with the nucleophile stated at $-40\text{ }^{\circ}\text{C}$, and stirred at rt for 24 h before being concentrated under reduced pressure to give the crude product which was purified by flash silica column chromatography.

4-Phenyl-3-(1*H*-pyrrol-1-yl)-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-2-one (240)

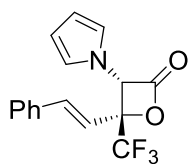


2-(1*H*-Pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.) was dissolved in anhydrous DMF (0.1 M) under an atmosphere of N_2 and cooled to $0\text{ }^{\circ}\text{C}$ before *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2 eq.) and pivaloyl chloride (0.062 mL, 0.5 mmol, 2 eq.) were added. The reaction was stirred at $0\text{ }^{\circ}\text{C}$ for 20 min before warming up to rt. HyperBTM **93** (7.7 mg, 10 mol%), CF₃ enone **144** (50.0 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) were added sequentially and the reaction stirred at rt. for 24 h. Upon completion of the reaction (checked by TLC), it was diluted with CH_2Cl_2 (equal volume) and washed with 1 M HCl ($\times 2$) and brine ($\times 2$) before being dried over MgSO_4 , filtered, and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography (15:85 EtOAc/petrol, R_f 0.33), to give the titled compound as a yellow solid (74.5 mg, 97%). mp $65\text{--}66\text{ }^{\circ}\text{C}$; Chiral HPLC analysis, Chiralpak OD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin^{-1} , 254 nm, $30\text{ }^{\circ}\text{C}$) t_R (major): 14.4 min, t_R (minor): 10.1 min, 80:20 er; ν_{max} (film, cm^{-1}) 3102 (C-H stretch), 1728 (C=O stretch), 1614; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 3.16 (1H, dd, J 17.7, 4.3, C(5) H_AH_B), 3.35 (1H, dd, J 17.6, 11.3, C(5) H_AH_B), 5.06 (1H, dqd, J 11.4, 5.6, 4.2, C(6) H), 6.19 (2H, t, J 2.2, C(3)Ar(3,4) H), 6.51 (2H, t, J 2.2, C(3)Ar(2,5) H), 6.98–7.02 (2H, m, C(4)ArC(2,6) H), 7.29–7.39 (3H, m, C(4)ArC(3,4,5) H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 28.2 (C(5)), 72.8 (q, $^2J_{\text{CF}}$ 34.4, C(6)), 110.1 (C(3)ArC(3,4) H), , 122.0 (C(3)ArC(2,5) H), 122.5 (q, $^1J_{\text{CF}}$ 280.2, CF₃), 125.2 (C(3)), 127.3 (C(4)ArC(2,6) H), 128.8 (C(4)ArC(3,5) H), 130.4 (C(4)ArC(2,6) H), 134.3 (C(4)ArC(1)), 144.5 (C(4)), 159.8 (C(2)); $^{19}\text{F}\{^1\text{H}\}$ NMR (377 MHz, CDCl_3) δ_{F} : -78.0 (CF₃); HRMS (NSI⁺) $\text{C}_{16}\text{H}_{13}\text{F}_3\text{NO}_2$ [M+H]⁺ found 308.0894, requires 308.0893 (+0.4 ppm).

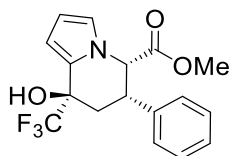
(3S,4S)-4-Phenyl-3-(1H-pyrrol-1-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one (241)

2-(1*H*-Pyrrol-1-yl)acetic acid **155** (37.5 mg, 0.30 mmol, 1.2 eq.) was dissolved in *i*-PrOAc (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2 eq.) and pivaloyl chloride (0.062 mL, 0.5 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before warming up to rt. HyperBTM **93** (7.7 mg, 10 mol%), CF₃ enone **144** (50.0 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) were added sequentially and the reaction stirred at rt. for 18 h. Then the mixture was concentrated under reduced pressure to give the crude product (82:18 dr) which was purified by flash silica column chromatography (5:95 Et₂O/petrol) and recrystallization in hexane to give the titled compound as fine colourless needles (15.4 mg, 20%). mp 83–85 °C; Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 13.6 min, t_R (minor): 19.1 min, 95:5 er; ν_{max} (film, cm⁻¹) 1782 (C=O), 1701; ¹H NMR (400 MHz, CDCl₃) δ_H: 4.28 (1H, dp, *J* 12.4, 2.8, C(4)*H*), 4.88 (1H, d, *J* 12.4, C(3)*H*), 6.15 (2H, t, *J* 2.2, C(3)Ar(3,4)*H*), 6.18 (1H, dq, *J* 2.4, 0.8, C(5)*H*), 6.50 (2H, t, *J* 2.1, C(3)Ar(2,5)*H*), 7.00–7.04 (2H, m, C(4)ArC(2,6)*H*), 7.28–7.33 (3H, m, C(4)ArC(3,4,5)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 44.6 (C(4)), 62.6 (C(3)), 109.8 (C(3)ArC(2,5)*H*), 110.6 (d, ³*J*_{CF} 3.4, C(5)), 118.2 (q, ¹*J*_{CF} 272.0, CF₃), 120.2 (C(3)ArC(3,4)*H*), 127.1 (C(4)ArC(2,6)*H*), 128.6 (C(4)ArC(3,5)*H*), 129.2 (C(4)ArC(4)*H*), 136.9 (C(4)ArC(1)), 140.7 (q, ²*J*_{CF} 38.9, C(6)), 163.1 (C(2)); ¹⁹F{¹H} NMR (377 MHz, CDCl₃) δ_F: -72.1 (CF₃); HRMS (NSI⁺) C₁₆H₁₃F₃NO₂ [M+H]⁺ found 308.0895, requires 308.0893 (+0.7 ppm); [α]_D²⁰ not measured due to product instability.

Selected data for minor diastereoisomer: Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 15.3 min, t_R (minor): 22.3 min, 90:10 er; ¹H NMR (400 MHz, CDCl₃) δ_H: 4.06–4.13 (1H, m, C(4)*H*), 5.49 (1H, d, *J* 7.3, C(3)*H*).

(3S,4R)-3-(1H-Pyrrol-1-yl)-4-((E)-styryl)-4-(trifluoromethyl)oxetan-2-one (242)

2-(1*H*-Pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.) was dissolved in CH₂Cl₂ (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2 eq.) and pivaloyl chloride (0.062 mL, 0.5 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before cooling to –60 °C. HyperBTM **93** (7.7 mg, 10 mol%), CF₃ enone **144** (50.0 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) were added sequentially and the reaction stirred at –60 °C for 15 h. Then the mixture was concentrated under reduced pressure to give the crude product (>95:5 dr) which was purified by flash silica column chromatography (10:90 Et₂O/petrol) to give the titled compound as a colourless oil (30.7 mg, 40%). Chiral HPLC analysis, Chiralpak IB (99:1 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 9.6 min, t_R (minor): 8.8 min, 96:4 er; ¹H NMR (500 MHz, CDCl₃) δ_H: 5.69 (1H, d, *J* 16.2, PhCH=CH), 6.09 (1H, s, C(3)H), 6.26 (2H, t, *J* 2.2, C(3)Ar(3,4)H), 6.65 (2H, t, *J* 2.1, C(3)Ar(2,5)H), 6.97 (1H, d, *J* 16.1, PhCH=CH), 7.25–7.27 (2H, m, ArC(2,6)H), 7.33–7.37 (3H, m, ArC(3,4,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 70.5 (C(3)), 81.3 (q, ²J_{CF} 33.5, C(4)), 111.2 (C(3)ArC(3,4)H), 113.1 (PhCH=CH), 120.8 (C(3)ArC(2,5)H), 127.8 (q, ¹J_{CF} 271.6, CF₃), 127.2 (PhC(2,6)H), 128.8 (PhC(3,5)H), 129.5 (PhC(4)H), 134.4 (PhCH=CH), 139.0 (PhC(1)), 162.5 (C(2)); ¹⁹F NMR (471 MHz, CDCl₃) δ_F: –78.8 (CF₃); HRMS (ASAP⁺) C₁₆H₁₃F₃NO₂ [M+H]⁺ found 308.0895, requires 308.0898 (–1.0 ppm); [α]_D²⁰ and IR not measured due to product instability.

Methyl (5S,6S,8R)-8-hydroxy-6-phenyl-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (246)

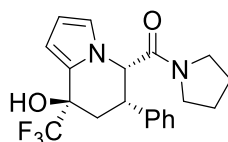
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), CF₃ enone **144** (40.0 mg, 0.20

mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product (91:9 dr) that was purified by column chromatography (10:90 EtOAc/petrol) to give the combined diastereoisomers (90:10 dr) (56.0 mg, 83%) as a light yellow oil. ν_{\max} (film, cm⁻¹) 3447 (br., O-H), 2953 (C-H), 1740 (C=O); $[\alpha]_{\text{D}}^{20}$ + 158.8 (*c* 0.8 in CHCl₃).

Data for major diastereoisomer (**5S,6S,8R**)-**246**: Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_{R} (major): 19.5 min, t_{R} (minor): 28.4 min, 98:2 er; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 2.28 (1H, dd, *J* 13.6, 2.7, C(7)H^AH^B), 2.39–2.40 (1H, s, OH), 3.08 (1H, td, *J* 13.6, 1.9, C(7)H^AH^B), 3.42 (3H, s, OCH₃), 4.07 (1H, ddd, *J* 13.6, 6.0, 2.7, C(6)H), 5.02 (1H, d, *J* 6.0, C(5)H), 6.29 (1H, dd, *J* 3.8, 2.8, C(2)H), 6.51 (1H, dp, *J* 3.4, 1.6, C(1)H), 6.66 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.27–7.30 (2H, m, C(6)ArC(2,6)H), 7.33–7.37 (1H, m, C(6)ArC(4)H), 7.38–7.42 (2H, m, C(6)ArC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 28.7 (C(7)), 37.8 (C(6)), 52.1 (OCH₃), 62.2 (C(5)), 70.6 (q, ²*J*_{CF} 30.5, C(8)), 107.7 (C(1)), 110.3 (C(2)), 121.3 (C(3)), 125.4 (q, ¹*J*_{CF} 272.0, CF₃), 125.8 (C(8a)), 127.6 (C(6)ArC(2,6)H), 128.0 (C(6)ArC(4)H), 128.8 (C(6)ArC(3,5)H), 137.8 (C(6)ArC(1)), 169.3 (C(5)CO); ¹⁹F{¹H} NMR (377 MHz, CDCl₃) δ_{F} : -80.6 (CF₃); HRMS (ASAP⁺) C₁₇H₁₇F₃NO₃ [M+H]⁺ found 340.1161, requires 340.1161 (0.0 ppm).

Selected data for minor diastereoisomer: Chiral HPLC analysis, Chiralpak AD-H (95:5 hexane:*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_{R} (major): 14.7 min, t_{R} (minor): 24.8 min, 96:4 er; ¹H NMR (400 MHz, CDCl₃) δ_{H} (selected): 3.64 (3H, s, OCH₃), 3.91 (1H, td, *J* 11.1, 4.8, C(6)H), 4.76 (1H, d, *J* 11.0, C(5)H), 6.60 (1H, dd, *J* 3.0, 1.5, C(1)H); ¹⁹F{¹H} NMR (377 MHz, CDCl₃) δ_{F} : -80.3 (CF₃).

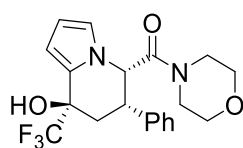
((5S,6S,8R)-8-Hydroxy-6-phenyl-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizin-5-yl)(pyrrolidin-1-yl)methanone (248)



Following General Procedure **A**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), CF₃ enone **144** (40.0 mg, 0.20

mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with pyrrolidine (300 eq.) at rt for 24 h gave crude product (93:7 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a white solid (53.0 mg, 70%). mp 170-172 °C; ν_{\max} (film, cm⁻¹) 3318 (O-H), 2982 (C-H), 1636 (amide CO); $[\alpha]_{\text{D}}^{20} + 175.3$ (c 0.6 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 7.7 min, t_{R} (minor): 14.5 min, 98:2 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.48–1.73 (4H, m, pyrrolidineCH), 2.11 (1H, dd, *J* 13.3, 2.8, C(7)H(A)H(B)), 2.15–2.21 (1H, m, pyrrolidineCH), 2.36 (1H, s, OH), 3.19 (2H, ddt, *J* 14.3, 12.0, 6.7, pyrrolidineCH), 3.35–3.41 (1H, m, pyrrolidineCH), 3.44 (1H, td, *J* 13.5, 1.5, C(7)H(A)H(B)), 4.01 (1H, ddd, *J* 13.5, 5.7, 2.7, C(6)H), 5.12 (1H, d, *J* 5.7, C(5)H), 6.27 (1H, dd, *J* 3.8, 2.8, C(2)H), 6.46–6.51 (1H, m, C(1)H), 6.54 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.31–7.38 (5H, m, ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 23.8 (pyrrolidineCH), 26.0 (pyrrolidineCH), 29.3 (C(7)), 39.3 (C(6)), 45.8 (pyrrolidineCH), 46.3 (pyrrolidineCH), 59.4 (C(5)), 70.8 (q, *J* 30.4, C(8)), 107.0 (app. d, *J* 2.7, C(1)), 110.0 (C(2)), 120.5 (C(3)), 125.5 (q, *J* 284.3, CF₃), 126.8 (C(8a)), 128.1 (ArCH), 128.4 (ArCH), 128.7 (ArCH), 138.3 (C(6)ArC(1)), 166.3 (C(5)CO); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -80.4 (CF₃); HRMS (ESI⁺) C₂₀H₂₁F₃N₂O₂Na [M+Na]⁺ found 401.1436, requires 401.1447 (+2.7 ppm).

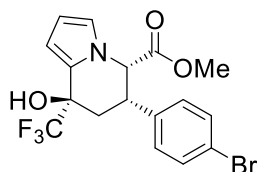
((5*S*,6*S*,8*R*)-8-Hydroxy-6-phenyl-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizin-5-yl)(morpholino)methanone (249)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), CF₃ enone **144** (40.0 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with morpholine (300 eq.) at rt for 24 h gave crude product (95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a white solid (48.9 mg, 62%). mp 174-175 °C; ν_{\max} (film, cm⁻¹) 3391 (O-H), 2995 (C-H), 2873 (C-H), 1636 (amide C=O); $[\alpha]_{\text{D}}^{20} + 116.2$ (c 3.0 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH,

flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 18.5 min, t_R (minor): 26.5 min, 97:3 er; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.11 (1H, dd, *J* 13.3, 2.8, C(7)H(A)H(B)), 2.36 (1H, s, OH), 2.50 (2H, dddd, *J* 15.9, 9.4, 6.4, 3.0, morpholineCH), 3.14 (1H, ddd, *J* 13.0, 7.4, 3.1, morpholineCH), 3.27–3.39 (4H, m, morpholineCH + C(7)H(A)H(B)), 3.44–3.53 (2H, m, morpholineCH), 4.02 (1H, ddd, *J* 13.5, 5.9, 2.8, C(6)H), 5.33 (1H, d, *J* 5.9, C(5)H), 6.26 (1H, dd, *J* 3.8, 2.8, C(2)H), 6.46–6.48 (1H, m, C(1)H), 6.49 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.31–7.41 (5H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 29.1 (C(7)), 38.9 (C(6)), 42.1 (morpholineCH), 45.8 (morpholineCH), 56.2 (C(5)), 65.6 (morpholineCH), 66.3 (morpholineCH), 70.7 (q, *J* 30.2, C(8)), 107.2 (app. d, *J* 2.7, C(1)), 110.2 (C(2)), 120.3 (C(3)), 125.5 (q, *J* 284.2, CF₃), 126.9 (C(8a)), 128.4 (C(6)ArCH), 128.5 (C(6)ArCH), 129.1 (C(6)ArCH), 138.2 (C(6)ArC(1)), 166.6 (C(5)CO); ¹⁹F NMR (471 MHz, CDCl₃) δ_F: -80.4 (CF₃); HRMS (ESI⁺) C₂₀H₂₁F₃N₂O₃Na [M+Na]⁺ found 417.1386, requires 417.1397 (+2.5 ppm).

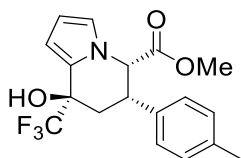
Methyl (5S,6S,8R)-6-(4-bromophenyl)-8-hydroxy-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (250)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-4-(4-bromophenyl)-1,1,1-trifluorobut-3-en-2-one (55.8 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product (90:10 dr) that was purified by column chromatography (15:85 to 20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (52.0 mg, 62%). ν_{max} (film, cm⁻¹) 3433 (O-H stretch), 2953 (C-H stretch), 1740 (C=O), 1157; [α]_D²⁰ + 117.3 (*c* 1.0 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5: 2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_R (major): 52.0 min, t_R (minor): 73.7 min, 97.5 : 2.5 er; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.22 (1H, dd, *J* 13.4, 2.7, C(7)H(a)H(b)), 2.41 (1H, s, *J* 1.8, OH), 3.01 (1H, td, *J* 13.5, 1.9, C(7)H(a)H(b)), 3.43 (3H, s, OCH₃), 4.00 (1H, ddd, *J* 13.5, 6.0, 2.7, C(6)H), 4.96 (1H, d, *J* 6.0, C(5)H), 6.27 (1H, dd, *J* 3.8, 2.8, C(2)H), 6.48 (1H, dt, *J* 3.6, 1.7, C(1)H), 6.64 (1H, dd, *J* 2.9, 1.6, C(3)H),

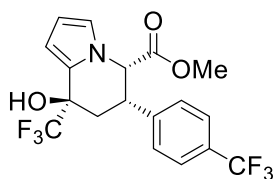
7.11–7.15 (2H, m, C(6)ArC(2,6)H), 7.48–7.52 (2H, m, C(6)ArC(3,5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 28.7 (C(7)), 37.4 (C(6)), 52.4 (OCH₃), 62.0 (C(5)), 70.6 (q, J 30.6, C(8)), 107.9 (app. d, J 2.7, C(1)), 110.5 (C(2)), 121.4 (C(3)), 122.1 (C(6)ArC(4)), 125.4 (q, J 284.1, CF₃), 125.7 (C(8a)), 129.4 (C(6)ArC(2,6)H), 132.1 (C(6)ArC(3,5)H), 137.0 (C(6)ArC(1)), 169.2 (C(5)C=O); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -80.6 (CF₃); HRMS (ASAP⁺) C₁₇H₁₆F₃NO₃⁷⁹Br [M+H]⁺ found 418.0266, requires 418.0260 (-1.4 ppm).

Methyl (5S,6S,8R)-8-hydroxy-6-(*p*-tolyl)-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (251)



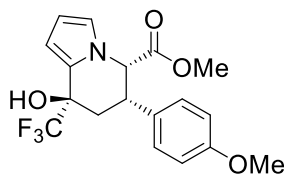
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-1,1,1-trifluoro-4-(*p*-tolyl)but-3-en-2-one (42.8 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product (80:20 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound as a light pink oil (41.0 mg, 58%). ν_{max} (film, cm⁻¹) 3458 (O-H stretch), 2953 (C-H stretch), 1744 (C=O), 1161; $[\alpha]_{\text{D}}^{20}$ +132.0 (*c* 0.4 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5: 2.5 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_{R} (major): 38.7 min, t_{R} (minor): 59.7 min, 98 : 2 er; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.23 (1H, dd, J 13.6, 2.8, C(7)H(a)H(b)), 2.34 (1H, d, J 1.9, OH), 2.35 (3H, s, CH₃), 3.03 (1H, td, J 13.6, 1.9, C(7)H(a)H(b)), 3.42 (3H, s, OCH₃), 3.99 (1H, ddd, J 13.6, 6.0, 2.7, C(6)H), 4.97 (1H, d, J 6.0, C(5)H), 6.26 (1H, dd, J 3.8, 2.8, C(2)H), 6.48 (1H, dt, J 3.6, 1.7, C(1)H), 6.63 (1H, dd, J 2.9, 1.6, C(3)H), 7.10–7.20 (4H, m, ArCH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 21.3 (CH₃), 28.9 (C(7)), 37.6 (C(6)), 52.3 (OCH₃), 62.4 (C(5)), 70.7 (q, J 30.3, C(8)), 107.8 (C(1)), 110.4 (C(2)), 121.4 (C(3)), 125.5 (q, J 284.1, CF₃), 125.9 (C(8a)), 127.5 (C(6)ArC(3,5)H), 129.6 (C(6)ArC(2,6)H), 134.8 (C(6)ArC(4)), 137.8 (C(6)ArC(1)), 169.5 (C(5)C=O); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -80.6 (CF₃); HRMS (ESI⁺) C₁₈H₁₈F₃NO₃Na [M+Na]⁺ found 376.1129, requires 376.1131 (-0.5 ppm).

Methyl (5*S*,6*S*,8*R*)-8-hydroxy-8-(trifluoromethyl)-6-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (251)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-1,1,1-trifluoro-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one (53.6 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound as a light pink oil (33.0 mg, 40%). ν_{\max} (film, cm⁻¹) 3472 (O-H stretch), 2955 (C-H stretch), 1742 (C=O), 1325, 1161; $[\alpha]_{\text{D}}^{20} + 128.6$ (*c* 0.5 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5 : 2.5 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 45.6 min, *t*_R (minor): 62.9 min, 97 : 3 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.27 (1H, dd, *J* 13.5, 2.7, C(7)H(a)H(b)), 2.40 (1H, d, *J* 1.8, OH), 3.06 (1H, td, *J* 13.5, 1.9, C(7)H(a)H(b)), 3.41 (3H, s, OCH₃), 4.11 (1H, ddd, *J* 13.5, 6.0, 2.6, C(6)H), 5.01 (1H, d, *J* 5.9, C(5)H), 6.28 (1H, dd, *J* 3.8, 2.8, C(2)H), 6.49 (1H, dt, *J* 3.7, 1.7, C(1)H), 6.65 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.40 (2H, d, *J* 8.1, C(6)ArC(2,6)H), 7.64 (2H, d, *J* 8.1, C(6)ArC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 28.7 (C(7)), 37.8 (C(6)), 52.4 (OCH₃), 61.9 (C(5)), 70.6 (q, *J* 30.8, C(8)), 108.0 (app. d, *J* 2.8, C(1)), 110.6 (C(2)), 121.5 (C(3)), 124.0 (q, *J* 272.1, C(6)ArC(4)CF₃), 125.4 (q, *J* 284.1, C(8)CF₃), 125.7 (C(8a)), 125.9 (q, *J* 3.7, C(6)ArC(3,5)H), 128.3 (C(6)ArC(2,6)H), 130.4 (q, *J* 32.6, C(6)ArC(4)), 142.0 (C(6)ArC(1)), 169.0 (C(5)C=O); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -80.6 (C(8)CF₃), -62.6 (ArCF₃); HRMS (ESI⁺) C₁₈H₁₅F₆NO₃Na [M+Na]⁺ found 430.0837, requires 430.0849 (-2.6 ppm).

Methyl (5S,6S,8R)-8-hydroxy-6-(4-methoxyphenyl)-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (254)

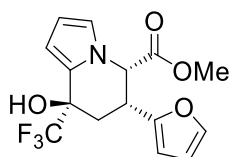


Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one (46.0 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product (84:16 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound as a light orange solid (50.2 mg, 68%). mp 114–116 °C; ν_{\max} (film, cm⁻¹) 3460 (O-H stretch), 2953 (C-H stretch), 2814 (C-H stretch), 1744 (C=O), 1514, 1259, 1160; $[\alpha]_{\text{D}}^{20} + 167.2$ (c 0.5 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 59.1 min, t_{R} (minor): 104.6 min, 99:1 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.21 (1H, dd, *J* 13.6, 2.7, C(7)*H*(a)*H*(b)), 2.33 (1H, d, *J* 1.8, *OH*), 3.02 (1H, t, *J* 13.6, C(7)*H*(a)*H*(b)), 3.43 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.97 (1H, ddd, *J* 13.6, 6.0, 2.7, C(6)*H*), 4.95 (1H, d, *J* 6.0, C(5)*H*), 6.26 (1H, dd, *J* 3.8, 2.8, C(2)*H*), 6.47 (1H, dt, *J* 3.6, 1.7, C(1)*H*), 6.63 (1H, dd, *J* 2.8, 1.6, C(3)*H*), 6.82–6.97 (2H, m, C(6)ArC(3,5)*H*), 7.08–7.22 (2H, m, C(6)ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 29.1 (C(7)), 37.1 (C(6)), 52.3 (OCH₃), 55.4 (OCH₃), 62.4 (C(5)), 70.7 (q, *J* 30.3, C(8)), 107.8 (app. d, *J* 2.7, C(1)), 110.3 (C(2)), 114.2 (C(6)ArC(3,5)*H*), 121.3 (C(3)), 125.5 (q, *J* 284.0, CF₃), 125.8 (C(8a)), 128.7 (C(6)ArC(2,6)*H*), 129.9 (C(6)ArC(1)), 159.2 (C(6)ArC(4)), 169.5 (C(5)CO); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -80.6 (CF₃); HRMS (NSI⁺) C₁₈H₁₉F₃NO₄ [M+H]⁺ found 370.1262, requires 370.1261 (+0.4 ppm).

Selected data for the minor diastereoisomer: Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 37.2 min, t_{R} (minor): 95.3 min, 95 : 5 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.24–2.37 (2H, m, C(7)*H*), 2.56 (1H, s, *OH*), 3.63 (3H, s, OCH₃), 3.83–3.89 (4H, m, OCH₃ + C(6)*H*), 4.68 (1H, d, *J* 11.1, C(5)*H*), 6.25 (1H, dd, *J* 3.8, 2.9, C(2)*H*),

6.46 (1H, dt, J 3.7, 1.7, C(1)H), 6.57 (1H, dd, J 2.9, 1.6, C(3)H), 6.84–6.94 (2H, m, C(6)ArC(3,5)H), 7.14–7.22 (2H, m, C(6)ArC(2,6)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 35.1 (C(7)), 39.0 (C(6)), 52.8 (OCH₃), 55.4 (OCH₃), 64.9 (C(5)), 70.3 (q, J 30.4, C(8)), 107.8 (C(1)), 110.1 (C(2)), 114.5 (C(6)ArC(3,5)H), 120.9 (C(3)), 125.4 (q, J 284.2, CF₃), 125.4 (C(8a)), 128.8 (C(6)ArC(2,6)H), 130.8 (C(6)ArC(1)), 159.3 (C(6)ArC(4)), 170.5 (C(5)CO); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -80.3 (CF₃).

methyl (5S,6R,8R)-6-(furan-2-yl)-8-hydroxy-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (258)



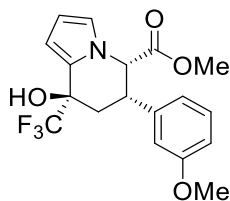
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one (38.0 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product (77:23 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the combined diastereoisomers (76:24 dr) (62.0 mg, 95%) as a light yellow oil. ν_{max} (film, cm^{-1}) 3456 (O-H stretch), 2957 (C-H stretch), 2361, 1746 (C=O), 1277, 1163; $[\alpha]_{\text{D}}^{20}$ + 81.5 (c 2.2 in CHCl_3).

Data for major diastereoisomer (**5S,6R,8R**)-**258**: Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 40.4 min, t_{R} (minor): 44.9 min, 97 : 3 er; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.31 (1H, dd, J 13.8, 2.9, C(7)H(a)H(b)), 2.38 (1H, s, OH), 2.79 (1H, td, J 13.6, 1.7, C(7)H(a)H(b)), 3.50 (3H, s, OCH₃), 4.05–4.11 (1H, m, C(6)H), 5.15 (1H, d, J 5.9, C(5)H), 6.19 (1H, dd, J 3.2, 0.9, C(6)ArH), 6.26 (1H, dd, J 3.9, 2.9, C(2)H), 6.35 (1H, dd, J 3.3, 1.9, C(6)ArH), 6.47 (1H, dt, J 3.7, 1.7, C(1)H), 6.65 (1H, dd, J 2.8, 1.6, C(3)H), 7.41–7.42 (1H, m, C(6)ArH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 28.0 (C(7)), 32.5 (C(6)), 52.5 (OCH₃), 59.9 (C(5)), 70.2 (q, J 30.6, C(8)), 106.7 (C(6)ArCH), 107.1 (C(6)ArCH), 107.8 (d, J 2.4, C(1)), 110.4 (C(2)), 121.6 (C(3)), 125.2 (q, J 284.2, CF₃), 125.7 (C(8a)), 142.5 (C(6)ArCH), 151.8 (C(6)ArC),

169.2 (C(5)CO); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -80.7 (CF_3); HRMS (ESI $^+$) $\text{C}_{15}\text{H}_{14}\text{F}_3\text{NO}_4\text{Na}$ [$\text{M}+\text{Na}$] $^+$ found 352.0763, requires 352.0767 (-1.2 ppm).

Data for minor diastereoisomer: Chiral HPLC analysis, Chiralpak AD-H (97.5 : 2.5 hexane/IPA, flow rate 1 mLmin $^{-1}$, 211 nm, 30 °C) t_{R} (major): 25.0 min, t_{R} (minor): 31.8 min, 92 : 8 er; ^1H NMR (500 MHz, CDCl_3) δ_{H} (selected): 2.69 (1H, s, OH), 3.75 (3H, s, OCH_3), 4.78 (1H, d, J 10.9, C(5)H), 6.20–6.21 (1H, m, C(6)ArH), 6.23–6.25 (1H, m, C(2)H), 6.33 (1H, dd, J 3.3, 1.9, C(6)ArH), 6.43–6.46 (1H, m, C(1)H), 6.59 (1H, dd, J 2.9, 1.5, C(3)H), 7.39 (1H, dd, J 1.8, 0.9, C(6)ArH); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -80.3 (CF_3).

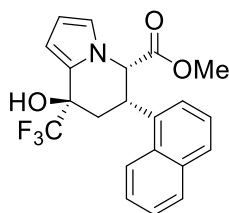
Methyl (5S,6S,8R)-8-hydroxy-6-(3-methoxyphenyl)-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (252)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr $_2$ NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-1,1,1-trifluoro-4-(3-methoxyphenyl)but-3-en-2-one (46.0 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr $_2$ NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product (87:13 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound as a light yellow oil (40.0 mg, 54%); ν_{max} (film, cm $^{-1}$) 3447 (O-H stretch), 2953 (C-H stretch), 2837 (C-H stretch), 1744 (C=O), 1165; $[\alpha]_{\text{D}}^{20}$ + 152.9 (c 0.3 in CHCl_3); Chiral HPLC analysis, Chiralpak IB (85:15 hexane/IPA, flow rate 1 mLmin $^{-1}$, 211 nm, 30 °C) t_{R} (major): 9.0 min, t_{R} (minor): 23.6 min, 96 : 4 er; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.24 (1H, dd, J 13.6, 2.7, C(7)H(a)H(b)), 2.46 (1H, s, OH), 3.02 (1H, t, J 13.5, C(7)H(a)H(b)), 3.43 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.00 (1H, ddd, J 13.5, 6.0, 2.7, C(6)H), 4.98 (1H, d, J 6.0, C(5)H), 6.26 (1H, dd, J 3.8, 2.8, C(2)H), 6.47 (1H, dt, J 3.7, 1.7, C(1)H), 6.63 (1H, dd, J 2.9, 1.6, C(3)H), 6.79 (1H, t, J 2.1, C(6)ArC(2)H), 6.81–6.88 (2H, m, C(6)ArC(4,6)H), 7.29 (1H, t, J 7.9, C(6)ArC(5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 28.8 (C(7)), 37.9 (C(6)), 52.3 (OCH_3), 55.4 (OCH_3), 62.2 (C(5)), 70.6 (q, J 30.4, C(8)), 107.8 (d, J 2.8, C(1)), 110.4 (C(2)), 113.1 (C(6)ArCH),

113.8 (C(6)ArCH), 119.9 (C(6)ArCH), 121.3 (C(3)), 125.5 (q, J 284.0, CF₃), 125.8 (C(8a)), 129.9 (C(6)ArC(2)H), 139.5 (C(6)ArC(1)), 160.0 (C(6)ArC(3)), 169.4 (C(5)C=O); ¹⁹F NMR (471 MHz, CDCl₃) δ_F: -80.6 (CF₃); HRMS (ASAP⁺) C₁₈H₁₉F₃NO₄ [M+H]⁺ found 370.1261, requires 370.1266 (-1.4 ppm).

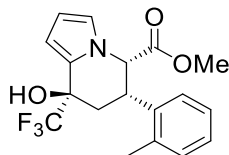
Methyl (5S,6S,8R)-8-hydroxy-6-(naphthalen-1-yl)-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (256)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-1,1,1-trifluoro-4-(naphthalen-1-yl)but-3-en-2-one (50.0 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product (80:20 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound as a light yellow oil (60.3 mg, 77%). ν_{\max} (film, cm⁻¹) 3466 (O-H stretch), 2961 (C-H stretch), 1744 (C=O), 1163; $[\alpha]_{\text{D}}^{20}$ + 193.3 (c 2.9 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5 : 2.5 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 52.9 min, t_{R} (minor): 45.2 min, 98 : 2 er; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.35 (1H, dd, J 13.3, 2.5, C(7)H(a)H(b)), 2.49 (1H, s, OH), 3.22–3.31 (4H, m, C(7)H(a)H(b) + OCH₃), 4.89 (1H, ddd, J 13.2, 5.9, 2.5, C(6)H), 5.27 (1H, d, J 5.8, C(5)H), 6.31 (1H, dd, J 3.9, 2.8, C(2)H), 6.54 (1H, dt, J 3.7, 1.7, C(1)H), 6.64 (1H, dd, J 2.8, 1.6, C(3)H), 7.32 (1H, d, J 7.2, C(6)ArCH), 7.45 (1H, dd, J 8.2, 7.2, C(6)ArCH), 7.56 (1H, ddd, J 8.0, 6.8, 1.2, C(6)ArCH), 7.61 (1H, ddd, J 8.4, 6.8, 1.5, C(6)ArCH), 7.84 (1H, d, J 8.2, C(6)ArCH), 7.92–7.95 (1H, m, C(6)ArCH), 8.17 (1H, d, J 8.4, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 29.3 (C(7)), 33.2 (C(6)), 52.0 (OCH₃), 61.0 (C(5)), 70.9 (q, J 30.2, C(8)), 107.9 (d, J 2.9, C(1)), 110.5 (C(2)), 121.5 (C(3)), 122.3 (C(6)ArCH), 123.9 (C(6)ArCH), 125.3 (C(6)ArCH), 125.6 (q, J 283.9, CF₃), 126.0 (C(8a)), 126.1 (C(6)ArCH), 127.0 (C(6)ArCH), 128.8 (C(6)ArCH), 129.5 (C(6)ArCH), 131.5 (C(6)ArC), 133.9 (C(6)ArC), 134.0 (C(6)ArC(1)), 169.3

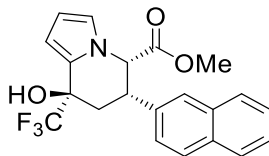
(C(5)CO); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -80.5 (CF_3); HRMS (NSI $^+$) $\text{C}_{21}\text{H}_{19}\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ found 390.1302, requires 390.1312 (-2.4 ppm).

Methyl (5*S*,6*S*,8*R*)-8-hydroxy-6-(*o*-tolyl)-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (255)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-1,1,1-trifluoro-4-(*o*-tolyl)but-3-en-2-one (42.8 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound as a light pink oil (18.0 mg, 25%). ν_{max} (film, cm^{-1}) 3300 (O-H stretch), 2953 (C-H stretch), 1746 (C=O), 1152; $[\alpha]_{\text{D}}^{20} + 180.3$ (c 0.3 in CHCl_3); Chiral HPLC analysis, Chiralpak AD-H (97.5 : 2.5 hexane : IPA, flow rate 1 mLmin $^{-1}$, 211 nm, 30 °C) t_{R} (major): 17.6 min, t_{R} (minor): 77.3 min, >99 : 1 er; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.18 (1H, dd, J 13.5, 2.6, C(7)H(a)H(b)), 2.39 (1H, d, J 1.8, OH), 2.47 (3H, s, CH_3), 3.10 (1H, td, J 13.4, 1.9, C(7)H(a)H(b)), 3.37 (3H, s, OCH_3), 4.23 (1H, ddd, J 13.4, 6.0, 2.6, C(6)H), 4.98 (1H, d, J 5.9, C(5)H), 6.28 (1H, dd, J 3.8, 2.8, C(2)H), 6.49 (1H, dt, J 3.6, 1.7, C(1)H), 6.63 (1H, dd, J 2.8, 1.6, C(3)H), 7.04–7.10 (1H, m, C(6)ArCH), 7.17–7.25 (3H, m, C(6)ArCH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 19.5 (CH_3), 29.2 (C(7)), 34.0 (C(6)), 52.2 (OCH_3), 60.1 (C(5)), 70.8 (q, J 30.3, C(8)), 107.7 (C(1)), 110.4 (C(2)), 121.4 (C(3)), 125.5 (q, J 284.2, CF_3), 125.9 (C(8a)), 126.0 (C(6)ArCH), 126.5 (C(6)ArCH), 127.9 (C(6)ArCH), 131.0 (C(6)ArCH), 135.9 (C(6)ArC(2)), 136.4 (C(6)ArC(1)), 169.5 (C(5)CO); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -80.6 (CF_3); HRMS (ASAP $^+$) $\text{C}_{18}\text{H}_{19}\text{F}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ found 354.1315, requires 354.1317 (-0.6 ppm).

Methyl (5S,6S,8R)-8-hydroxy-6-(naphthalen-2-yl)-8-(trifluoromethyl)-5,6,7,8-tetrahydroindolizine-5-carboxylate (257)

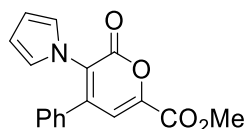


Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (30.0 mg, 0.24 mmol, 1.2 eq.), *i*-Pr₂NEt (0.070 mL, 0.40 mmol), pivaloyl chloride (0.050 mL, 0.40 mmol) in *i*-PrOAc (2 mL) at 0 °C for 20 min followed by HyperBTM **93** (6.2 mg, 10 mol%), (*E*)-1,1,1-trifluoro-4-(naphthalen-2-yl)but-3-en-2-one (50.0 mg, 0.20 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.089 mL, 0.5 mmol) at -40 °C for 20 h. Ring-opening with MeOH (2 mL) and DMAP (4.9 mg, 20 mol%) at rt for 24 h gave crude product (85:15 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (65.0 mg, 83%). ν_{\max} (film, cm⁻¹) 3472 (O-H stretch), 3055 (C-H stretch), 2903 (C-H stretch), 1742 (C=O), 1171; $[\alpha]_{\text{D}}^{20} + 118.9$ (*c* 2.7 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (97.5:2.5 hexane/IPA, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) t_{R} (major): 69.1 min, t_{R} (minor): 91.9 min, 98 : 2 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.37 (1H, dd, *J* 13.5, 2.7, C(7)*H*(a)*H*(b)), 2.40 (1H, d, *J* 1.8, OH), 3.19 (1H, td, *J* 13.5, 1.9, C(7)*H*(a)*H*(b)), 3.31 (3H, s, OCH₃), 4.20 (1H, ddd, *J* 13.5, 6.0, 2.7, C(6)*H*), 5.10 (1H, d, *J* 6.0, C(5)*H*), 6.29 (1H, dd, *J* 3.8, 2.8, C(2)*H*), 6.52 (1H, dt, *J* 3.6, 1.7, C(1)*H*), 6.66 (1H, dd, *J* 2.8, 1.6, C(3)*H*), 7.39 (1H, dd, *J* 8.5, 1.9, C(6)ArCH), 7.48–7.54 (2H, m, C(6)ArCH), 7.68–7.74 (1H, m, C(6)ArCH), 7.80–7.89 (3H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 28.9 (C(7)), 38.1 (C(6)), 52.3 (OCH₃), 62.2 (C(5)), 70.7 (q, *J* 30.3, C(8)), 107.9 (C(1)), 110.5 (C(2)), 121.4 (C(3)), 125.5 (q, *J* 280.9, CF₃), 125.9 (C(8a)), 125.9 (C(6)ArCH), 126.3 (C(6)ArCH), 126.4 (C(6)ArCH), 126.6 (C(6)ArCH), 127.8 (C(6)ArCH), 128.0 (C(6)ArCH), 128.7 (C(6)ArCH), 133.0 (C(6)ArC), 133.5 (C(6)ArC), 135.4 (C(6)ArC(1)), 169.4 (C(5)CO); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -80.5 (CF₃); HRMS (ASAP⁺) C₂₁H₁₉F₃NO₃ [M+H]⁺ found 390.1314, requires 390.1317 (-0.8 ppm).

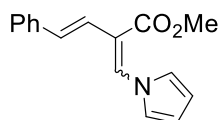
Selected data for minor diastereoisomer: Chiral HPLC analysis, Chiralpak AD-H (97.5 : 2.5 hexane:IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 40.5 min, t_{R} (minor): 75.5 min, 98 : 2 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.42–2.48 (2H, m, C(7)*H*₂), 2.66 (1H, m, OH), 3.58 (3H, s, OCH₃), 4.07 (1H, td, *J* 10.7, 5.8, C(6)*H*), 4.87 (1H, d, *J* 11.0, C(5)*H*), 6.28 (1H, dd, *J* 3.9, 2.9, C(2)*H*), 6.50 (1H, dd, *J* 3.7, 1.8, C(1)*H*), 6.61 (1H, dd, *J* 2.9, 1.6, C(3)*H*), 7.39 (1H, dd, *J* 8.5, 1.9, C(6)ArCH),

7.47–7.53 (2H, m, C(6)ArCH), 7.75 (1H, d, J 1.8, C(6)ArCH), 7.78–7.86 (3H, m, C(6)ArCH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} (selected): 35.0 (C(7)), 39.9 (C(6)), 52.9 (OCH₃), 64.4 (C(5)), 70.3 (d, J 30.5, C(8)), 107.9 (C(1)), 110.1 (C(2)), 121.0 (C(3)), 125.5 (C(8a)), 126.4 (C(6)ArCH), 126.6 (C(6)ArCH), 127.0 (C(6)ArCH), 127.9 (C(6)ArCH), 128.0 (C(6)ArCH), 129.1 (C(6)ArCH), 133.1 (C(6)ArC), 133.6 (C(6)ArC), 136.3 (C(6)ArC(1)), 170.5 (C(5)CO); ^{19}F NMR (471 MHz, CDCl_3) δ_{F} : -80.2 (CF₃)

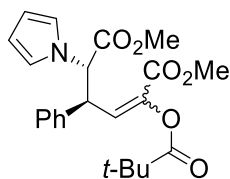
Methyl 2-oxo-4-phenyl-3-(1H-pyrrol-1-yl)-2H-pyran-6-carboxylate (**264**)



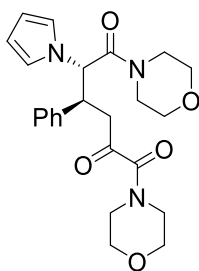
2-(1H-Pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.) was dissolved in anhydrous MeCN (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2 eq.) and pivaloyl chloride (0.062 mL, 0.5 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before warming up to rt. HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **132** (47.6 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) were added sequentially and the reaction stirred at rt. for 24 h. Upon completion of the reaction (checked by TLC), the solvent was concentrated under reduced pressure and the crude was purified by flash silica column chromatography (15:85 EtOAc/petrol) to give the titled compound as a yellow oil (34.2 mg, 58%). ν_{max} (film, cm⁻¹) 3107 (C-H), 2955 (C-H), 1736 (C=O), 1726 (C=O), 1643 (C=C), 1244; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 4.00 (3H, s, CH₃), 6.21 (2H, t, J 2.2, C(3)Ar(3,4)H), 6.59 (2H, t, J 2.2, C(3)Ar(2,5)H), 7.06–7.12 (2H, m, C(4)ArC(2,6)H), 7.34–7.42 (4H, m, C(4)ArC(3,4,5)H + C(5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 53.3 (CH₃), 110.5 (C(3)ArC(3,4)H), 113.7 (C(5)H), 121.8 (C(3)ArC(2,5)H), 127.7 (C(4)ArC(2,6)H), 129.0 (C(4)ArC(3,5)H), 130.3 (C(4)ArC(4)H), 133.7 (C(3)ArC(1)), 144.8 (C(4)), 145.7 (C(3)), 158.4 (C(2)CO), 159.6 (C(6)CO₂Me); HRMS (ESI⁺) C₁₇H₁₄NO₄ [M+H]⁺ found 296.0918, requires 296.0917 (+0.2 ppm).

Methyl (3E)-2-((1H-pyrrol-1-yl)methylene)-4-phenylbut-3-enoate (265)

2-(1*H*-Pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.) was dissolved in anhydrous MeCN (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2 eq.) and pivaloyl chloride (0.062 mL, 0.5 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before warming up to rt. HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **132** (47.6 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) were added sequentially and the reaction stirred at rt. for 24 h. Upon completion of the reaction (checked by TLC), the solvent was concentrated under reduced pressure and the crude was purified by flash silica column chromatography (15:85 EtOAc/petrol) to give the titled compound as a colourless oil (11.4 mg, 18%, 88:12 mixture of stereoisomers). ν_{\max} (film, cm⁻¹) 3026 (C-H stretch), 2951 (C-H stretch), 1713 (C=C), 1225; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 3.86 (3H, s, OCH₃), 6.32 (2H, t, *J* 2.2, pyrroleC(3,4)*H*), 6.97 (1H, dd, *J* 16.4, 1.0, CH=CHPh), 7.05 (2H, t, *J* 2.2, pyrroleC(2,5)*H*), 7.18 (1H, d, *J* 16.4, CH=CHPh), 7.27–7.30 (1H, Ar*H*), 7.33–7.38 (2H, m, Ar*H*), 7.45–7.49 (2H, m, Ar*H*), 7.84 (1H, s, C(1)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 52.3 (OCH₃), 112.0 (pyrroleC(3,4)*H*), 115.6 (CH=CHPh), 120.0 (pyrroleC(2,5)*H*), 122.9 (CH=CHPh), 126.8 (ArCH), 128.2 (ArCH), 128.9 (ArCH), 135.4 (C(1)), 136.2 (ArC(1)), 137.3 (C(2)), 167.7 (CO₂Me); HRMS (NSI⁺) C₁₆H₁₆NO₂ [M+H]⁺ found 254.1177, requires 254.1176 (+0.6 ppm).

Dimethyl (4*S*,5*S*)-4-phenyl-2-(pivaloyloxy)-5-(1*H*-pyrrol-1-yl)hex-2-enedioate (268)

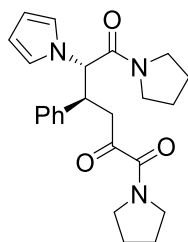
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **132** (47.6 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with MeOH (2 mL) and DMAP (6.1 mg, 20 mol%) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as an off-white gum (72.4 mg, 70%). ν_{\max} (film, cm⁻¹) 2980 (C-H stretch), 2968 (C-H stretch), 1740 (C=O), 1277, 1111; $[\alpha]_D^{20}$ +83.1 (c 1.4 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (99:1 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 15.4 min, t_R (minor): 26.9 min, >99:1 er; ¹H NMR (500 MHz, CDCl₃) δ_H : 1.36 (9H, s, 3 x CH₃), 3.74 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 4.41 (1H, t, *J* 10.4, C(4)*H*), 4.85 (1H, d, *J* 10.5, C(5)*H*), 5.98 (2H, t, *J* 2.2, C(5)Ar(3,4)*H*), 6.58 (2H, t, *J* 2.2, C(5)Ar(2,5)*H*), 6.69 (1H, d, *J* 10.4, C(3)*H*), 6.99–7.06 (2H, m, C(4)ArC(2,6)*H*), 7.14–7.24 (3H, m, C(4)ArC(3,4,5)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 27.1 (3 x CH₃), 39.2 (3CH₃C), 46.6 (C(4)), 52.7 (OCH₃), 52.9 (OCH₃), 66.1 (C(5)), 108.8 (C(5)ArC(3,4)*H*), 120.5 (C(5)ArC(2,5)*H*), 127.1 (C(4)ArC(2,6)*H*), 127.8 (C(4)ArC(3,5)*H*), 127.9 (C(4)ArC(4)*H*), 128.9 (C(2)), 137.0 (C(4)ArC(1)), 139.7 (C(3)*H*), 162.1 (C(6)OOMe), 169.3 (C(1)OOMe), 176.0 (C(2)OCO); HRMS (NSI⁺) C₂₃H₂₈NO₆ [M+H]⁺ found 414.1905, requires 414.1911 (-1.5 ppm).

(4*S*,5*S*)-1,6-Dimorpholino-4-phenyl-5-(1*H*-pyrrol-1-yl)hexane-1,2,6-trione (269)

Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5

mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **132** (47.6 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (300 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a white solid (76.9 mg, 70%). mp 154–156 °C; $[\alpha]_D^{20}$ - 50.7 (*c* 1.1 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 25.2 min, *t*_R (minor): 33.3 min, >99:1 er; v_{\max} (film, cm⁻¹) 2967 (C-H), 2920 (C-H), 2857 (C-H), 1713 (C=O), 1638 (amide C=O), 1441, 1271, 1113; ¹H NMR (500 MHz, CDCl₃) δ _H: 2.94 (1H, ddd, *J* 11.2, 7.8, 3.1, morpholineCH), 3.09 (2H, dd, *J* 5.7, 4.0, morpholineCH), 3.25–3.43 (7H, m, morpholineCH + C(3)H₂), 3.46–3.73 (7H, m, morpholineCH), 3.89 (1H, ddd, *J* 13.4, 5.3, 3.0, morpholineCH), 4.11 (1H, td, *J* 9.7, 4.6, C(4)H), 4.80 (1H, d, *J* 10.0, C(5)H), 5.93 (2H, t, *J* 2.1, C(5)Ar(3,4)H), 6.36 (2H, t, *J* 2.1, C(5)Ar(2,5)H), 7.01–7.05 (2H, m, PhH), 7.14–7.20 (3H, m, PhH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ _C: 41.9 (morpholineC), 42.7 (C(3)), 43.0 (morpholineC), 44.4 (C(4)), 45.7 (morpholineC), 46.3 (morpholineC), 63.5 (C(5)), 66.2 (morpholineC), 66.5 (morpholineC), 66.6 (morpholineC), 66.7 (morpholineC), 108.9 (C(5)ArC(3,4)H), 119.6 (C(5)ArC(2,5)H), 127.4 (C(4)PhCH), 128.0 (C(4)PhCH), 128.5 (C(4)PhCH), 139.2 (C(4)PhC(1)), 164.3 (C(6)), 166.4 (C(2)), 197.7 (C(1)); HRMS (ESI⁺) C₂₄H₂₉N₃O₅Na [M+Na]⁺ found 462.1988, requires 462.1999 (-2.5 ppm).

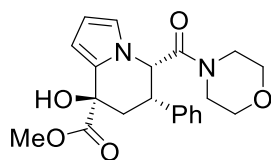
(4S,5S)-4-Phenyl-5-(1*H*-pyrrol-1-yl)-1,6-di(pyrrolidin-1-yl)hexane-1,2,6-trione (270)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **132** (47.6 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with pyrrolidine (300 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a

white solid (75.4 mg, 74%). mp 148–151 °C; $[\alpha]_D^{20} + 91.0$ (*c* 1.5 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (90:10 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 21.3 min, *t*_R (minor): 27.8 min, >99:1 er; ν_{\max} (film, cm⁻¹) 2974 (C-H), 2878 (C-H), 1715 (C=O), 1638 (amide C=O), 1605 (C=O), 1447; ¹H NMR (500 MHz, CDCl₃) δ_H : 1.72–2.02 (8H, m, pyrrolidineCH), 3.18–3.34 (4H, m, C(3)H(a)H(b) + pyrrolidineCH), 3.39–3.60 (6H, m, C(3)H(a)H(b) + pyrrolidineCH), 4.10 (1H, td, *J* 10.2, 4.3, C(4)H), 4.72 (1H, d, *J* 10.4, C(5)H), 5.92 (2H, t, *J* 2.1, C(5)Ar(3,4)H), 6.51 (2H, t, *J* 2.2, C(5)Ar(2,5)H), 7.05–7.08 (2H, m, C(6)ArC(2,6)H), 7.11–7.18 (3H, m, C(6)ArC(3,4,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 23.5 (pyrrolidineC), 24.1 (pyrrolidineC), 26.0 (pyrrolidineC), 26.3 (pyrrolidineC), 41.7 (C(3)), 44.5 (C(4)), 46.3 (pyrrolidineC), 46.4 (pyrrolidineC), 46.4 (pyrrolidineC), 47.1 (pyrrolidineC), 65.6 (C(5)), 108.2 (C(5)ArC(3,4)H), 120.1 (C(5)ArC(2,5)H), 127.0 (C(4)ArC(2,6)H), 128.0 (C(4)ArC(3,5)H), 128.3 (C(4)ArC(4)H), 139.6 (C(4)ArC(1)), 162.2 (C(6)), 166.5 (C(2)), 197.7 (C(1)); HRMS (ESI⁺) C₂₄H₂₉N₃O₃Na [M+Na]⁺ found 430.2091, requires 430.2101 (-2.4 ppm).

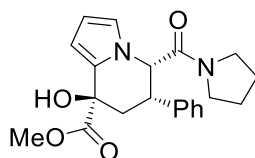
Methyl (5S,6S,8R)-8-hydroxy-5-(morpholine-4-carbonyl)-6-phenyl-5,6,7,8-tetrahydroindolizine-8-carboxylate (271)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **132** (47.6 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a light yellow oil (72.1 mg, 75%). ν_{\max} (film, cm⁻¹) 3399 (O-H stretch), 2961 (C-H), 2926 (C-H), 2857 (C-H), 1732 (C=O), 1643 (amide C=O); $[\alpha]_D^{20} + 50.2$ (*c* 2.4 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (80:20 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 18.8 min, *t*_R (minor): 31.9 min, >99.5 : 0.5 er; ¹H NMR (500 MHz, CDCl₃) δ_H : 2.02 (1H, dd, *J* 13.1, 2.6, C(7)H(a)H(b)), 2.46–2.57 (2H, m, morpholineCH), 3.16 (1H, ddd, *J* 13.7, 7.5, 3.1,

morpholineCH), 3.26–3.40 (3H, m, morpholineCH), 3.47–3.54 (2H, m, morpholineCH), 3.55 (1H, d, J 1.3, OH), 3.73 (1H, td, J 13.3, 1.4, C(7)H(a)H(b)), 3.90 (3H, s, OCH₃), 4.10 (1H, ddd, J 13.5, 6.1, 2.6, C(6)H), 5.34 (1H, d, J 6.0, C(5)H), 6.10 (1H, dd, J 3.7, 1.6, C(2)H), 6.21 (1H, dd, J 3.7, 2.8, C(1)H), 6.41 (1H, dd, J 2.8, 1.6, C(3)H), 7.31–7.39 (5H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 32.8 (C(7)), 39.5 (C(6)), 42.1 (morpholineC), 45.9 (morpholineC), 53.7 (OCH₃), 56.2 (C(5)), 65.8 (morpholineC), 66.4 (morpholineC), 71.2 (C(8)), 105.9 (C(2)), 110.1 (C(1)), 119.5 (C(3)), 128.3 (C(6)ArCH), 128.8 (C(6)ArCH), 129.1 (C(6)ArCH), 130.3 (C(8a)), 138.9 (C(6)ArC(1)), 167.2 (C(5)C=O), 175.1 (C(8)C=O); HRMS (NSI⁺) C₂₁H₂₅N₂O₅ [M+H]⁺ found 385.1760, requires 385.1758 (+0.5 ppm).

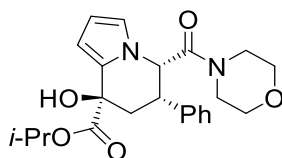
Methyl (5S,6S,8R)-8-hydroxy-6-phenyl-5-(pyrrolidine-1-carbonyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (272)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α-keto-β,γ-unsaturated ester **132** (47.6 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at –40 °C for 24 h. Ring-opening with pyrrolidine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a light yellow oil (66.3 mg, 72%). ν_{max} (film, cm⁻¹) 3393 (O-H stretch), 2972 (C-H), 2951 (C-H), 1732 (C=O), 1643 (amide C=O); [α]_D²⁰ + 122.7 (c 1.8 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80: 20 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 21.2 min, t_R (minor): 29.3 min, >99.5:0.5 er; ¹H NMR (500 MHz, CDCl₃) δ_H: 1.43–1.74 (4H, m, pyrrolidineCH), 1.99 (1H, dd, J 13.0, 2.5, C(7)H(a)H(b)), 2.22 (1H, ddd, J 9.5, 7.7, 5.2, pyrrolidineCH), 3.16 (2H, dt, J 12.1, 7.0, pyrrolidineCH), 3.36 (1H, ddd, J 12.7, 7.5, 5.3, pyrrolidineCH), 3.55 (1H, s, OH), 3.78 (1H, t, J 13.3, C(7)H(a)H(b)), 3.88 (3H, s, OCH₃), 4.07 (1H, ddd, J 13.5, 5.9, 2.6, C(6)H), 5.11 (1H, d, J 5.9, C(5)H), 6.09 (1H, dd, J 3.7, 1.6, C(2)H), 6.20 (1H, dd, J 3.7, 2.8, C(1)H), 6.44 (1H, dd, J 2.8, 1.6, C(3)H), 7.27–7.38 (5H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 23.9 (pyrrolidineC),

26.1 (pyrrolidineC), 32.9 (C(7)), 39.8 (C(6)), 45.8 (pyrrolidineC), 46.4 (pyrrolidineC), 53.6 (OCH₃), 59.5 (C(5)), 71.2 (C(8)), 105.7 (C(2)), 109.9 (C(1)), 119.7 (C(3)), 128.0 (C(6)ArCH), 128.6 (C(6)ArCH), 128.6 (C(6)ArCH), 130.2 (C(8a)), 139.0 (C(6)ArC(1)), 166.8 (C(5)C=O), 175.2 (C(8)C=O); HRMS (NSI⁺) C₂₁H₂₅N₂O₄ [M+H]⁺ found 369.1810, requires 369.1809 (+0.3 ppm).

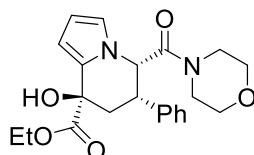
Isopropyl (5S,6S,8R)-8-hydroxy-5-(morpholine-4-carbonyl)-6-phenyl-5,6,7,8-tetrahydroindolizine-8-carboxylate (273)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α-keto-β,γ-unsaturated ester **485** (54.6 mg, 0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a brown oil (66.0 mg, 64%). ν_{\max} (film, cm⁻¹) 3414 (O-H stretch), 2974 (C-H), 2936 (C-H), 2922 (C-H), 1713 (C=O), 1649 (amide C=O), 1234, 1111; $[\alpha]_D^{20} + 77.5$ (c 1.0 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90: 10 hexane : IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 27.3 min, t_R (minor): 56.9 min, >99.5:0.5 er; ¹H NMR (400 MHz, CDCl₃) δ_H : 1.33 (3H, d, *J* 6.2, CH₃), 1.36 (3H, d, *J* 6.3, CH₃), 1.98 (1H, dd, *J* 13.1, 2.6, C(7)H(a)H(b)), 2.51–2.58 (2H, m, morpholineCH), 3.16 (1H, ddd, *J* 12.7, 7.2, 3.1, morpholineCH), 3.23–3.40 (3H, m, morpholineCH), 3.46–3.54 (2H, m, morpholineCH), 3.61 (1H, s, OH), 3.70 (1H, t, *J* 13.3, C(7)H(a)H(b)), 4.12 (1H, ddd, *J* 13.2, 6.0, 2.4, C(6)H), 5.20 (1H, septet, *J* 6.3, *i*Pr(CH)), 5.34 (1H, d, *J* 6.2, C(5)H), 6.08 (1H, dd, *J* 3.7, 1.6, C(2)H), 6.19 (1H, dd, *J* 3.7, 2.8, C(1)H), 6.40 (1H, dd, *J* 2.8, 1.7, C(3)H), 7.29–7.43 (5H, m, C(6)ArCH); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C : 21.5 (CH₃), 21.8 (CH₃), 32.7 (C(7)), 39.4 (C(6)), 42.1 (morpholineC), 45.9 (morpholineC), 56.2 (C(5)), 65.8 (morpholineC), 66.5 (morpholineC), 70.6 (*i*Pr(CH)), 71.1 (C(8)), 105.6 (C(2)), 110.0 (C(1)), 119.4 (C(3)), 128.2 (C(6)ArCH), 128.8 (C(6)ArCH), 129.0 (C(6)ArCH), 130.7 (C(8a)), 139.1 (C(6)ArC(1)),

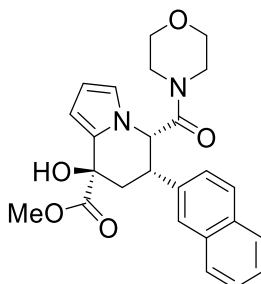
167.3 (C(5)C=O), 173.7 (C(8)C=O); HRMS (ESI⁺) C₂₃H₂₈N₂O₅Na [M+Na]⁺ found 435.1882, requires 435.1890 (-1.9 ppm).

Ethyl (5S,6S,8R)-8-hydroxy-5-(morpholine-4-carbonyl)-6-phenyl-5,6,7,8-tetrahydroindolizine-8-carboxylate (274)



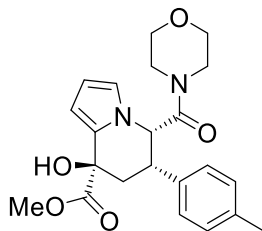
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α-keto-β,γ-unsaturated ester **486** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a colourless oil (54.8 mg, 55%). ν_{\max} (film, cm⁻¹) 3420 (O-H stretch), 2978 (C-H), 2928 (C-H), 2859 (C-H), 1730 (C=O), 1649 (amide C=O); $[\alpha]_{\text{D}}^{20}$ + 101.6 (*c* 1.2 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90: 10 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 31.4 min, *t*_R (minor): 63.7 min, >99.5:0.5 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.36 (3H, t, *J* 7.1, CH₃), 2.01 (1H, dd, *J* 13.0, 2.6, C(7)*H*(a)*H*(b)), 2.51 (2H, ddt, *J* 10.2, 6.8, 3.4, morpholineCH), 3.17 (1H, ddd, *J* 13.8, 7.3, 3.1, morpholineCH), 3.26–3.39 (3H, m, morpholineCH), 3.45–3.53 (2H, m, morpholineCH), 3.57 (1H, d, *J* 1.3, OH), 3.71 (1H, t, *J* 13.3, C(7)*H*(a)*H*(b)), 4.12 (1H, ddd, *J* 13.5, 6.1, 2.5, C(6)*H*), 4.37 (2H, qd, *J* 7.1, 1.1, CH₂), 5.34 (1H, d, *J* 6.1, C(5)*H*), 6.10 (1H, dd, *J* 3.7, 1.6, C(2)*H*), 6.20 (1H, dd, *J* 3.7, 2.8, C(1)*H*), 6.41 (1H, dd, *J* 2.8, 1.6, C(3)*H*), 7.29–7.40 (5H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 14.3 (CH₃), 32.8 (C(7)), 39.4 (C(6)), 42.1 (morpholineC), 45.9 (morpholineC), 56.2 (C(5)), 62.8 (CH₂), 65.8 (morpholineC), 66.5 (morpholineC), 71.1 (C(8)), 105.8 (C(2)), 110.1(C(1)), 119.5 (C(3)), 128.3 (C(6)ArCH), 128.8 (C(6)ArCH), 129.1 (C(6)ArCH), 130.5 (C(8a)), 139.0 (C(6)ArC(1)), 167.3 (C(5)C=O), 174.4 (C(8)C=O); HRMS (ESI⁺) C₂₂H₂₆N₂O₅Na [M+Na]⁺ found 421.1723, requires 421.1734 (-2.6 ppm).

Methyl (5S,6S,8R)-8-hydroxy-5-(morpholine-4-carbonyl)-6-(naphthalen-2-yl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (275)



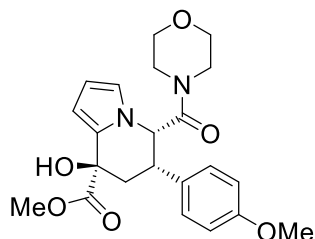
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **487** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a colourless oil (85.8 mg, 79%). ν_{max} (film, cm⁻¹) 3402 (O-H stretch), 3055 (C-H), 2955 (C-H), 2857 (C-H), 1719 (C=O), 1645 (amide C=O); $[\alpha]_{\text{D}}^{20} + 75.6$ (*c* 2.3 in CHCl₃); Chiral HPLC analysis, Chiralpak IB (80 : 20 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t_R* (major): 50.6 min, *t_R* (minor): 65.4 min, >99.5:0.5 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.08–2.14 (2H, m, C(7)H(a)H(b) + morpholineCH), 2.39 (1H, ddd, *J* 13.0, 6.3, 3.0, morpholineCH), 3.03–3.14 (3H, m, morpholineCH), 3.30 (1H, ddd, *J* 12.4, 7.3, 2.4, morpholineCH), 3.36–3.49 (2H, m, morpholineCH), 3.61 (1H, d, *J* 1.3, OH), 3.85 (1H, td, *J* 13.3, 1.4, C(7)H(a)H(b)), 3.93 (3H, s, OCH₃), 4.26 (1H, ddd, *J* 13.5, 6.0, 2.6, C(6)H), 5.43 (1H, d, *J* 6.0, C(5)H), 6.13 (1H, dd, *J* 3.7, 1.6, C(2)H), 6.23 (1H, dd, *J* 3.7, 2.7, C(1)H), 6.44 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.41–7.55 (3H, m, C(6)ArCH), 7.76–7.88 (4H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 33.0 (C(7)), 39.7 (C(6)), 42.1 (morpholineC), 45.9 (morpholineC), 53.7 (OCH₃), 56.3 (C(5)), 65.6 (morpholineC), 66.3 (morpholineC), 71.2 (C(8)), 105.9 (C(2)), 110.1 (C(1)), 119.6 (C(3)), 126.6 (C(6)ArCH), 126.7 (C(6)ArCH), 126.9 (C(6)ArCH), 127.4 (C(6)ArCH), 127.8 (C(6)ArCH), 127.9 (C(6)ArCH), 128.6 (C(6)ArCH), 130.4 (C(8a)), 132.9 (C(6)ArC), 133.6 (C(6)ArC), 136.2 (C(6)ArC(1)), 167.2 (C(5)C=O), 175.0 (C(8)C=O); HRMS (ESI⁺) C₂₅H₂₆N₂O₅Na [M+Na]⁺ found 457.1726, requires 457.1734 (-1.7 ppm).

Methyl (5S,6S,8R)-8-hydroxy-5-(morpholine-4-carbonyl)-6-(*p*-tolyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (276)



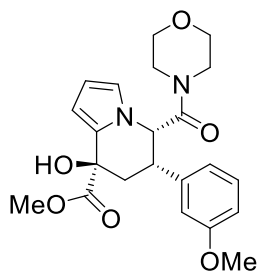
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **488** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (94.6 mg, 95%); ν_{\max} (film, cm⁻¹) 3410 (O-H stretch), 2955 (C-H), 2926 (C-H), 2859 (C-H), 1715 (C=O), 1645 (amide C=O); $[\alpha]_{\text{D}}^{20}$ + 97.0 (*c* 2.1 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90 : 10 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 38.5 min, t_{R} (minor): 55.0 min, >99.5:0.5 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.98 (1H, dd, *J* 13.1, 2.6, C(7)*H*(a)*H*(b)), 2.36 (3H, s, CH₃), 2.49–2.58 (2H, m, morpholineCH), 3.12–3.19 (1H, m, morpholineCH), 3.28–3.39 (3H, m, morpholineCH), 3.45–3.53 (2H, m, morpholineCH), 3.55 (1H, s, OH), 3.68 (1H, td, *J* 13.3, 1.3, C(7)*H*(a)*H*(b)), 3.89 (3H, s, OCH₃), 4.05 (1H, ddd, *J* 13.6, 6.0, 2.6, C(6)*H*), 5.31 (1H, d, *J* 6.0, C(5)*H*), 6.09 (1H, dd, *J* 3.7, 1.6, C(2)*H*), 6.20 (1H, dd, *J* 3.7, 2.8, C(1)*H*), 6.41 (1H, dd, *J* 2.8, 1.6, C(3)*H*), 7.13–7.24 (4H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 21.3 (CH₃), 33.0 (C(7)), 39.1 (C(6)), 42.1 (morpholineC), 45.9 (morpholineC), 53.7 (OCH₃), 56.3 (C(5)), 65.8 (morpholineC), 66.5 (morpholineC), 71.2 (C(8)), 105.8 (C(2)), 110.1 (C(1)), 119.5 (C(3)), 128.6 (C(6)ArC(3,5)H), 129.6 (C(6)ArC(2,6)H), 130.3 (C(8a)), 135.8 (C(6)ArC(4)), 138.0 (C(6)ArC(1)), 167.3 (C(5)C=O), 175.1 (C(8)C=O); HRMS (ESI⁺) C₂₂H₂₆N₂O₅Na [M+Na]⁺ found 421.1729, requires 421.1734 (-1.2 ppm).

Methyl (5S,6S,8R)-8-hydroxy-6-(4-methoxyphenyl)-5-(morpholine-4-carbonyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (277)



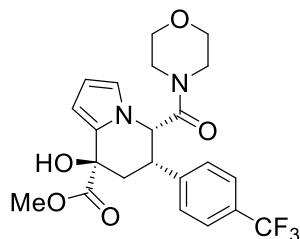
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous CH₂Cl₂ (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α-keto-β,γ-unsaturated ester **489** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (51.8 mg, 50%). ν_{\max} (film, cm⁻¹) 3406 (O-H stretch), 2959 (C-H), 2857 (C-H), 1732 (C=O), 1645 (amide C=O); $[\alpha]_{\text{D}}^{20} + 99.3$ (c 1.7 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90 : 10 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{R} (major): 56.4 min, t_{R} (minor): 80.8 min, >99.5:0.5 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.94–1.99 (1H, m, C(7)H(a)H(b)), 2.54 (1H, ddd, *J* 13.2, 6.5, 3.0, morpholineCH), 2.68 (1H, ddd, *J* 11.5, 6.8, 3.0, morpholineCH), 3.17–3.23 (1H, m, morpholineCH), 3.32–3.45 (3H, m, morpholineCH), 3.47–3.56 (2H, m, morpholineCH), 3.57 (1H, s, OH), 3.62–3.72 (1H, m, C(7)H(a)H(b)), 3.81 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 4.03 (1H, ddd, *J* 13.6, 6.0, 2.6, C(6)H), 5.31 (1H, d, *J* 6.1, C(5)H), 6.09 (1H, dd, *J* 3.7, 1.6, C(2)H), 6.19 (1H, dd, *J* 3.7, 2.7, C(1)H), 6.40 (1H, dd, *J* 2.8, 1.6, C(3)H), 6.84–6.90 (2H, m, C(6)ArC(3,5)H), 7.21–7.25 (2H, m, C(6)ArC(2,4)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 33.0 (C(7)), 38.5 (C(6)), 42.0 (morpholineC), 45.8 (morpholineC), 53.5 (OCH₃), 55.4 (OCH₃), 56.2 (C(5)), 65.8 (morpholineC), 66.4 (morpholineC), 71.1 (C(8)), 105.7 (C(2)), 110.0 (C(1)), 114.2 (C(6)ArC(3,5)H), 119.4 (C(3)), 129.6 (C(6)ArC(2,6)H), 130.2 (C(8a)), 130.7 (C(6)ArC(1)), 159.4 (C(6)ArC(4)), 167.3 (C(5)C=O), 175.0 (C(8)C=O); HRMS (ESI⁺) C₂₂H₂₆N₂O₆Na [M+Na]⁺ found 437.1668, requires 437.1683 (-3.5 ppm).

Methyl (5S,6S,8R)-8-hydroxy-6-(3-methoxyphenyl)-5-(morpholine-4-carbonyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (278)



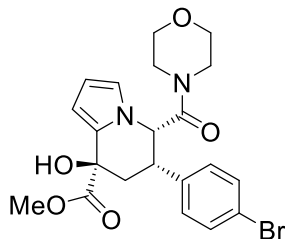
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **490** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (65.3 mg, 63%). ν_{\max} (film, cm⁻¹) 3416 (O-H stretch), 2955 (C-H), 2857 (C-H), 1732 (C=O), 1645 (amide C=O); $[\alpha]_D^{20} + 84.5$ (*c* 1.3 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90 : 10 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 46.8 min, t_R (minor): 68.2 min, >99.5:0.5 er; ¹H NMR (500 MHz, CDCl₃) δ_H : 2.01 (1H, dd, *J* 13.1, 2.6, C(7)H(a)H(b)), 2.56–2.64 (2H, m, morpholineCH), 3.17–3.22 (1H, m, morpholineCH), 3.29–3.37 (3H, m, morpholineCH), 3.51–3.56 (3H, m, OH + morpholineCH), 3.68 (1H, td, *J* 13.3, 1.3, C(7)H(a)H(b)), 3.81 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 4.07 (1H, ddd, *J* 13.5, 6.0, 2.6, C(6)H), 5.33 (1H, d, *J* 6.0, C(5)H), 6.09 (1H, dd, *J* 3.7, 1.6, C(2)H), 6.20 (1H, dd, *J* 3.7, 2.8, C(1)H), 6.41 (1H, dd, *J* 2.8, 1.6, C(3)H), 6.84–6.88 (2H, m, C(6)ArC(4,5)H), 6.90–6.93 (1H, m, C(6)ArC(6)H), 7.27–7.31 (1H, m, C(6)ArC(2)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 32.9 (C(7)), 39.6 (C(6)), 42.2 (morpholineC), 46.0 (morpholineC), 53.7 (OCH₃), 55.6 (OCH₃), 56.1 (C(5)), 65.9 (morpholineC), 66.5 (morpholineC), 71.2 (C(8)), 105.9 (C(2)), 110.1 (C(1)), 113.1 (C(6)ArCH), 114.8 (C(6)ArCH), 119.5 (C(3)), 121.0 (C(6)ArCH), 130.0 (C(6)ArCH), 130.3 (C(8a)), 140.5 (C(6)ArC(1)), 160.2 (C(6)ArC(3)), 167.2 (C(5)C=O), 175.0 (C(8)C=O); HRMS (ESI⁺) C₂₂H₂₆N₂O₆Na [M+Na]⁺ found 437.1670, requires 437.1683 (-3.0 ppm).

Methyl (5S,6S,8R)-8-hydroxy-5-(morpholine-4-carbonyl)-6-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (279)



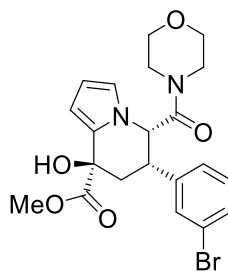
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **491** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (62.2 mg, 55%). ν_{\max} (film, cm⁻¹) 3387 (O-H stretch), 2961 (C-H), 2860 (C-H), 1732 (C=O), 1645 (amide C=O); $[\alpha]_{\text{D}}^{20} + 98.4$ (c 1.1 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90 : 10 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_{r} (major): 88.3 min, t_{r} (minor): 134.8 min, >99:1 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.00–2.04 (1H, m, C(7)H(a)H(b)), 2.51–2.63 (2H, m, morpholineCH), 3.16–3.31 (2H, m, morpholineCH), 3.34–3.48 (3H, m, morpholineCH), 3.53 (1H, ddd, *J* 11.5, 5.9, 3.3, morpholineCH), 3.58 (1H, s, OH), 3.78 (1H, t, *J* 13.2, C(7)H(a)H(b)), 3.91 (3H, s, OCH₃), 4.18 (1H, ddd, *J* 13.5, 6.0, 2.6, C(6)H), 5.35 (1H, d, *J* 6.0, C(5)H), 6.11 (1H, dd, *J* 3.8, 1.6, C(2)H), 6.22 (1H, dd, *J* 3.7, 2.8, C(1)H), 6.42 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.49 (2H, d, *J* 8.0, C(6)ArC(2,6)H), 7.64 (2H, d, *J* 8.1, C(6)ArC(3,5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 32.6 (C(7)), 39.4 (C(6)), 42.2 (morpholineC), 46.1 (morpholineC), 53.8 (OCH₃), 55.7(C(5)), 65.8 (morpholineC), 66.5 (morpholineC), 71.0 (C(8)), 106.1 (C(2)), 110.3 (C(1)), 119.6 (C(3)), 123.4 (q, *J* 272.0, CF₃), 125.9 (app. d, *J* 4.0, C(6)ArC(3,5)H), 129.2 (C(6)ArC(2,6)H), 130.1 (C(8a)), 130.7 (q, *J* 33.1, C(6)ArC(4)), 143.1 (C(6)ArC(1)), 166.9 (C(5)C=O), 174.7 (C(8)C=O); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -62.5 (CF₃); HRMS (ESI⁺) C₂₂H₂₃N₂O₅F₃Na [M+Na]⁺ found 475.1451, requires 475.1451 (-0.1 ppm).

Methyl (5S,6S,8R)-6-(4-bromophenyl)-8-hydroxy-5-(morpholine-4-carbonyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (280)



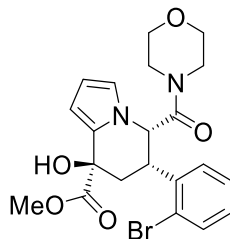
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **492** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (69.5 mg, 60%). ν_{\max} (film, cm⁻¹) 3406 (O-H stretch), 2955 (C-H), 2859 (C-H), 1734 (C=O), 1647 (amide C=O); $[\alpha]_{\text{D}}^{20} + 80.2$ (*c* 1.4 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (80 : 20 hexane : IPA, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_{R} (major): 41.5 min, t_{R} (minor): 63.8 min, >99.5:0.5 er; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.98 (1H, dd, *J* 13.0, 2.6, C(7)*H*(a)*H*(b)), 2.57 (1H, ddd, *J* 13.2, 6.5, 3.0, morpholineCH), 2.74 (1H, ddd, *J* 11.5, 6.8, 3.0, morpholineCH), 3.22 (1H, ddd, *J* 13.1, 6.8, 3.1, morpholineCH), 3.31–3.46 (4H, m, morpholineCH), 3.49–3.54 (1H, m, morpholineCH), 3.55 (1H, d, *J* 1.4, OH), 3.69 (1H, td, *J* 13.3, 1.4, C(7)*H*(a)*H*(b)), 3.89 (3H, s, OCH₃), 4.06 (1H, ddd, *J* 13.5, 6.0, 2.6, C(6)*H*), 5.32 (1H, d, *J* 6.0, C(5)*H*), 6.10 (1H, dd, *J* 3.7, 1.6, C(2)*H*), 6.20 (1H, dd, *J* 3.7, 2.8, C(1)*H*), 6.41 (1H, dd, *J* 2.8, 1.6, C(3)*H*), 7.20–7.24 (2H, m, C(6)ArC(2,6)*H*), 7.48–7.53 (2H, m, C(6)ArC(3,5)*H*); ¹³C{¹H} NMR (101 MHz, CDCl₃) δ_{C} : 32.8 (C(7)), 39.0 (C(6)), 42.2 (morpholineC), 46.1 (morpholineC), 53.7 (OCH₃), 55.8 (C(5)), 65.9 (morpholineC), 66.6 (morpholineC), 71.0 (C(8)), 106.0 (C(2)), 110.3 (C(1)), 119.6 (C(3)), 122.2 (C(6)ArC(1)), 130.2 (C(8a)), 130.4 (C(6)ArC(2,6)*H*), 132.1 (C(6)ArC(3,5)*H*), 138.0 (C(6)ArC(4)), 167.0 (C(5)C=O), 174.8 (C(8)C=O); HRMS (ESI⁺) C₂₁H₂₃N₂O₅⁷⁹BrNa [M+Na]⁺ found 485.0675, requires 485.0683 (-1.6 ppm).

Methyl (5S,6S,8R)-6-(3-bromophenyl)-8-hydroxy-5-(morpholine-4-carbonyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (281)



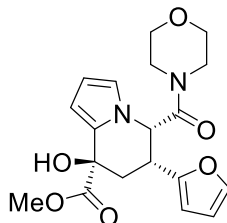
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α-keto-β,γ-unsaturated ester **493** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (113.5 mg, 98%). ν_{\max} (film, cm⁻¹) 3422 (O-H stretch), 2955 (C-H), 2855 (C-H), 1734 (C=O), 1647 (amide C=O); $[\alpha]_D^{20} + 72.3$ (c 1.6 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90 : 10 hexane/IPA, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 63.3 min, t_R (minor): 87.9 min, >99.5:0.5 er; ¹H NMR (500 MHz, CDCl₃) δ_H : 2.00 (1H, dd, *J* 13.0, 2.6, C(7)H(a)H(b)), 2.58 (1H, ddd, *J* 10.9, 7.5, 3.0, morpholineCH), 2.64 (1H, ddd, *J* 13.1, 5.7, 3.0, morpholineCH), 3.22 (1H, ddd, *J* 13.1, 7.5, 3.1, morpholineCH), 3.34 (2H, d, *J* 9.7, morpholineCH), 3.39 (1H, ddd, *J* 11.6, 5.7, 3.1, morpholineCH), 3.52–3.62 (3H, m, morpholineCH + OH), 3.69 (1H, td, *J* 13.3, 1.5, C(7)H(a)H(b)), 3.90 (3H, s, OCH₃), 4.08 (1H, ddd, *J* 13.5, 5.9, 2.6, C(6)H), 5.32 (1H, d, *J* 6.0, C(5)H), 6.10 (1H, dd, *J* 3.7, 1.6, C(2)H), 6.21 (1H, dd, *J* 3.7, 2.8, C(1)H), 6.41 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.23–7.29 (2H, m, C(6)ArCH), 7.48–7.50 (2H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 32.7 (C(7)), 39.3 (C(6)), 42.2 (morpholineC), 46.1 (morpholineC), 53.7 (OCH₃), 55.9 (C(5)), 65.9 (morpholineC), 66.6 (morpholineC), 71.0 (C(8)), 106.0 (C(2)), 110.2 (C(1)), 119.6 (C(3)), 123.2 (C(6)ArC(1)), 127.6 (C(6)ArCH), 130.2 (C(8a)), 130.6 (C(6)ArCH), 131.4 (C(6)ArCH), 131.6 (C(6)ArCH), 141.4 (C(6)ArC(3)), 166.9 (C(5)C=O), 174.8 (C(8)C=O); HRMS (ESI⁺) C₂₁H₂₃N₂O₅⁷⁹BrNa [M+Na]⁺ found 485.0684, requires 485.0683 (+0.3 ppm).

Methyl (5S,6S,8R)-6-(2-bromophenyl)-8-hydroxy-5-(morpholine-4-carbonyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (282)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **494** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (67.2 mg, 58%). ν_{max} (film, cm⁻¹) 3424 (O-H stretch), 2959 (C-H), 2926 (C-H), 2859 (C-H), 1717 (C=O), 1651 (amide C=O); $[\alpha]_{\text{D}}^{20}$ + 168.7 (*c* 1.4 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (90 : 10 hexane/IPA, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_{R} (major): 37.6 min, t_{R} (minor): 58.4 min, >99:1 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.99 (1H, dd, *J* 12.9, 2.7, C(7)H(a)H(b)), 2.49 (1H, ddd, *J* 11.2, 7.7, 2.9, morpholineCH), 2.77 (1H, ddd, *J* 13.3, 5.7, 2.9, morpholineCH), 3.10–3.17 (1H, m, morpholineCH), 3.21–3.33 (2H, m, morpholineCH), 3.37–3.44 (1H, m, morpholineCH), 3.45–3.55 (3H, m, morpholineCH + OH), 3.78 (1H, t, *J* 13.2, 1.3, C(7)H(a)H(b)), 3.90 (3H, s, OCH₃), 4.50 (1H, ddd, *J* 13.4, 6.0, 2.6, C(6)H), 5.59 (1H, d, *J* 5.9, C(5)H), 6.11 (1H, dd, *J* 3.7, 1.6, C(2)H), 6.21 (1H, dd, *J* 3.7, 2.8, C(1)H), 6.44 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.19–7.24 (1H, m, C(6)ArCH), 7.32–7.35 (2H, m, C(6)ArCH), 7.61–7.65 (1H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 32.7 (C(7)), 38.3 (C(6)), 42.2 (morpholineC), 46.0 (morpholineC), 53.1 (OCH₃), 53.6 (C(5)), 66.1 (morpholineC), 66.5 (morpholineC), 71.0 (C(8)), 105.9 (C(2)), 110.1 (C(1)), 119.8 (C(3)), 125.8 (C(6)ArC(5)H), 128.3 (C(6)ArC(6)H), 129.7 (C(6)ArC(2)), 129.8 (C(6)ArC(4)H), 130.1 (C(8a)), 133.2 (C(6)ArC(3)H), 138.0 (C(6)ArC(1)), 167.0 (C(5)C=O), 174.8 (C(8)C=O); HRMS (ESI⁺) C₂₁H₂₃N₂O₅⁷⁹BrNa [M+Na]⁺ found 485.0681, requires 485.0683 (-0.3 ppm).

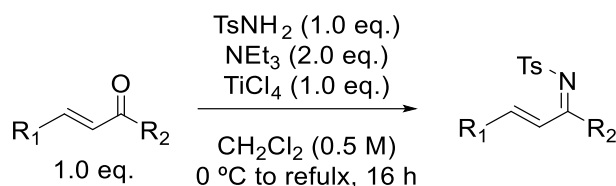
Methyl (5S,6R,8R)-6-(furan-2-yl)-8-hydroxy-5-(morpholine-4-carbonyl)-5,6,7,8-tetrahydroindolizine-8-carboxylate (283)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol), pivaloyl chloride (0.062 mL, 0.5 mmol) in anhydrous MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (7.7 mg, 10 mol%), α -keto- β,γ -unsaturated ester **495** (0.25 mmol, 1 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol) at -40 °C for 24 h. Ring-opening with morpholine (2 eq.) at rt for 24 h gave crude product (>95:5 dr) that was purified by column chromatography (20:80 EtOAc/petrol) to give the titled compound as a light yellow oil (58.0 mg, 62%). ν_{\max} (film, cm⁻¹) 3410 (O-H stretch), 2955 (C-H), 2857 (C-H), 1734 (C=O), 1649 (amide C=O); $[\alpha]_{\text{D}}^{20} + 83.2$ (c 1.3 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (90 : 10 hexane/IPA, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_{R} (major): 89.3 min, t_{R} (minor): 53.1 min, >99:1 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.09 (1H, dd, *J* 13.2, 2.7, C(7)H(a)H(b)), 3.03 (1H, ddd, *J* 13.2, 6.6, 3.0, morpholineCH), 3.22 (1H, ddd, *J* 11.6, 6.7, 3.0, morpholineCH), 3.40–3.59 (8H, m, morpholineCH + C(7)H(a)H(b) + OH), 3.88 (3H, s, OCH₃), 4.17 (1H, ddd, *J* 13.5, 6.0, 2.7, C(6)H), 5.49 (1H, d, *J* 5.9, C(5)H), 6.10 (1H, dd, *J* 3.7, 1.6, C(2)H), 6.18–6.24 (2H, m, C(6)ArCH + C(1)H), 6.39 (1H, dd, *J* 3.4, 1.9, C(6)ArCH), 6.44 (1H, dd, *J* 2.8, 1.6, C(3)H), 7.39–7.40 (1H, m, C(6)ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 31.6 (C(7)), 33.5 (C(6)), 42.4 (morpholineC), 45.9 (morpholineC), 53.7 (OCH₃), 54.6 (C(5)), 66.5 (morpholineC), 66.8 (morpholineC), 70.8 (C(8)), 106.0 (C(2)), 107.5 (C(6)ArCH), 110.2 (C(1)), 111.2 (C(6)ArCH), 119.8 (C(3)), 130.3 (C(8a)), 142.1 (C(6)ArCH), 153.2 (C(6)ArC(1)), 167.2 (C(5)C=O), 174.7 (C(8)C=O); HRMS (ESI⁺) C₁₉H₂₂N₂O₆Na [M+Na]⁺ found 397.1364, requires 397.1370 (-1.5 ppm).

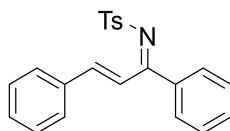
8.5. Experimentals for Chapter 5

General Procedure A: Synthesis of *N*-tosyl- α,β -unsaturated ketimines

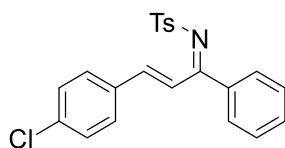


To a solution of the corresponding commercial available α,β -unsaturated ketone (1.0 eq.) in dry CH_2Cl_2 (0.5 M) was added *p*-toluenesulfonamide (1.0 eq.), NEt_3 (2.0 eq.) and titanium tetrachloride (1.0 eq.) at 0 °C under an atmosphere of N_2 . The reaction mixture was refluxed for 16 h. Then it was cooled to rt and quenched with brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried with MgSO_4 and concentrated under reduced pressure. Purification of the crude residue by flash silica column chromatography (EtOAc/petrol 20:80) and recrystallization in *ca.* 1:1 petrol:EtOAc gave the desired α,β -unsaturated ketimines **323-336**.

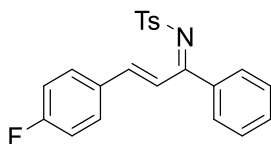
N-((1*E*,2*E*)-1,3-Diphenylallylidene)-4-methylbenzenesulfonamide (**323**)



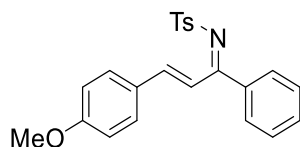
Following general procedure **A**: (*E*)-chalcone (2.08 g, 10.0 mmol, 1.0 eq.), TsNH_2 (1.71 g, 10.0 mmol, 1.0 eq.), Et_3N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl_4 (1.1 mL, 10.0 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL, 0.5 M) gave **323** as a light yellow solid (3.11 g, 86%). Spectroscopic data were in accordance with the literature.¹² mp 118-121 °C {Lit.¹² 116-120 °C}; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.45 (3H, s, CH_3), 7.09 (1H, d, J 16.1, C(2)*H*), 7.34 (2H, d, J 7.9, Ar*H*), 7.39–7.77 (10H, m, Ar*H* + C(3)*H*), 7.86–8.23 (3H, m, Ar*H*).

***N*-((1*E*,2*E*)-3-(4-Chlorophenyl)-1-phenylallylidene)-4-methylbenzenesulfonamide (324)**

Following general procedure **A**: (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (2.43 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **324** as a white solid (2.18 g, 55%). Spectroscopic data were in accordance with the literature.¹² mp 105-106 °C {Lit.¹² 104-106 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 2.44 (3H, s, CH₃), 7.01 (1H, d, *J* 16.1, C(2)*H*), 7.33–7.67 (11H, m, ArH+C(3)*H*), 7.94 (2H, d, *J* 7.9, ArH), 7.99–8.21 (1H, m, ArH).

***N*-((1*E*,2*E*)-3-(4-Fluorophenyl)-1-phenylallylidene)-4-methylbenzenesulfonamide (325)**

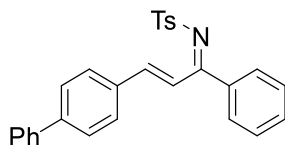
Following general procedure **A**: (*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (2.26 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **325** as a white solid (1.78 g, 47%). Spectroscopic data were in accordance with the literature.¹³ mp 136-137 °C {Lit.¹³ 138-139 °C}; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.43 (3H, s, CH₃), 7.03 (1H, d, *J* 16.2, C(2)*H*), 7.11 (2H, t, *J* 8.4, ArH), 7.32 (2H, d, *J* 7.9, ArH), 7.44 (2H, t, *J* 7.7, ArH), 7.53–7.64 (5H, m, ArH+C(3)*H*), 7.92–8.01 (3H, m, ArH); ¹⁹F NMR (471 MHz, CDCl₃) δ_F: -107.9 (s, ArC(4)*F*).

***N*-((1*E*,2*E*)-3-(4-Methoxyphenyl)-1-phenylallylidene)-4-methylbenzenesulfonamide (326)**

Following general procedure **A**: (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (2.38 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **326** as a yellow solid (1.78 g, 80%). Spectroscopic data were in accordance with the literature.¹² mp 55-57 °C; ¹H NMR (400

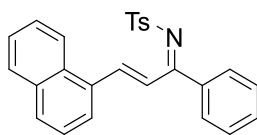
MHz, CDCl₃) δ_H: 3.85 (3H, s, OCH₃), 6.90–6.94 (2H, m, ArH), 7.04 (1H, d, *J* 15.9, C(2)H), 7.31 (2H, d, *J* 8.0, ArH), 7.41–7.45 (2H, m, ArH), 7.50–7.55 (3H, m, ArH+C(3)H), 7.58–7.66 (2H, m, ArH), 7.91–7.93 (3H, m, ArH).

***N*-((1*E*,2*E*)-3-([1,1'-Biphenyl]-4-yl)-1-phenylallylidene)-4-methylbenzenesulfonamide (327)**



Following general procedure **A**: (*E*)-3-([1,1'-biphenyl]-4-yl)-1-phenylprop-2-en-1-one (2.84 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **327** as a yellow solid (2.32 g, 53%). mp 56–58 °C; ν_{max} (film, cm⁻¹) 3057 (C-H), 3026 (C-H), 1612, 1597, 1530, 1514, 1310, 1288; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.43 (3H, s, OCH₃), 7.11 (1H, d, *J* 16.0, C(2)H), 7.32 (2H, d, *J* 8.0, ArH), 7.37–7.41 (1H, m, ArH), 7.43–7.49 (4H, m, ArH), 7.53–7.58 (1H, m, ArH), 7.61–7.70 (8H, m, ArH+C(3)H), 7.94 (2H, d, *J* 7.4, ArH), 8.08–8.19 (1H, m, ArH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.7 (CH₃), 127.2 (ArCH), 127.4 (ArCH+C(2)H), 127.8 (ArCH), 128.2 (ArCH), 128.5 (ArCH), 129.1 (ArCH), 129.5 (ArCH), 129.6 (ArCH), 133.7 (C), 140.1 (2xC), 143.6 (2xC), 144.0 (C), 148.7 (C(3)H), 163.1 (C(1)); HRMS (ESI⁺) C₂₈H₂₃NO₂SNa [M+Na]⁺ found 460.1335, requires 460.1342 (-1.5 ppm).

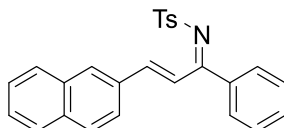
4-Methyl-*N*-((1*E*,2*E*)-3-(naphthalen-1-yl)-1-phenylallylidene)benzenesulfonamide (328)



Following general procedure **A**: (*E*)-3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one (2.58 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **328** as a yellow solid (2.67 g, 65%). mp 116–118 °C; ν_{max} (film, cm⁻¹) 3059 (C-H), 1595, 1578, 1524, 1506, 1298, 1285; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.43 (3H, s, OCH₃), 7.33 (2H, d, *J* 8.0, ArH), 7.48–7.54 (4H, m, ArH+C(2)H), 7.55–7.63 (2H, m, ArH), 7.75–8.02 (9H, m, ArH+C(3)H), 8.09–8.24 (1H, m, ArH); ¹³C{¹H} NMR (126

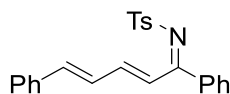
MHz, CDCl₃) δ_c : 21.7 (CH₃), 123.0 (ArCH), 125.9 (ArCH), 126.3 (ArCH), 126.4 (ArCH), 127.2 (ArCH), 127.4 (ArCH+C(2)H), 128.6 (ArCH), 129.1 (ArCH), 129.6 (ArCH), 131.5 (C), 131.6 (C), 132.0 (C), 133.8 (C), 138.8 (C), 143.6 (C), 145.5 (C(3)H), 163.2 (C(1)); HRMS (ESI⁺) C₂₆H₂₂NO₂S [M+H]⁺ found 412.1358, requires 412.1366 (-1.9 ppm).

4-Methyl-*N*-((1*E*,2*E*)-3-(naphthalen-2-yl)-1-phenylallylidene)benzenesulfonamide (**329**)

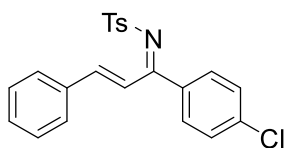


Following general procedure **A**: (*E*)-3-(naphthalen-2-yl)-1-phenylprop-2-en-1-one (2.58 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **329** as a yellow solid (2.55 g, 62%). mp 122-124 °C; ν_{\max} (film, cm⁻¹) 2972 (C-H), 2922 (C-H), 1611, 1595, 1528, 1314, 1285; ¹H NMR (500 MHz, CDCl₃) δ_H : 2.43 (3H, s, OCH₃), 7.24 (1H, d, *J* 16.1, C(2)H), 7.32 (2H, d, *J* 8.0, ArH), 7.44–7.59 (5H, m, ArH+C(3)H), 7.68 (2H, app. s, ArH), 7.78–7.97 (7H, m, ArH), 8.09–8.31 (1H, m, ArH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_c : 21.7 (CH₃), 124.0 (ArCH), 127.0 (ArCH), 127.4 (ArCH+C(2)H), 127.9 (ArCH), 128.0 (ArCH), 128.5 (ArCH), 128.9 (ArCH), 129.1 (ArCH), 129.6 (ArCH), 131.2 (C), 132.3 (C), 133.4 (C), 134.8 (C), 138.9 (C), 143.6 (C), 149.3 (C(3)H), 163.5 (C(1)); HRMS (ESI⁺) C₂₆H₂₂NO₂S [M+H]⁺ found 412.1359, requires 412.1366 (-1.6 ppm).

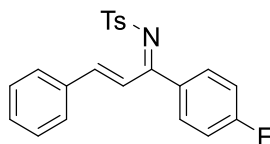
N-((1*E*,2*E*,4*E*)-1,5-Diphenylpenta-2,4-dien-1-ylidene)-4-methylbenzenesulfonamide (**330**)



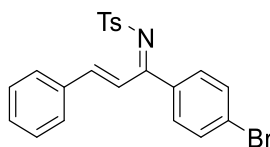
Following general procedure **A**: (*E*,*E*)-1,5-diphenylpenta-2,4-dien-1-one (2.34 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **330** as a yellow solid (3.26 g, 84%). Spectroscopic data were in accordance with the literature.¹⁴ mp 144-145 °C {Lit.¹⁴ 143-144 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H : 2.43 (3H, s, CH₃), 6.86 (1H, d, *J* 15.4, C(5)H), 6.89–6.94 (1H, m, C(3)H), 7.10 (1H, dd, *J* 15.5, 10.9, C(4)H), 7.30–7.62 (13H, m, C(2)H+ArH), 7.92 (2H, d, *J* 7.9, ArH).

***N*-((1*E*,2*E*)-1-(4-Chlorophenyl)-3-phenylallylidene)-4-methylbenzenesulfonamide (331)**

Following general procedure **A**: (*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (2.43 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **331** as a white solid (2.14 g, 54%). Spectroscopic data were in accordance with the literature.¹² mp 102–103 °C {Lit.¹² 104–108 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 2.44 (3H, s, CH₃), 7.04 (1H, d, *J* 16.1, C(2)*H*), 7.33 (2H, d, *J* 8.3, Ar*H*), 7.40–7.62 (9H, m, Ar*H*+C(3)*H*), 7.92 (2H, d, *J* 8.2, Ar*H*), 8.01–8.18 (1H, m, Ar*H*).

***N*-((1*E*,2*E*)-1-(4-Fluorophenyl)-3-phenylallylidene)-4-methylbenzenesulfonamide (332)**

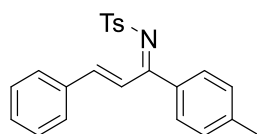
Following general procedure **A**: (*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (2.26 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **332** as a white solid (1.59 g, 42%). Spectroscopic data were in accordance with the literature.¹³ mp 168–169 °C {Lit.¹³ 173–174 °C}; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.43 (3H, s, CH₃), 7.04 (1H, d, *J* 16.1, C(2)*H*), 7.08–7.17 (2H, m, Ar*H*), 7.28–7.35 (2H, m, Ar*H*), 7.37–7.48 (3H, m, Ar*H*+C(3)*H*), 7.49–7.77 (4H, m, Ar*H*), 7.92 (2H, d, *J* 7.9, Ar*H*), 8.05–8.16 (1H, m, Ar*H*); ¹⁹F NMR (471 MHz, CDCl₃) δ_F: –106.6 (s, ArC(4)*F*).

***N*-((1*E*,2*E*)-1-(4-Bromophenyl)-3-phenylallylidene)-4-methylbenzenesulfonamide (333)**

Following general procedure **A**: (*E*)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (2.87 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **333** as a white solid (2.64 g, 60%). mp 106–108 °C; ν_{max} (film, cm⁻¹) 3036 (C-H), 2988 (C-H), 2920 (C-H), 1612, 1589, 1576, 1533,

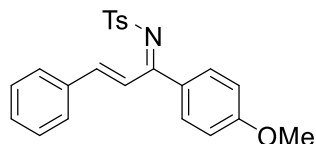
1447, 1285; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.43 (3H, s, CH_3), 7.04 (1H, d, J 16.0, $\text{C}(2)\text{H}$), 7.32 (2H, d, J 8.0, ArH), 7.39–7.46 (3H, m, ArH), 7.52–7.61 (6H, m, $\text{ArH}+\text{C}(3)\text{H}$), 7.91 (2H, d, J 7.1, ArH), 8.00–8.17 (1H, m, ArH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 21.7 (CH_3), 127.4 (ArCH), 128.9 ($\text{C}(2)\text{H}$), 129.2 (ArCH), 129.6 (ArCH), 131.4 (ArCH), 131.8 (ArCH), 134.5 (2xC), 138.6 (2xC), 143.8 (C), 149.0 ($\text{C}(3)\text{H}$), 162.1 ($\text{C}(1)$); HRMS (ESI^+) $\text{C}_{22}\text{H}_{19}\text{NO}_2\text{S}^{79}\text{Br}$ $[\text{M}+\text{H}]^+$ found 440.0307, requires 440.0314 (-1.7 ppm).

4-Methyl-*N*-((1*E*,2*E*)-3-phenyl-1-(*p*-tolyl)allylidene)benzenesulfonamide (**334**)



Following general procedure **A**: (*E*)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (2.22 g, 10.0 mmol, 1.0 eq.), TsNH_2 (1.71 g, 10.0 mmol, 1.0 eq.), Et_3N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl_4 (1.1 mL, 10.0 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL, 0.5 M) gave **334** as a light yellow solid (1.54 g, 41%). mp 108–110 °C; ν_{max} (film, cm^{-1}) 3049 (C-H), 1612, 1576, 1522, 1445, 1314, 1296, 1285; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.42 (6H, s, 2x CH_3), 7.07 (1H, d, J 16.0, $\text{C}(2)\text{H}$), 7.23–7.25 (2H, m, ArH), 7.30–7.32 (2H, m, ArH), 7.40–7.43 (3H, m, ArH), 7.56–7.58 (4H, m, $\text{ArH}+\text{C}(3)\text{H}$), 7.92 (2H, d, J 7.9, ArH), 7.98–8.07 (1H, m, ArH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 21.7 (CH_3), 127.3 (ArCH), 128.8 ($\text{C}(2)\text{H}$), 129.2 (ArCH), 129.2 (ArCH), 129.5 (ArCH), 131.1 (ArCH), 134.8 (2xC), 139.0 (C), 143.5 (2xC), 148.4 ($\text{C}(3)\text{H}$), 162.4 ($\text{C}(1)$); HRMS (ESI^+) $\text{C}_{23}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$ found 376.1359, requires 376.1366 (-1.8 ppm).

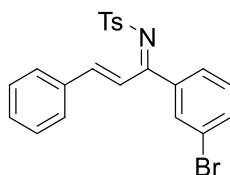
N-((1*E*,2*E*)-1-(4-Methoxyphenyl)-3-phenylallylidene)-4-methylbenzenesulfonamide (**335**)



Following general procedure **A**: (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (2.38 g, 10.0 mmol, 1.0 eq.), TsNH_2 (1.71 g, 10.0 mmol, 1.0 eq.), Et_3N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl_4 (1.1 mL, 10.0 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL, 0.5 M) gave **335** as a yellow solid (2.78 g, 71%). Spectroscopic data were in accordance with the literature.¹² mp 65–67 °C; ^1H NMR (400

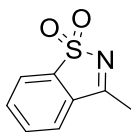
MHz, CDCl₃) δ_H : 2.43 (3H, s, CH₃), 3.89 (3H, s, OCH₃), 6.95 (2H, d, *J* 8.8, ArH), 7.08 (1H, d, *J* 16.1, C(2)H), 7.33 (2H, d, *J* 8.7, ArH), 7.43–7.45 (3H, m, ArH+C(3)H), 7.55–7.61 (2H, m, ArH), 7.73 (2H, d, *J* 8.7, ArH), 7.90–8.11 (3H, m, ArH).

***N*-((1*E*,2*E*)-1-(3-Bromophenyl)-3-phenylallylidene)-4-methylbenzenesulfonamide (336)**



Following general procedure **A**: (E)-1-(3-bromophenyl)-3-phenylprop-2-en-1-one (2.87 g, 10.0 mmol, 1.0 eq.), TsNH₂ (1.71 g, 10.0 mmol, 1.0 eq.), Et₃N (2.8 mL, 20.0 mmol, 2.0 eq.) and TiCl₄ (1.1 mL, 10.0 mmol, 1.0 eq.) in CH₂Cl₂ (20 mL, 0.5 M) gave **336** as a white solid (1.94 g, 44%). mp 120–121 °C; ν_{\max} (film, cm⁻¹) 3063 (C-H), 1607, 1574, 1533, 1310, 1290; ¹H NMR (500 MHz, CDCl₃) δ_H : 2.46 (3H, s, CH₃), 7.07 (1H, d, *J* 16.0, C(2)H), 7.31–7.38 (3H, m, ArH), 7.42–7.50 (3H, m, ArH), 7.55–7.65 (3H, m, ArH+C(3)H), 7.67–7.71 (1H, m, ArH), 7.80 (1H, app. s, ArH), 7.94 (2H, app. s, ArH), 8.06–8.19 (1H, m, ArH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 21.8 (CH₃), 127.4 (ArCH), 129.0 (ArCH), 129.3 (ArCH), 129.7 (C(2)H), 130.0 (ArCH), 131.5 (ArCH), 134.5 (2xC), 138.5 (C), 143.9 (2xC), 149.3 (C(3)H), 163.4 (C(1)); HRMS (ESI⁺) C₂₂H₁₉NO₂S⁷⁹Br [M+H]⁺ found 440.0306, requires 440.0314 (-1.9 ppm).

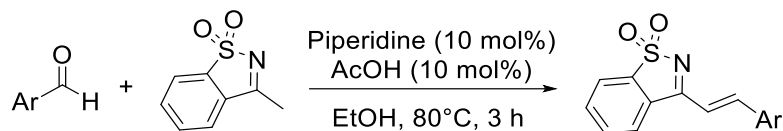
3-Methylbenzo[*d*]isothiazole 1,1-dioxide (337)



Following literature procedure,¹⁵ in a flame-dried flask, to a solution of saccharin (10.0 g, 54.6 mmol, 1 eq.) in anhydrous THF (500 mL) at 0 °C was added methyl magnesium bromide (3.0 M in Et₂O, 36 mL, 109 mmol, 2 eq.) dropwise. The reaction was warmed to rt and stirred for 16 hours before being quenched with sat. aq. NH₄Cl, extracted with CH₂Cl₂ (3 x 200 mL). Combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to give crude reaction product. The crude material was purified by trituration in CH₂Cl₂ to give a white solid (4.55 g, 46%). Spectroscopic data were in accordance with the literature.¹⁶ mp

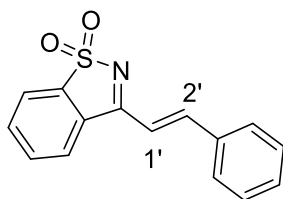
221-223 °C {Lit.¹⁶ 216-219 °C}; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.68 (3H, s, CH₃), 7.67–7.70 (1H, m, ArH), 7.73–7.78 (2H, m, ArH), 7.91–7.94 (1H, m, ArH).

General Procedure B: Preparation of sulfonyl imine substrates

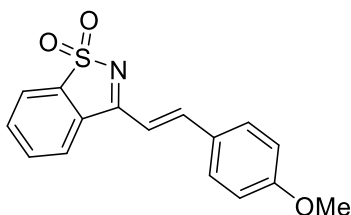


Imine **337** (1.0 eq.) was dissolved in ethanol (0.3 M) and heated to 80 °C. The aldehyde (1.0 eq.), acetic acid (10 mol%) and piperidine (10 mol%) were added. The reaction was stirred at 80 °C for 3 hours then cooled to 0 °C and filtered. The solid was washed with cold ethanol to give the unsaturated ketimine, which was used without further purification.

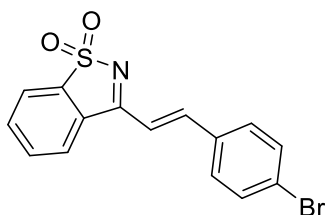
(E)-3-Styrylbenzo[d]isothiazole 1,1-dioxide (**339**)



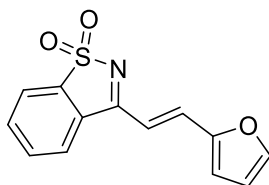
Imine **337** (3.0 g, 11.1 mmol, 1.0 eq.) was dissolved in ethanol (37 mL, 0.3 M) and heated to 80 °C. Benzaldehyde (2.5 mL, 24.5 mmol, 2.2 eq.) and piperidine (25 drops) were added. The reaction was stirred at 80 °C for 30 minutes. Acetic acid (25 drops) was added and the reaction was stirred at 80 °C for 17 hours. The reaction was cooled to rt and filtered. The collected solid was then washed with petrol (50 mL) to give **339** as a yellow solid (2.00 g, 67%). Spectroscopic data were in accordance with the literature.¹⁷ mp 247 °C {Lit.¹⁷ 244-246 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 7.30 (1H, d, *J* 15.6, C(1')H), 7.45–7.52 (3H, m, C(2')ArCH+ArH), 7.68–7.73 (2H, m, C(2')ArCH), 7.74–7.80 (2H, m, C(2')ArCH), 7.86–7.92 (1H, m, ArH), 7.94–8.00 (1H, m, ArH), 8.33 (1H, d, *J* 15.6, C(2')H).

(E)-3-(4-Methoxystyryl)benzo[d]isothiazole 1,1-dioxide (341)

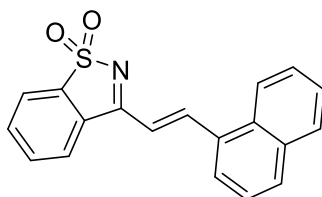
Following general procedure **B**, imine **337** (301 mg, 1.66 mmol, 1 eq.), 4-methoxybenzaldehyde (0.20 mL, 1.66 mmol, 1 eq.), acetic acid (10 μ L, 0.17 mmol, 10 mol%) and piperidine (17 μ L, 0.17 mmol, 10 mol%) gave the titled compound as an orange solid (267 mg, 53%). Spectroscopic data were in accordance with the literature.¹⁷ mp 224–226 °C {Lit.¹⁷ 218–220 °C}; ¹H NMR (500 MHz, CDCl₃) δ _H: 3.86 (3H, s, OCH₃), 7.75 (2H, d, *J* 8.8, C(3)ArC(3,5)*H*), 7.75 (1H, d, *J* 15.6, C(2)*H*), 7.88–7.97 (2H, m, Ar*H*), 8.00 (2H, d, *J* 8.8, C(3)ArC(2,6)*H*), 8.17 (1H, d, *J* 7.8, Ar*H*), 8.26 (1H, d, *J* 15.6, C(3)*H*), 8.49 (1H, d, *J* 7.0, Ar*H*).

(E)-3-(4-Bromostyryl)benzo[d]isothiazole 1,1-dioxide (340)

Following general procedure **B**, imine **337** (498 mg, 2.75 mmol, 1 eq.), 4-bromobenzaldehyde (509 mg, 2.75 mmol, 1 eq.), acetic acid (16 μ L, 0.28 mmol, 10 mol%) and piperidine (28 μ L, 0.28 mmol, 10 mol%) gave the titled compound as an orange solid (628 mg, 66%). Spectroscopic data were in accordance with the literature.¹⁷ mp 258–261 °C {Lit.¹⁷ 256–260 °C}; ¹H NMR (500 MHz, *d*₆-DMSO) δ _H: 7.75 (2H, d, *J* 8.3, C(3)ArC(3,5)*H*), 7.89–8.00 (5H, m, C(3)ArC(2,6)*H* + C(2)*H* + Ar*H*), 8.17–8.21 (1H, m, Ar*H*), 8.25 (1H, d, *J* 15.8, C(3)*H*), 8.51 (1H, dd, *J* 1.3, 6.4, Ar*H*).

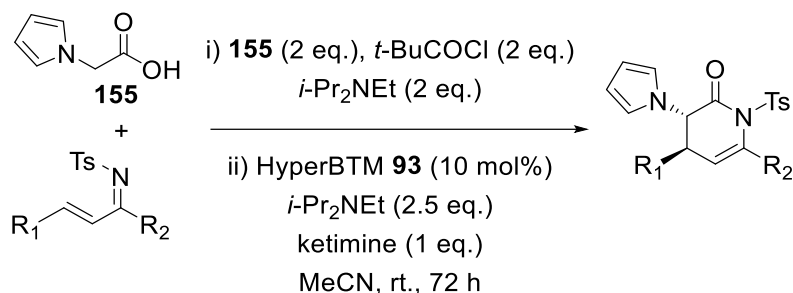
(E)-3-(2-(Furan-2-yl)vinyl)benzo[d]isothiazole 1,1-dioxide (342)

Following general procedure **B**, imine **337** (498 mg, 2.75 mmol, 1 eq.), furfural (0.23 mL, 2.75 mmol, 1 eq.), acetic acid (16 μ L, 0.28 mmol, 10 mol%) and piperidine (28 μ L, 0.28 mmol, 10 mol%) gave the titled compound as a dark-yellow solid (430 mg, 60%). Spectroscopic data were in accordance with the literature.¹⁷ mp 226-228 °C {Lit.¹⁷ 230-233 °C (dec.)}; ¹H NMR (400 MHz, CDCl₃) δ _H: 6.62 (1 H, dd, *J* 3.3, 1.7, FurC(4)*H*), 6.90 (1 H, d, *J* 3.4, FurC(3)*H*), 7.19 (1 H, d, *J* 15.2, C(2)*H*), 7.66 (1H, s, FurC(5)*H*), 7.87–8.01 (2H, m, Ar*H*), 7.75–7.80 (2H, m, Ar*H*), 8.07 (1H, d, *J* 15.2, C(3)*H*).

(E)-3-(2-(Naphthalen-1-yl)vinyl)benzo[d]isothiazole 1,1-dioxide (343)

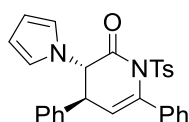
Following general procedure **B**, imine **337** (498 mg, 2.75 mmol, 1 eq.), 1-naphthaldehyde (0.37 mL, 2.75 mmol, 1 eq.), acetic acid (16 μ L, 0.28 mmol, 10 mol%) and piperidine (28 μ L, 0.28 mmol, 10 mol%) gave the titled compound as a yellow solid (585 mg, 67%). Spectroscopic data were in accordance with the literature.¹⁷ mp 275-278 °C {Lit.¹⁷ 277-279 °C}; ¹H NMR (500 MHz, *d*₆-DMSO) δ _H: 7.62–7.67 (1H, m, Nap*H*), 7.68–7.75 (2H, m, Nap*H*), 7.92–8.00 (2H, m, Ar*H*), 8.01–8.08 (2H, m, C(2)*H* + Nap*H*), 8.16 (1H, d, *J* 8.1, Nap*H*), 8.22 (1H, dd, *J* 6.2, 1.9, Ar*H*), 8.42 (2H, t, *J* 7.5, Nap*H*), 8.51–8.58 (1H, m, Ar*H*), 9.06 (1H, d, *J* 15.4, C(3)*H*).

General Procedure C: Michael addition-lactamization with chalcone derived α,β -unsaturated ketimines



2-(1*H*-Pyrrol-1-yl)acetic acid **155** (2 eq.) was dissolved in freshly distilled anhydrous MeCN (0.05 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (2 eq.) and pivaloyl chloride (2 eq.) were added. The reaction was stirred at 0 °C for 20 min before warming up to room temperature. HyperBTM **93** (10 mol%), the required α,β -unsaturated ketimine (1 eq.), and *i*-Pr₂NEt (2.5 eq.) were added sequentially and the reaction stirred at rt. for 72 h. After that, the reaction was diluted with CH₂Cl₂ (equal volume) and washed with 1 M HCl (×2) and brine (×2) before being dried over MgSO₄, filtered, and concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography.

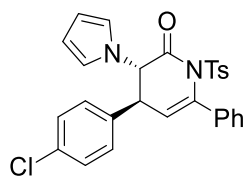
(3*S*,4*S*)-4,6-Diphenyl-3-(1*H*-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1*H*)-one (344)



Following **General Procedure C**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **323** (45.2 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (10:90 EtOAc/petrol, R_f 0.27) to give the titled compound **344** as a white solid (53.9 mg, 92%). mp 174-175 °C; $[\alpha]_D^{20}$ – 63.1 (c 0.42 in DMSO); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) t_R (major): 20.7 min, t_R (minor): 11.1 min, 78:22 er; ν_{\max} (film, cm⁻¹) 3098 (C-H), 3036 (C-H), 1734 (C=O), 1597, 1491; ¹H NMR (500 MHz, CDCl₃) δ _H: 2.51 (3H, s, NSO₂PhCH₃), 4.17 (1H, dd, *J* 12.7, 3.4, C(4)*H*), 4.75 (1H, d, *J* 12.7, C(3)*H*), 5.99 (2H, t, *J*

2.1, C(3)Ar(3,4)H), 6.03 (1H, d, *J* 3.4, C(5)H), 6.24 (2H, t, *J* 2.2, C(3)Ar(2,5)H), 7.08 (2H, dd, *J* 6.6, 2.9, ArH), 7.22–7.24 (3H, m, ArH), 7.35 (2H, d, *J* 8.1, NSO₂ArC(3,5)H), 7.39–7.48 (5H, m, ArH), 7.92 (2H, d, *J* 8.2, NSO₂ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.8 (NSO₂PhCH₃), 45.2 (C(4)), 67.3 (C(3)), 109.0 (C(3)ArC(3,4)H), 120.2 (C(3)ArC(2,5)H), 121.6 (C(5)), 126.0 (ArCH), 127.3 (ArCH), 127.8 (ArCH), 128.6 (ArCH), 128.8 (ArCH), 128.9 (ArCH), 129.3 (NSO₂ArC(3,5)H), 129.5 (NSO₂ArC(2,6)H), 135.9 (NSO₂ArC(4)), 136.5 (C(4)ArC(1)), 137.9 (C(6)), 140.0 (C(6)ArC(1)), 145.6 (NSO₂ArC(1)), 169.4 (C(2)); HRMS (ASAP⁺) C₂₈H₂₅N₂O₃S [M+H]⁺ found 469.1583, requires 469.1586 (-0.6 ppm).

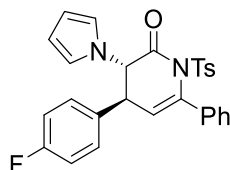
(3S,4S)-4-(4-Chlorophenyl)-6-phenyl-3-(1*H*-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1*H*)-one (345)



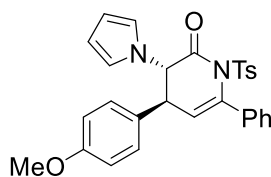
Following **General Procedure C**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **324** (49.5 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **345** as a white solid (59.7 mg, 95%). mp 160–162 °C; [α]_D²⁰ + 27.0 (c 0.1 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 25.9 min, t_R (minor): 12.8 min, 83:17 er; ν_{max} (film, cm⁻¹) 3028, 1734 (C=O), 1491, 1356, 1159; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.50 (3H, s, NSO₂PhCH₃), 4.17 (1H, dd, *J* 12.7, 3.4, C(4)H), 4.69 (1H, d, *J* 12.7, C(3)H), 5.96 (1H, d, *J* 3.4, C(5)H), 6.01 (2H, t, *J* 2.1, C(3)Ar(3,4)H), 6.24 (2H, t, *J* 2.1, C(3)Ar(2,5)H), 7.01–7.03 (2H, m, C(4)ArC(2,6)H), 7.19–7.21 (2H, m, C(4)ArC(3,5)H), 7.35 (2H, app. d, *J* 8.2, NSO₂ArC(3,5)H), 7.41–7.44 (5H, m, C(6)ArCH), 7.90–7.91 (2H, m, NSO₂ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.8 (NSO₂PhCH₃), 44.7 (C(4)), 67.1 (C(3)), 109.2 (C(3)ArC(3,4)H), 120.2 (C(3)ArC(2,5)H), 120.9 (C(5)), 126.0 (C(6)ArCH), 128.6 (C(6)ArCH), 128.7 (C(6)ArCH), 129.0 (C(4)ArC(2,6)H), 129.0

(C(4)ArC(3,5)H), 129.3 (NSO₂ArC(3,5)H), 129.5 (NSO₂ArC(2,6)H), 133.7 (C(4)ArC(1)), 135.8 (NSO₂ArC(4)), 136.3 (C(6)), 136.4 (C(4)ArC(4)), 140.3 (C(6)ArC(1)), 145.7 (NSO₂ArC(1)), 169.1 (C(2)); HRMS (NSI⁺) C₂₈H₂₄N₂O₃S³⁵Cl [M+H]⁺ found 503.1185, requires 503.1191 (-1.1 ppm).

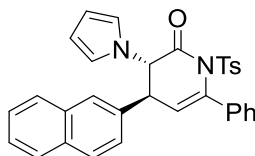
(3S,4S)-4-(4-Fluorophenyl)-6-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (346)



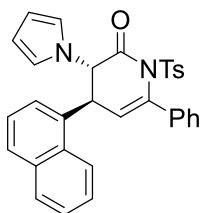
Following **General Procedure C**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **325** (47.4 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **346** as a light yellow solid (36.5 mg, 60%). mp 152-155 °C; [α]_D²⁰ + 33.4 (c 0.4 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 24.6 min, t_R (minor): 12.3 min, 76:24 er; ν_{max} (film, cm⁻¹) 3028 (C-H), 1742 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.51 (3H, s, NSO₂PhCH₃), 4.17 (1H, dd, *J* 12.7, 3.4, C(4)H), 4.69 (1H, d, *J* 12.7, C(3)H), 5.99 (1H, d, *J* 3.4, C(5)H), 6.01 (2H, t, *J* 2.1, C(3)Ar(3,4)H), 6.23 (2H, t, *J* 2.1, C(3)Ar(2,5)H), 6.90–6.93 (2H, m, C(4)ArC(2,6)H), 7.03–7.07 (2H, m, C(4)ArC(3,5)H), 7.35 (2H, d, *J* 8.1, NSO₂ArC(3,5)H), 7.40–7.46 (5H, m, C(6)ArCH), 7.90–7.92 (2H, m, NSO₂ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.8 (NSO₂PhCH₃), 44.6 (C(4)), 67.4 (C(3)), 109.2 (C(3)ArC(3,4)H), 115.8 (d, ³J_{CF} 21.7, C(4)ArC(2,6)H), 120.2 (C(3)ArC(2,5)H), 121.3 (C(5)), 126.0 (C(6)ArCH), 128.6 (C(6)ArCH), 128.9 (d, ²J_{CF} 8.2, C(4)ArC(3,5)H), 129.0 (C(6)ArCH), 129.3 (NSO₂ArC(3,5)H), 129.5 (NSO₂ArC(2,6)H), 133.6 (d, ⁴J_{CF} 3.2, C(4)ArC(1)), 135.9 (NSO₂ArC(4)), 136.4 (C(6)), 140.2 (C(6)ArC(1)), 145.7 (NSO₂ArC(1)), 162.1 (d, ¹J_{CF} 246.8, C(4)ArC(4)), 169.3 (C(2)); ¹⁹F NMR (471 MHz, CDCl₃) δ_F: -114.0; HRMS (NSI⁺) C₂₈H₂₄N₂O₃SF [M+H]⁺ found 478.1481, requires 478.1486 (-1.1 ppm).

(3*S*,4*S*)-4-(4-Methoxyphenyl)-6-phenyl-3-(1*H*-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1*H*)-one (347)

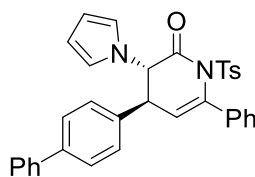
Following **General Procedure C**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **326** (48.9 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **347** as a yellow oil (41.8 mg, 67%). $[\alpha]_D^{20} + 18.4$ (c 1.2 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 29.3 min, t_R (minor): 18.1 min, 77:23 er; ν_{max} (film, cm⁻¹) 2972 (C-H), 2934 (C-H), 1732 (C=O), 1597, 1514; ¹H NMR (500 MHz, CDCl₃) δ_H : 2.50 (3H, s, NSO₂PhCH₃), 3.76 (3H, s, OCH₃), 4.12 (1H, dd, *J* 12.6, 3.5, C(4)*H*), 4.69 (1H, d, *J* 12.6, C(3)*H*), 6.00–6.01 (3H, m, C(5)*H* + C(3)Ar(3,4)*H*), 6.24 (2H, t, *J* 2.2, C(3)Ar(2,5)*H*), 6.74–6.77 (2H, m, C(4)ArC(3,5)*H*), 6.98–7.00 (2H, m, C(4)ArC(2,6)*H*), 7.35 (2H, d, *J* 8.1, NSO₂ArC(3,5)*H*), 7.39–7.46 (5H, m, C(6)ArCH), 7.90–7.92 (2H, m, NSO₂ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 21.8 (NSO₂PhCH₃), 44.4 (C(4)), 55.2 (OCH₃), 67.4 (C(3)), 108.9 (C(3)ArC(3,4)*H*), 114.1 (C(4)ArC(3,5)*H*), 120.3 (C(3)ArC(2,5)*H*), 122.1 (C(5)), 126.0 (C(6)ArCH), 128.4 (C(4)ArC(2,6)*H*), 128.6 (C(6)ArCH), 128.9 (C(6)ArCH), 129.3 (NSO₂ArC(3,5)*H*), 129.5 (NSO₂ArC(2,6)*H*), 129.8 (C(4)ArC(1)), 135.9 (NSO₂ArC(4)), 136.5 (C(6)), 139.8 (C(6)ArC(1)), 145.6 (NSO₂ArC(1)), 159.0 (C(4)ArC(4)), 169.6 (C(2)); HRMS (NSI⁺) C₂₉H₂₇N₂O₄S [M+H]⁺ found 499.1681, requires 499.1686 (-1.0 ppm).

(3S,4S)-4-(Naphthalen-2-yl)-6-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (348)

Following **General Procedure C**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **329** (51.4 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **348** as a yellow solid (51.2 mg, 79%). mp 190-192 °C; $[\alpha]_{\text{D}}^{20} + 61.5$ (*c* 0.5 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 32.8 min, *t*_R (minor): 17.2 min, 78:22 er; *v*_{max} (film, cm⁻¹) 3067 (C-H), 3036 (C-H), 2959 (C-H), 2926 (C-H), 2874 (C-H), 1730 (C=O), 1358, 1161; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.48 (3H, s, NSO₂PhCH₃), 4.33 (1H, dd, *J* 12.5, 3.4, C(4)*H*), 4.85 (1H, d, *J* 12.5, C(3)*H*), 5.92 (2H, t, *J* 2.1, C(3)Ar(3,4)*H*), 6.09 (1H, d, *J* 3.5, C(5)*H*), 6.24 (2H, t, *J* 2.2, C(3)Ar(2,5)*H*), 7.16 (1H, dd, *J* 8.5, 1.9, C(4)Ar*CH*), 7.32–7.33 (2H, m, NSO₂ArC(3,5)*H*), 7.40–7.47 (7H, m, C(6)Ar*CH* + C(4)Ar*CH*), 7.53–7.55 (1H, m, C(4)Ar*CH*), 7.68–7.71 (2H, m, C(4)Ar*CH*), 7.74–7.77 (1H, m, C(4)Ar*CH*), 7.89–7.92 (2H, m, NSO₂ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 21.9 (NSO₂PhCH₃), 45.3 (C(4)), 67.2 (C(3)), 109.2 (C(3)ArC(3,4)*H*), 120.4 (C(3)ArC(2,5)*H*), 121.6 (C(5)), 124.9 (Ar*CH*), 126.1 (Ar*CH*), 126.3 (Ar*CH*), 126.5 (Ar*CH*), 126.8 (Ar*CH*), 127.8 (Ar*CH*), 127.8 (Ar*CH*), 128.7 (Ar*CH*), 128.9 (Ar*CH*), 129.1 (Ar*CH*), 129.5 (NSO₂ArC(3,5)*H*), 129.7 (NSO₂ArC(2,6)*H*), 132.8 (ArC), 133.4 (ArC), 135.4 (NSO₂ArC(4)), 136.0 (C(6)ArC(1)), 136.7 (C(4)ArC(1)), 140.2 (C(6)), 145.7 (NSO₂ArC(1)), 169.6 (C(2)); HRMS (NSI⁻) C₃₂H₂₇N₂O₄S [M+OH]⁻ found 535.1700, requires 535.1697 (+0.6 ppm).

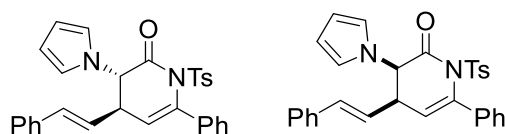
(3S,4S)-4-(Naphthalen-1-yl)-6-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (349)

Following **General Procedure C**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **328** (51.4 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **349** as a yellow gum (53.8 mg, 83%). $[\alpha]_D^{20} + 49.7$ (c 0.8 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 23.0 min, *t*_R (minor): 14.8 min, 85:15 er; *v*_{max} (film, cm⁻¹) 3066 (C-H), 3036 (C-H), 1732 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.50 (3H, s, NSO₂PhCH₃), 4.97 (1H, dd, *J* 11.0, 4.2, C(4)*H*), 5.21 (1H, d, *J* 11.0, C(3)*H*), 5.96 (2H, t, *J* 2.2, C(3)Ar(3,4)*H*), 6.04 (1H, d, *J* 4.2, C(5)*H*), 6.36 (2H, t, *J* 2.2, C(3)Ar(2,5)*H*), 7.34–7.37 (4H, m, C(4)ArCH + NSO₂ArC(3,5)*H*), 7.40–7.47 (5H, m, C(6)ArCH), 7.52–7.60 (2H, m, C(4)ArCH), 7.74–7.79 (1H, m, C(4)ArCH), 7.87–7.90 (1H, m, C(4)ArCH), 7.92–7.98 (3H, m, C(4)ArCH + NSO₂ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.8 (NSO₂PhCH₃), 40.6 (C(4)), 65.3 (C(3)), 109.1 (C(3)ArC(3,4)*H*), 120.3 (C(3)ArC(2,5)*H*), 121.7 (C(5)), 122.5 (ArCH), 125.0 (ArCH), 125.3 (ArCH), 125.9 (ArCH), 126.1 (ArCH), 126.7 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 128.9 (ArCH), 129.3 (ArCH), 129.5 (NSO₂ArC(3,5)*H*), 129.6 (NSO₂ArC(2,6)*H*), 130.9 (ArC), 132.8 (ArC), 134.1 (NSO₂ArC(1)), 135.9 (C(6)ArC(1)), 136.4 (C(4)ArC(1)), 139.9 (C(6)), 145.7 (NSO₂ArC(4)), 169.6 (C(2)); HRMS (NSI⁺) C₃₂H₂₇N₂O₃S [M+H]⁺ found 519.1731, requires 519.1737 (-1.1 ppm).

(3S,4S)-4-([1,1'-Biphenyl]-4-yl)-6-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (350)

Following **General Procedure C**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **327** (54.7 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **350** as a yellow solid (53.8 mg, 70%). mp 177-179 °C; $[\alpha]_D^{20} + 10.8$ (*c* 0.2 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 51.4 min, *t*_R (minor): 31.1 min, 80:20 er; *v*_{max} (film, cm⁻¹) 2980 (C-H), 1730 (C=O), 1508, 1358; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.51 (3H, s, NSO₂PhCH₃), 4.23 (1H, dd, *J* 12.6, 3.4, C(4)*H*), 4.79 (1H, d, *J* 12.6, C(3)*H*), 6.01 (2H, t, *J* 2.1, C(3)Ar(3,4)*H*), 6.05 (1H, d, *J* 3.3, C(5)*H*), 6.29 (2H, t, *J* 2.1, C(3)Ar(2,5)*H*), 7.14–7.17 (2H, m, C(4)ArC(2,6)*H*), 7.33–7.37 (3H, m, NSO₂ArC(3,5)*H* + C(4)ArC(4)Ph*H*), 7.40–7.49 (9H, m, C(4)ArC(4)Ph*H* + C(6)Ar*H*), 7.53–7.55 (2H, m, C(4)ArC(3,5)*H*), 7.91–7.94 (2H, m, NSO₂ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.8 (NSO₂PhCH₃), 44.8 (C(4)), 67.2 (C(3)), 109.1 (C(3)ArC(3,4)*H*), 120.3 (C(3)ArC(2,5)*H*), 121.5 (C(5)), 126.0 (ArCH), 127.0 (C(4)ArC(3,5)*H*), 127.5 (ArCH), 127.5 (ArCH), 127.8 (C(4)ArC(2,6)*H*), 128.6 (ArCH), 128.8 (ArCH), 129.0 (ArCH), 129.3 (NSO₂ArC(3,5)*H*), 129.6 (NSO₂ArC(2,6)*H*), 135.9 (NSO₂ArC(1)), 136.5 (C(6)ArC(1)), 136.9 (C(4)ArC(4)PhC(1)), 140.1 (C(6)), 140.3 (C(4)ArC(4)), 140.6 (C(4)ArC(1)), 145.6 (NSO₂ArC(4)), 169.5 (C(2)); HRMS (NSI⁺) C₃₄H₂₉N₂O₃S [M+H]⁺ found 545.1889, requires 545.1893 (-0.8 ppm).

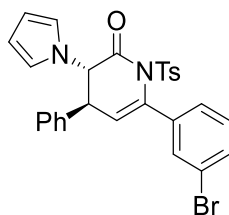
(3S,4R)-6-Phenyl-3-(1H-pyrrol-1-yl)-4-((E)-styryl)-1-tosyl-3,4-dihydropyridin-2(1H)-one and
(3R,4R)-6-phenyl-3-(1H-pyrrol-1-yl)-4-((E)-styryl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (351)



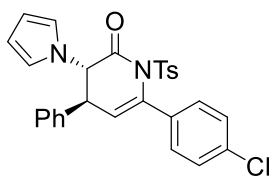
Following **General Procedure C**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **330** (48.4 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (70:30 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to the combined *anti* and *syn* diastereoisomers (78:22 dr) (24.7 mg, 40%) as a light yellow oil. ν_{\max} (film, cm⁻¹) 1732 (C=O), 1717 (C=O); HRMS (ESI⁺) C₃₀H₂₆N₂O₃SNa [M+Na]⁺ found 517.1555, requires 517.1556 (-0.3 ppm).

(3S,4R)-351: Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (3S,4R): 34.6 min, *t*_R (3R,4S): 20.8 min, 66:34 er; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.48 (3H, s, NSO₂PhCH₃), 3.79 (1H, dddd, *J* 11.6, 7.7, 3.7, 1.2, C(4)H), 4.57 (1H, d, *J* 11.7, C(3)H), 5.88 (1H, dd, *J* 15.8, 7.8, C(4)CH), 5.96 (1H, d, *J* 3.7, C(5)H), 6.15 (2H, t, *J* 2.1, C(3)Ar(3,4)H), 6.41 (1H, d, *J* 16.0, C(4)CH=CHPh), 6.46 (2H, t, *J* 2.2, C(3)Ar(2,5)H), 7.14–7.39 (8H, m, NSO₂ArC(3,5)H + ArH), 7.41–7.54 (4H, m, ArH), 7.88–7.89 (2H, m, NSO₂ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} (selected): 21.8 (NSO₂PhCH₃), 41.6 (C(4)), 65.6 (C(3)), 109.3 (C(3)ArC(3,4)H), 119.9 (C(5)), 120.3 (C(3)ArC(2,5)H), 124.6 (C(4)CH), 133.8 (C(4)CH=CHPh), 169.3 (C(2)).

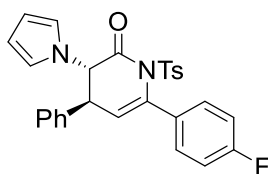
(3R,4R)-351: ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.44 (3H, s, NSO₂PhCH₃), 3.62 (1H, dddd, *J* 8.5, 7.4, 5.3, 1.1, C(4)H), 5.05 (1H, d, *J* 5.3, C(3)H), 6.04–6.09 (1H, m, C(4)CH), 6.10 (1H, d, *J* 7.3, C(5)H), 6.17 (2H, t, *J* 2.2, C(3)Ar(3,4)H), 6.54 (1H, d, *J* 15.7, C(4)CH=CHPh), 6.63 (2H, t, *J* 2.2, C(3)Ar(2,5)H), 7.14–7.39 (8H, m, NSO₂ArC(3,5)H + ArH), 7.41–7.54 (4H, m, ArH), 7.88 (2H, dd, *J* 7.9, 6.0, NSO₂ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} (selected): 21.8 (NSO₂PhCH₃), 42.8 (C(4)), 64.3 (C(3)), 108.8 (C(3)ArC(3,4)H), 119.4 (C(5)), 121.5 (C(3)ArC(2,5)H), 122.5 (C(4)CH), 135.4 (C(4)CH=CHPh), 168.7 (C(2)).

(3S,4S)-(6-(3-Bromophenyl)-4-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (352)

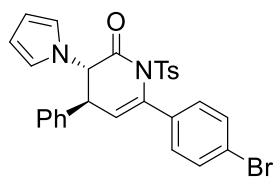
Following **General Procedure C**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **336** (55.1 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **352** as a yellow solid (53.4 mg, 78%). mp 104–106 °C; $[\alpha]_D^{20} + 37.5$ (*c* 0.4 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) *t*_R (major): 26.6 min, *t*_R (minor): 9.4 min, 80:20 er; *v*_{max} (film, cm⁻¹) 2995 (C-H), 1743 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.51 (3H, s, NSO₂PhCH₃), 4.22 (1H, dd, *J* 12.7, 3.4, C(4)*H*), 4.74 (1H, d, *J* 12.7, C(3)*H*), 6.01 (2H, t, *J* 2.2, C(3)Ar(3,4)*H*), 6.05 (1H, d, *J* 3.4, C(5)*H*), 6.29 (2H, t, *J* 2.1, C(3)Ar(2,5)*H*), 7.06–7.10 (2H, m, C(4)ArC(2,6)*H*), 7.22–7.26 (3H, m, C(4)ArC(3,4,5)*H*), 7.31 (1H, t, *J* 7.9, C(6)ArC(4)*H*), 7.36–7.39 (2H, m, NSO₂ArC(3,5)*H*), 7.40–7.42 (1H, m, C(6)ArC(6)*H*), 7.45 (1H, t, *J* 1.8, C(6)ArC(2)*H*), 7.55 (1H, ddd, *J* 8.0, 2.0, 1.0, C(6)ArC(5)*H*), 7.89–7.93 (2H, m, NSO₂ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.8 (NSO₂PhCH₃), 45.1 (C(4)), 67.2 (C(3)), 109.1 (C(3)ArC(3,4)*H*), 120.3 (C(3)ArC(2,5)*H*), 122.5 (C(4)ArC(4)*H*), 122.9 (C(5)), 124.8 (C(6)ArC(6)*H*), 127.3 (C(4)ArC(2,6)*H*), 127.9 (C(4)ArC(3,5)*H*), 128.9 (C(6)ArC(2)*H*), 129.5 (NSO₂ArC(3,5)*H*), 129.6 (NSO₂ArC(2,6)*H*), 130.3 (C(6)ArC(4)*H*), 131.9 (C(6)ArC(5)*H*), 135.7 (NSO₂ArC(4)), 137.6 (C(4)ArC(1)), 138.4 (C(6)), 138.6 (C(6)ArC(1,3)), 145.8 (NSO₂ArC(1)), 169.3 (C(2)); HRMS (NSI⁺) C₂₈H₂₄N₂O₃S⁷⁹Br [M+H]⁺ found 547.0681, requires 547.0686 (-0.8 ppm).

(3S,4S)-6-(4-Chlorophenyl)-4-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (353)

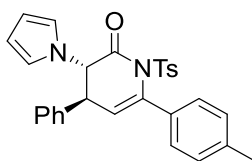
Following **General Procedure C**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **331** (49.5 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **353** as a white solid (50.3 mg, 80%). mp 118-120 °C; $[\alpha]_D^{20} + 16.6$ (*c* 1.1 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 31.4 min, *t*_R (minor): 10.4 min, 77:23 er; *v*_{max} (film, cm⁻¹) 3025 (C-H), 1732 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.51 (3H, s, NSO₂PhCH₃), 4.14 (1H, dd, *J* 12.7, 3.4, C(4)*H*), 4.74 (1H, d, *J* 12.7, C(3)*H*), 5.98 (2H, t, *J* 2.1, C(3)Ar(3,4)*H*), 6.02 (1H, d, *J* 3.4, C(5)*H*), 6.21 (2H, t, *J* 2.2, C(3)Ar(2,5)*H*), 7.06–7.08 (2H, m, C(4)ArC(2,6)*H*), 7.22–7.25 (3H, m, C(4)ArC(3,4,5)*H*), 7.36–7.40 (6H, m, NSO₂ArC(3,5)*H* + C(6)ArC(2,3,5,6)*H*), 7.91–7.95 (2H, m, NSO₂ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.8 (NSO₂PhCH₃), 45.2 (C(4)), 67.1 (C(3)), 109.0 (C(3)ArC(3,4)*H*), 120.2 (C(3)ArC(2,5)*H*), 122.0 (C(5)), 127.2 (C(4)ArC(2,6)*H*), 127.3 (C(6)ArC(2,6)*H*), 127.9 (C(6)ArC(3,5)*H*), 128.9 (C(4)ArC(4)*H*), 129.4 (C(4)ArC(3,5)*H*), 129.5(NSO₂ArC(3,5)*H* + NSO₂ArC(2,6)*H*), 134.8 (C(4)ArC(1)), 135.0 (NSO₂ArC(4)), 135.8 (C(6)ArC(1)), 137.7 (C(6)), 139.0 (C(6)ArC(4)), 145.8 (NSO₂ArC(1)), 169.3 (C(2)); HRMS (NSI⁺) C₂₈H₂₄N₂O₃S³⁵Cl [M+H]⁺ found 503.1186, requires 503.1191 (-0.9 ppm).

(3S,4S)-6-(4-Fluorophenyl)-4-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (354)

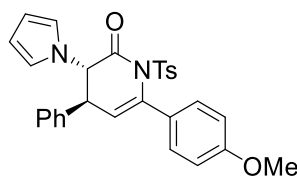
Following **General Procedure C**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **332** (47.4 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **354** as a light yellow solid (46.2 mg, 76%). mp 106-108 °C; $[\alpha]_D^{20} + 13.9$ (c 0.6 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 26.0 min, *t*_R (minor): 10.0 min, 78:22 er; ν_{\max} (film, cm⁻¹) 3020 (C-H), 1745 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H : 2.51 (3H, s, NSO₂PhCH₃), 4.15 (1H, dd, *J* 12.7, 3.4, C(4)H), 4.74 (1H, d, *J* 12.7, C(3)H), 5.98–5.99 (3H, m, C(5)H + C(3)Ar(3,4)H), 6.22 (2H, t, *J* 2.1, C(3)Ar(2,5)H), 7.07–7.13 (4H, m, C(4)ArC(2,6)H + C(6)ArC(2,6)H), 7.21–7.25 (3H, m, C(4)ArC(3,4,5)H), 7.35–7.38 (2H, m, NSO₂ArC(3,5)H), 7.40–7.44 (2H, m, C(6)ArC(3,5)H), 7.90–7.93 (2H, m, NSO₂ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 21.8 (NSO₂PhCH₃), 45.2 (C(4)), 67.2 (C(3)), 109.0 (C(3)ArC(3,4)H), 115.7 (d, ³*J*_{CF} 21.8, C(6)ArC(2,6)H), 120.2 (C(3)ArC(2,5)H), 121.5 (C(5)), 127.3 (C(4)ArC(2,6)H), 127.8 (d, ²*J*_{CF} 8.2, C(6)ArC(3,5)H), 127.9 (C(4)ArC(3,5)H), 128.9 (C(4)ArC(4)H), 129.4 (NSO₂ArC(3,5)H), 129.4 (NSO₂ArC(2,6)H), 132.6 (d, ⁴*J*_{CF} 3.4, C(6)ArC(1)), 135.9 (NSO₂ArC(4)), 137.8 (C(4)ArC(1)), 139.1 (C(6)), 145.8 (NSO₂ArC(1)), 163.0 (d, ¹*J*_{CF} 248.8, C(6)ArC(4)), 169.3 (C(2)); ¹⁹F NMR (471 MHz, CDCl₃) δ_F : -112.1; HRMS (NSI⁺) C₂₈H₂₄N₂O₃SF [M+H]⁺ found 478.1481, requires 478.1486 (-1.1 ppm).

(3S,4S)-6-(4-Bromophenyl)-4-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (355)

Following **General Procedure C**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **333** (55.1 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **355** as a yellow solid (65.7 mg, 96%). mp 118-120 °C; $[\alpha]_D^{20} + 44.7$ (*c* 0.7 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 220 nm, 30 °C) *t*_R (major): 33.9 min, *t*_R (minor): 10.5 min, 75:25 er; *v*_{max} (film, cm⁻¹) 3011 (C-H), 1740 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H : 2.51 (3H, s, NSO₂PhCH₃), 4.13 (1H, dd, *J* 12.7, 3.4, C(4)*H*), 4.73 (1H, d, *J* 12.7, C(3)*H*), 5.98 (2H, t, *J* 2.1, C(3)Ar(3,4)*H*), 6.03 (1H, d, *J* 3.4, C(5)*H*), 6.21 (2H, t, *J* 2.1, C(3)Ar(2,5)*H*), 7.06–7.08 (2H, m, C(4)ArC(2,6)*H*), 7.22–7.25 (3H, m, C(4)ArC(3,4,5)*H*), 7.31–7.34 (2H, m, C(6)ArC(2,6)*H*), 7.36–7.39 (2H, m, NSO₂ArC(3,5)*H*), 7.54–7.57 (2H, m, C(6)ArC(3,5)*H*), 7.91–7.96 (2H, m, NSO₂ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 21.8 (NSO₂PhCH₃), 45.2 (C(4)), 67.1 (C(3)), 109.0 (C(3)ArC(3,4)*H*), 120.2 (C(3)ArC(2,5)*H*), 122.1 (C(5)), 127.3 (C(4)ArC(2,6)*H*), 127.5 (C(6)ArC(2,6)*H*), 127.9 (NSO₂ArC(2,6)*H*), 128.9 (C(4)ArC(4)*H*), 129.4 (C(4)ArC(3,5)*H*), 129.5 (NSO₂ArC(3,5)*H*), 131.8 (C(6)ArC(3,5)*H*), 135.5 (C(4)ArC(1)), 135.8 (C(6)ArC(1) + NSO₂ArC(4)), 137.6 (C(6)), 139.1 (C(6)ArC(4)), 145.8 (NSO₂ArC(1)), 169.3 (C(2)); HRMS (NSI⁺) C₂₈H₂₄N₂O₃S⁷⁹Br [M+H]⁺ found 547.0680, requires 547.0686 (-1.0 ppm).

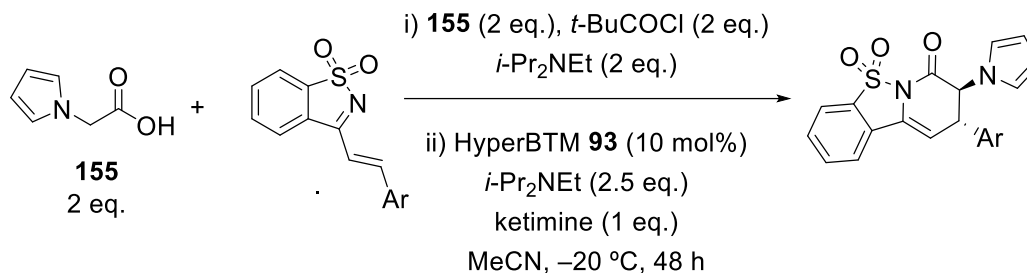
(3S,4S)-4-Phenyl-3-(1H-pyrrol-1-yl)-6-(p-tolyl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (356)

Following **General Procedure C**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **334** (46.9 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **356** as a white solid (65.7 mg, 70%). mp 136-138 °C; $[\alpha]_D^{20} + 18.7$ (*c* 0.2 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) *t*_R (major): 20.7 min, *t*_R (minor): 8.9 min, 75:25 er; *v*_{max} (film, cm⁻¹) 2988 (C-H), 1738 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.43 (3H, s, C(6)ArC(4)CH₃), 2.51 (3H, s, NSO₂PhCH₃), 4.14 (1H, dd, *J* 12.7, 3.4, C(4)H), 4.73 (1H, d, *J* 12.7, C(3)H), 5.97 (2H, t, *J* 2.1, C(3)Ar(3,4)H), 5.99 (1H, d, *J* 3.4, C(5)H), 6.21 (2H, t, *J* 2.1, C(3)Ar(2,5)H), 7.05–7.10 (2H, m, C(4)ArC(2,6)H), 7.21–7.24 (5H, m, C(4)ArC(3,4,5)H + C(6)ArC(3,5)H), 7.34–7.38 (4H, m, C(6)ArC(2,4)H + NSO₂ArC(3,5)H), 7.93–7.96 (2H, m, NSO₂ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 21.4 (C(6)ArC(4)CH₃), 21.8 (NSO₂PhCH₃), 45.2 (C(4)), 67.3 (C(3)), 108.9 (C(3)ArC(3,4)H), 120.2 (C(3)ArC(2,5)H), 120.8 (C(5)), 125.8 (C(4)ArC(2,6)H), 127.3 (C(6)ArC(2,6)H), 127.8 (NSO₂ArC(2,6)H), 128.8 (C(4)ArC(4)H), 129.3 (C(4)ArC(3,5)H), 129.6 (NSO₂ArC(3,5)H + C(6)ArC(3,5)H), 133.7 (C(4)ArC(1)), 136.0 (C(6)ArC(4)), 138.0 (C(6)), 139.0 (C(6)ArC(1)), 140.0 (NSO₂ArC(4)), 145.5 (NSO₂ArC(1)), 169.5 (C(2)); HRMS (NSI⁺) C₂₉H₂₇N₂O₃S [M+H]⁺ found 483.1732, requires 483.1737 (-1.0 ppm).

(3S,4S)-6-(4-Methoxyphenyl)-4-phenyl-3-(1H-pyrrol-1-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (357)

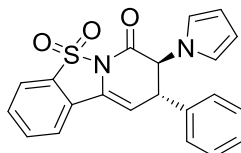
Following **General Procedure C**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), ketimine **335** (48.9 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (15:85 EtOAc/petrol) to give the titled compound **357** as a yellow oil (37.4 mg, 60%); $[\alpha]_D^{20} + 8.0$ (*c* 0.2 in CHCl₃); Chiral HPLC analysis, Chiralpak OD-H (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 35.2 min, *t*_R (minor): 13.8 min, 72:28 er; *v*_{max} (film, cm⁻¹) 2965 (C-H), 2925 (C-H), 1734 (C=O); ¹H NMR (500 MHz, CDCl₃) δ _H: 2.50 (3H, s, NSO₂PhCH₃), 3.88 (3H, s, C(6)ArC(4)OCH₃), 4.13 (1H, dd, *J* 12.7, 3.5, C(4)H), 4.73 (1H, d, *J* 12.7, C(3)H), 5.94 (1H, d, *J* 3.4, C(5)H), 5.97 (2H, t, *J* 2.1, C(3)Ar(3,4)H), 6.20 (2H, t, *J* 2.2, C(3)Ar(2,5)H), 6.92–6.96 (2H, m, C(6)ArC(3,5)H), 7.07–7.09 (2H, m, C(4)ArC(2,6)H), 7.20–7.24 (3H, m, C(4)ArC(3,4,5)H), 7.32–7.42 (4H, m, C(6)ArC(2,6)H + NSO₂ArC(3,5)H), 7.92–7.94 (2H, m, NSO₂ArC(2,6)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ _C: 21.8 (NSO₂PhCH₃), 45.2 (C(4)), 55.4 (C(6)ArC(4)OCH₃), 67.4 (C(3)), 108.9 (C(3)ArC(3,4)H), 114.0 (C(6)ArC(3,5)H), 120.1 (C(3)ArC(2,5)H), 120.2 (C(5)), 127.3 (C(4)ArC(2,6)H), 127.4 (C(6)ArC(2,6)H), 127.8 (NSO₂ArC(2,6)H), 128.8 (C(4)ArC(4)H), 129.0 (C(4)ArC(3)H), 129.3 (NSO₂ArC(3,5)H), 129.5 (C(4)ArC(5)H), 136.1 (C(4)ArC(1) + C(6)ArC(1)), 138.0(C(6)), 139.7 (NSO₂ArC(4)), 145.6 (NSO₂ArC(1)), 160.1 (C(6)ArC(4)), 169.6 (C(2)); HRMS (NSI⁺) C₂₉H₂₇N₂O₄S [M+H]⁺ found 499.1681, requires 499.1686 (-1.0 ppm).

General Procedure D: Michael addition-lactamization with saccharin derived α,β -unsaturated ketimines and 2-(1*H*-Pyrrol-1-yl)acetic acid **155**



2-(1*H*-Pyrrol-1-yl)acetic acid **155** (2 eq.) was dissolved in anhydrous MeCN (0.05 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (2 eq.) and pivaloyl chloride (2 eq.) were added. The reaction was stirred at 0 °C for 20 min before cooling to -20 °C. HyperBTM **93** (10 mol%), the required saccharin-derived ketimine (1 eq.), and *i*-Pr₂NEt (2.5 eq.) were added sequentially and the reaction stirred at -20 °C for 48 h. After that, the solvent was concentrated under reduced pressure to give the crude product, which was purified by flash silica column chromatography

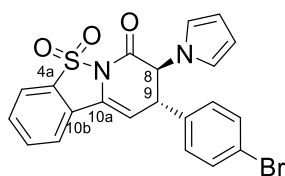
(8*S*,9*S*)-9-Phenyl-8-(1*H*-pyrrol-1-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide (358**)**



Following **General Procedure D**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), saccharin-derived ketimine **339** (33.7 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 to 50:50 EtOAc/petrol) to give the titled compound as a white solid (32.9 mg, 70%). mp 250–252 °C; $[\alpha]_D^{20}$ - 95.0 (*c* 0.2 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (70:30 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 21.0 min, *t*_R (minor): 17.5 min, 99:1 er; ν_{\max} (film, cm⁻¹) 3063 (C-H), 3030 (C-H), 1736 (C=O), 1462, 1314; ¹H NMR (500 MHz, CDCl₃) δ _H: 4.37 (1H, dd, *J* 11.6, 3.0, C(9)H), 4.93 (1H, d, *J* 11.5, C(8)H), 6.09–6.14 (3H, m, C(10)H

+ C(8)Ar(3,4)H), 6.52 (2H, t, J 2.2, C(8)Ar(2,5)H), 7.05–7.08 (2H, m, C(9)ArC(2,6)H), 7.28–7.31 (3H, m, C(9)ArC(3,4,5)H), 7.70 (1H, dq, J 8.2, 4.3, ArCH), 7.78 (2H, d, J 4.1, ArCH), 7.90 (1H, d, J 7.9, ArCH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 47.3 (C(9)), 65.7 (C(8)), 105.1 (C(10)), 109.5 (C(8)ArC(3,4)H), 120.5 (C(8)ArC(2,5)H), 121.9 (ArCH), 122.0 (ArCH), 126.2 (ArC(10b)), 127.5 (C(9)ArC(2,6)H), 128.4 (C(9)ArC(4)H), 129.3 (C(9)ArC(3,5)H), 129.9 (ArC(10a)), 131.5 (ArCH), 132.9 (C(4a)), 134.5 (ArCH), 138.9 (C(9)ArC(1)), 163.0 (C(7)); HRMS (ESI⁺) $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$ found 399.0773, requires 399.0774 (-0.2 ppm).

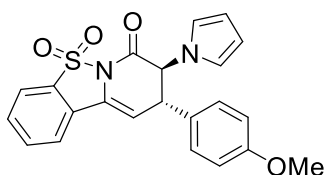
(8*S*,9*S*)-9-(4-Bromophenyl)-8-(1*H*-pyrrol-1-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide (361)



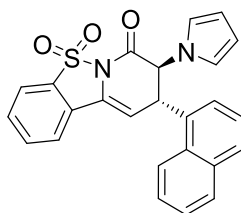
Following **General Procedure D**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), saccharin-derived ketimine **340** (43.5 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 to 50:50 EtOAc/petrol) to give the titled compound as a light yellow solid (37.6 mg, 66%). mp 258–260 °C; $[\alpha]_{\text{D}}^{20}$ – 82.6 (c 0.5 in DMSO); Chiral HPLC analysis, Chiralpak AS-H (70:30 hexane/*i*-PrOH, flow rate 0.7 mLmin⁻¹, 211 nm, 40 °C) t_{R} (major): 60.6 min, t_{R} (minor): 40.9 min, 98:2 er; ν_{max} (film, cm⁻¹) 3084 (C-H), 1719 (C=O), 1489, 1342; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 4.35 (1H, dd, J 12.0, 2.8, C(9)H), 4.86 (1H, d, J 12.0, C(8)H), 6.04 (1H, d, J 2.8, C(10)H), 6.13 (2H, t, J 2.1, C(8)Ar(3,4)H), 6.50 (2H, t, J 2.1, C(8)Ar(2,5)H), 6.91–6.94 (2H, m, C(9)ArC(2,6)H), 7.40–7.43 (2H, m, C(9)ArC(3,5)H), 7.68–7.74 (1H, m, ArCH), 7.77–7.81 (2H, m, ArCH), 7.90–7.92 (1H, m, ArCH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 46.8 (C(9)), 65.5 (C(8)), 104.2 (C(10)), 109.8 (C(8)ArC(3,4)H), 120.5 (C(8)ArC(2,5)H), 121.9 (ArCH), 122.1 (ArCH), 122.4 (C(9)ArC(4)), 126.0 (ArC(10b)), 129.2 (C(9)ArC(2,6)H), 130.3 (ArC(10a)), 131.7 (ArCH), 132.4

(C(9)ArC(3,5)H), 133.0 (C(4a)), 134.5 (ArCH), 137.9 (C(9)ArC(1)), 162.8 (C(7)); HRMS (ESI⁺) C₂₁H₁₅N₂O₃S⁷⁹BrNa [M+Na]⁺ found 476.9882, requires 476.9879 (+0.6 ppm).

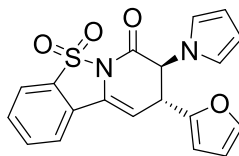
(8*S*,9*S*)-9-(4-Methoxyphenyl)-8-(1*H*-pyrrol-1-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide (362)



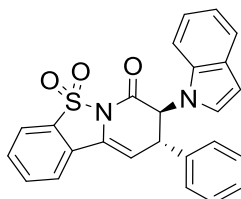
Following **General Procedure D**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), saccharin-derived ketimine **341** (37.4 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 to 50:50 EtOAc/petrol) to give the titled compound as a light yellow solid (45.7 mg, 90%). mp 208–210 °C; [α]_D²⁰ – 58.5 (c 1.2 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R(major): 20.5 min, t_R(minor): 15.5 min, 97:3 er; ν_{\max} (film, cm⁻¹) 3052 (C-H), 1732 (C=O), 1611, 1514; ¹H NMR (500 MHz, CDCl₃) δ _H: 3.78 (3H, s, CH₃), 4.32 (1H, dd, *J* 11.5, 3.0, C(9)H), 4.87 (1H, d, *J* 11.5, C(8)H), 6.09 (1H, d, *J* 3.0, C(10)H), 6.12 (2H, t, *J* 2.1, C(8)Ar(3,4)H), 6.52 (2H, t, *J* 2.1, C(8)Ar(2,5)H), 6.79–6.83 (2H, m, C(9)ArC(3,5)H), 6.95–6.98 (2H, m, C(9)ArC(2,6)H), 7.70 (1H, dq, *J* 8.2, 4.2, ArCH), 7.77–7.78 (2H, m, ArCH), 7.89–7.91 (1H, m, ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ _C: 46.5 (C(9)), 55.4 (CH₃), 65.9 (C(8)), 105.5 (C(10)), 109.5 (C(8)ArC(3,4)H), 114.6 (C(9)ArC(3,5)H), 120.5 (C(8)ArC(2,5)H), 121.8 (ArCH), 122.0 (ArCH), 126.2 (ArC(10b)), 128.6 (C(9)ArC(2,6)H), 129.7 (ArC(10a)), 130.8 (C(9)ArC(1)), 131.5 (ArCH), 132.9 (C(4a)), 134.5 (ArCH), 159.5 (C(9)ArC(4)), 163.1 (C(7)); HRMS (ESI⁺) C₂₂H₁₈N₂O₄SNa [M+Na]⁺ found 429.0881, requires 429.0879 (+0.4 ppm).

(8*S*,9*S*)-9-(Naphthalen-1-yl)-8-(1*H*-pyrrol-1-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide (363)

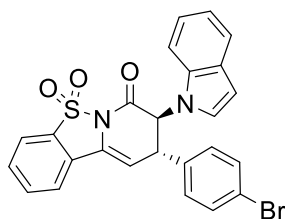
Following **General Procedure D**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), saccharin-derived ketimine **343** (79.8 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 to 50:50 EtOAc/petrol) to give the titled compound as a white solid (51.7 mg, 97%). mp 226–228 °C; $[\alpha]_D^{20}$ – 57.8 (*c* 1.0 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) *t*_R (major): 13.6 min, *t*_R (minor): 16.6 min, 98:2 er; ν_{\max} (film, cm⁻¹) 3057 (C-H), 1736 (C=O), 1491, 1470, 1329; ¹H NMR (500 MHz, CDCl₃) δ _H: 5.09 (1H, app. s, C(9)*H*), 5.30 (1H, app. s, C(8)*H*), 6.06 (2H, t, *J* 2.1, C(8)Ar(3,4)*H*), 6.24 (1H, d, *J* 3.8, C(10)*H*), 6.58 (2H, app. s, C(8)Ar(2,5)*H*), 7.27–7.43 (2H, m, ArCH), 7.54 (2H, dt, *J* 6.4, 3.5, ArCH), 7.68–8.00 (7H, m, ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ _C (selected): 63.8 (C(8)), 105.2 (C(10)), 109.6 (C(8)ArC(3,4)*H*), 120.1 (C(8)ArC(2,5)*H*), 121.9 (ArCH), 122.0 (ArCH), 122.3 (ArCH), 125.5 (ArCH), 126.1 (ArCH), 126.9 (ArC(10b)), 129.2 (ArCH), 129.6 (ArCH), 130.6 (ArC(10a)), 131.5 (ArCH), 132.7 (C(4a)), 133.3 (C(9)ArC), 134.3 (ArCH), 134.4 (C(9)ArC), 162.7 (C(7)); HRMS (ESI⁺) C₂₅H₁₈N₂O₃SNa [M+Na]⁺ found 449.0938, requires 449.0930 (+1.7 ppm).

**(8*S*,9*R*)-9-(Furan-2-yl)-8-(1*H*-pyrrol-1-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-
a]pyridin-7-one 5,5-dioxide (364)**

Following **General Procedure D**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.), *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.), pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by HyperBTM **93** (3.9 mg, 10 mol%), saccharin-derived ketimine **342** (32.4 mg, 0.125 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.055 mL, 0.32 mmol, 2.5 eq.) at rt for 72 h gave crude product (>95:5 dr) that was purified by column chromatography (30:70 to 50:50 EtOAc/petrol) to give the titled compound as a dark brown solid (23.8 mg, 52%). mp 222–224 °C; $[\alpha]_{\text{D}}^{20}$ – 64.9 (*c* 0.8 in DMSO); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) *t*_R(major): 15.9 min, *t*_R(minor): 12.5 min, 96:4 er; *v*_{max} (film, cm⁻¹) 2972 (C-H), 1732 (C=O), 1493, 1470, 1339; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 4.51 (1H, dd, *J* 10.6, 3.4, C(9)*H*), 5.15 (1H, d, *J* 10.5, C(8)*H*), 5.99 (1H, d, *J* 3.3, C(9)ArC(3)*H*), 6.13 (1H, d, *J* 3.4, C(10)*H*), 6.17 (2H, t, *J* 2.1, C(8)Ar(3,4)*H*), 6.28 (1H, dd, *J* 3.3, 1.9, C(9)ArC(4)*H*), 6.62 (2H, t, *J* 2.1, C(8)Ar(2,5)*H*), 7.38 (1H, d, *J* 1.7, C(9)ArC(5)*H*), 7.68–7.73 (1H, m, ArCH), 7.76–7.80 (2H, m, ArCH), 7.88–7.91 (1H, m, ArCH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 40.7 (C(9)), 62.5 (C(8)), 102.3 (C(10)), 108.4 (C(9)ArC(3)*H*), 109.7 (C(8)ArC(3,4)*H*), 111.0 (C(9)ArC(4)*H*), 120.4 (C(8)ArC(2,5)*H*), 122.0 (ArCH), 122.0 (ArCH), 126.1 (ArC(10b)), 129.9 (ArC(10a)), 131.7 (ArCH), 133.0 (C(4a)), 134.5 (ArCH), 143.0 (C(9)ArC(5)*H*), 149.9 (C(9)ArC(1)), 162.8 (C(7)); HRMS (ESI⁺) C₁₉H₁₄N₂O₄SNa [M+Na]⁺ found 389.0568, requires 389.0566 (+0.4 ppm).

(8*S*,9*S*)-8-(1*H*-Indol-1-yl)-9-phenyl-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide (365) (by Lucas)

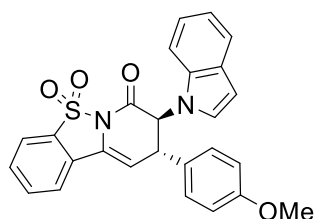
2-(1*H*-Indol-1-yl)acetic acid **223** (46.0 mg, 0.25 mmol, 1.5 eq.) was dissolved in anhydrous MeCN (2.5 mL, 0.07 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (58 μL, 0.34 mmol, 2 eq.) and pivaloyl chloride (42 μL, 0.34 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before cooled to -40 °C. HyperBTM **93** (10.0 mg, 0.03 mmol, 20 mol%), saccharin-derived ketimine **339** (45.8 mg, 0.17 mmol, 1 eq.), and *i*-Pr₂NEt (73 μL, 0.43 mmol, 2.5 eq.) were added sequentially and the reaction stirred at -40 °C for 2 h. The reaction mixture was quenched with aq. HCl (10 mL, 0.1 M) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a white solid (55.9 mg, 77%). mp 248 °C; [α]_D²⁰ + 3.4 (c 1.4 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 11.2 min, t_R (minor): 12.8 min, 98:2 er; ν_{max} (film, cm⁻¹) 2922 (C-H), 1722 (C=O); ¹H NMR (500 MHz, DMSO) δ_H: 5.05 (1H, dd, *J* 13.4, 2.3, C(9)*H*), 6.34 (1H, d, *J* 13.5, C(8)*H*), 6.45 (1H, d, *J* 3.2, C(8)indolylC(3)*H*), 6.61 (1H, d, *J* 3.2, C(10)*H*), 6.92 (1H, m, C(8)indolylC(5)*H*), 6.97 (1H, m, C(8)indolylC(6)*H*), 7.04 (1H, m, C(9)Ar(4)*H*), 7.16 (2H, m, C(9)Ar(3,5)*H*), 7.26 (2H, m, C(9)Ar(2,6)*H*), 7.39 (1H, m, C(8)indolylC(7)*H*), 7.42 (1H, m, C(8)indolylC(4)*H*), 7.63 (1H, d, *J* 3.2, C(8)indolylC(2)*H*), 7.80 (1H, m, C(3)*H*), 7.92 (1H, m, C(2)*H*), 8.18 (1H, m, C(4)*H*), 8.30 (1H, m, C(1)*H*); ¹³C{¹H} NMR (126 MHz, DMSO) δ_C: 44.3 (C(9)*H*), 60.1 (C(8)*H*), 102.5 (C(8)indolylC(3)*H*), 108.4 (C(10)), 109.7 (C(8)indolylC(7)*H*), 119.2 (C(8)indolylC(5)*H*), 120.2 (C(8)indolylC(4)*H*), 112.1 (C(8)indolylC(6)*H*), 121.7 (C(4)*H*), 122.8 (C(1)*H*), 126.1 (C(10b)), 126.9 (C(8)indolylC(2)*H*), 127.4 (C(9)ArC(4)*H*), 127.6 (C(8)indolylC(3a)), 127.9 (C(10a)), 128.0 (C(9)ArC(2,6)*H*), 128.5 ((C(9)ArC(3,5)*H*), 131.6 (C(3)*H*), 131.9 (C(4a)), 135.0 (C(2)*H*), 137.2 (C(8)indolylC(7a)), 139.8 (C(9)ArC(1)), 164.6 (C(7)); HRMS (ESI⁺) C₂₅H₁₈N₂NaO₃S [M+Na]⁺ found 449.0925, requires 449.0936 (-2.4 ppm).

**(8*S*,9*S*)-9-(4-Bromophenyl)-8-(1*H*-indol-1-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-
a]pyridin-7-one 5,5-dioxide (366) (by Lucas)**

2-(1*H*-Indol-1-yl)acetic acid **223** (48.0 mg, 0.22 mmol, 1.5 eq.) was dissolved in anhydrous MeCN (2.2 mL, 0.07 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (49 μL, 0.29 mmol, 2 eq.) and pivaloyl chloride (35 μL, 0.29 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before cooled to -40 °C. HyperBTM **93** (10.0 mg, 0.03 mmol, 20 mol%), saccharin-derived ketimine **340** (50 mg, 0.14 mmol, 1 eq.), and *i*-Pr₂NEt (61 μL, 0.36 mmol, 2.5 eq.) were added sequentially and the reaction stirred at -40 °C for 48 h. The reaction mixture was quenched with aq. HCl (10 mL, 0.1 M) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a yellow solid (19.2 mg, 26%). mp 230 °C; $[\alpha]_D^{20} + 6.5$ (c 1.4 in CHCl₃); Chiral HPLC analysis, Chiralpak IB (80:20 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) *t*_R (major): 59.4 min, *t*_R (minor): 72.1 min, 97:3 er; *v*_{max} (film, cm⁻¹) 2924 (C-H), 1718 (C=O); ¹H NMR (500 MHz, DMSO) δ_H: 5.08 (1H, dd, *J* 13.4, 2.2, C(9)*H*), 6.35 (1H, d, *J* 13.4, C(8)*H*), 6.48 (1H, d, *J* 3.2, C(8)indolylC(3)*H*), 6.50 (1H, d, *J* 3.2, C(10)*H*), 6.92–6.98 (1H, m, C(8)indolylC(5)*H*), 6.98–7.03 (1H, m, C(8)indolylC(6)*H*), 7.20–7.24 (2H, m, C(9)Ar(2,6)*H*), 7.36–7.39 (2H, m, C(9)Ar(3,5)*H*), 7.38–7.42 (1H, m, C(8)indolylC(4)*H*), 7.44–7.47 (1H, m, C(8)indolylC(7)*H*), 7.64 (1H, d, *J* 3.2, C(8)indolylC(2)*H*), 7.81 (1H, t, *J* 7.7, ArC(3)*H*), 7.91–7.96 (1H, m, ArC(2)*H*), 8.20 (1H, d, *J* 7.9, ArC(4)*H*), 8.29 (1H, d, *J* 7.9 ArC(1)*H*); ¹³C{¹H} NMR (126 MHz, DMSO) δ_C: 43.8 (C(9)*H*), 59.8 (C(8)*H*), 102.7 (C(8)indolylC(3)*H*), 107.7 (C(10)*H*), 109.6 (C(8)indolylC(7)*H*), 119.3 (C(8)indolylC(5)*H*), 120.3 (C(8)indolylC(4)*H*), 120.6 (C(9)ArC(4)), 121.2 (C(8)indolylC(6)*H*), 121.7 (ArC(4)*H*), 122.8 (ArC(1)*H*), 126.0 (C(10b)), 126.9 (C(8)indolylC(2)*H*), 127.6 (C(8)indolylC(3a)*H*), 128.2 (C(10a)), 130.3 (C(9)ArC(2,6)), 131.4 (C(9)ArC(3,5)), 131.7 (ArC(3)*H*), 131.9 (ArC(4a)*H*), 135.0 (ArC(2)*H*), 137.2 (C(8)indolylC(7a)),

139.7 (C(9)ArC(1)), 164.4 (C(7)); HRMS (ESI⁺) C₂₅H₁₇N₂NaO₃S⁷⁹Br [M+Na]⁺, found 527.0026, requires 527.0041 (-2.8 ppm).

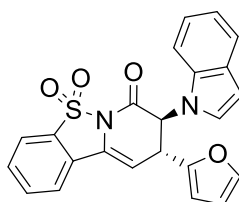
(8*S*,9*S*)-8-(1*H*-Indol-1-yl)-9-(4-methoxyphenyl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide (367) (by Lucas)



2-(1*H*-Indol-1-yl)acetic acid **223** (46.0 mg, 0.25 mmol, 1.5 eq.) was dissolved in anhydrous MeCN (2.5 mL, 0.07 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (58 μL, 0.34 mmol, 2 eq.) and pivaloyl chloride (42 μL, 0.34 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before cooled to -40 °C. HyperBTM **93** (10 mg, 0.03 mmol, 20 mol%), saccharin-derived ketimine **341** (50.0 mg, 0.17 mmol, 1 eq.), and *i*-Pr₂NEt (73 μL, 0.43 mmol, 2.5 eq.) were added sequentially and the reaction stirred at -40 °C for 48 h. The reaction mixture was quenched with aq. HCl (10 mL, 0.1 M) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a yellow solid (47.2 mg, 62%). mp 210 °C; [α]_D²⁰ + 6.2 (c 1.4 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 254 nm, 30 °C) t_R (major): 14.9 min, t_R (minor): 17.7 min, 95:5 er; ν_{max} (film, cm⁻¹) 2926 (C-H), 1722 (C=O); ¹H NMR (500 MHz, DMSO) δ_H: 3.61 (3H, s, OCH₃), 5.00 (1H, dd, *J* 13.4, 2.1, C(9)*H*), 6.29 (1H, d, *J* 13.5, C(8)*H*), 6.45 (1H, d, *J* 3.2, C(8)indolyC(3)*H*), 6.56 (1H, d, *J* 2.3, C(10)*H*), 6.71–6.75 (2H, m, C(9)Ar(3,5)*H*), 6.92–6.97 (1H, m, C(8)indolyC(5)*H*), 7.00 (1H, t, *J* 7.5, C(8)indolyC(6)*H*), 7.19 (2H, d, *J* 8.7, C(9)Ar(2,6)*H*), 7.41 (1H, d, *J* 8.4, C(8)indolyC(7)*H*), 7.44 (1H, d, *J* 7.8, C(8)indolyC(4)*H*), 7.62 (1H, d, *J* 3.2, C(8)indolyC(2)*H*), 7.79 (1H, t, *J* 7.7, ArC(3)*H*), 7.98–7.95 (1H, m, ArC(2)*H*), 8.18 (1H, d, *J* 7.9, ArC(4)*H*), 8.28 (1H, d, *J* 8.0, ArC(1)*H*); ¹³C{¹H} NMR (126 MHz, DMSO) δ_C: 43.5 (C(9)), 54.9 (OCH₃), 60.2 (C(8)*H*), 102.4 (C(8)indolyC(3)*H*), 108.9 (C(10)), 109.7 (C(8)indolyC(7)*H*), 113.9 (C(9)ArC(3,5)*H*), 119.2 (C(8)indolyC(5)*H*), 120.2 (C(8)indolyC(4)*H*), 121.1 (C(8)indolyC(6)*H*), 121.7 (ArC(4)*H*), 122.8

(ArC(1)H), 126.1 (ArC(10b)), 126.9 (C(8)indolyC(2)H), 127.6 (C(8)indolyC(3a)), 127.7 (C(10a)), 129.1 (C(9)ArC(2,6)H), 131.5 (ArC(3)H), 131.6 (C(8)indolyC(7a)), 131.9 (C(9)ArC(1)), 135.0 (ArC(2)H), 137.2 (ArC(4a)), 158.4 (C(9)ArC(4)), 164.6 (C(7)); HRMS (ESI⁺) C₂₆H₂₀N₂NaO₄S [M+Na]⁺, found 479.1024, requires 479.1041 (-3.5 ppm).

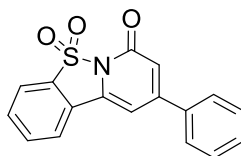
(8*S*,9*R*)-9-(Furan-2-yl)-8-(1*H*-indol-1-yl)-8,9-dihydro-7*H*-benzo[4,5]isothiazolo[2,3-*a*]pyridin-7-one 5,5-dioxide (368) (by Lucas)



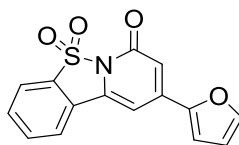
2-(1*H*-Indol-1-yl)acetic acid **223** (50.0 mg, 0.29 mmol, 1.5 eq.) was dissolved in anhydrous MeCN (2.9 mL, 0.07 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (65 μL, 0.39 mmol, 2 eq.) and pivaloyl chloride (47 μL, 0.39 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before cooled to -40 °C. HyperBTM **93** (11.9 mg, 0.04 mmol, 20 mol%), saccharin-derived ketimine **342** (50.0 mg, 0.19 mmol, 1 eq.), and *i*-Pr₂NEt (81 μL, 0.48 mmol, 2.5 eq.) were added sequentially and the reaction stirred at -40 °C for 2 h. The reaction mixture was quenched with aq. HCl (10 mL, 0.1 M) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product (>95:5 dr) that was purified by column chromatography (30:70 EtOAc/petrol) to give the titled compound as a brown solid (60.1 mg, 76%). mp 220 °C; [α]_D²⁰ + 6.2 (c 1.4 in CHCl₃); Chiral HPLC analysis, Chiralpak AD-H (60:40 hexane/*i*-PrOH, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) t_R (major): 13.5 min, t_R (minor): 14.8 min, >99:1 er; ν_{max} (film, cm⁻¹) 3078 (C-H), 1736 (C=O); ¹H NMR (500 MHz, DMSO) δ_H: 5.23 (1H, dd, *J* 13.4, 2.4, C(9)H), 6.02–6.04 (1H, m, C(9)furanC(3)H), 6.18 (1H, dd, *J* 3.2, 1.9 (C(9)furanC(4)H), 6.32 (1H, d, *J* 13.4 C(8)H), 6.49 (1H, d, *J* 3.3, C(8)indolyC(3)H), 6.65 (1H, d, *J* 2.5, C(10)H), 6.96–7.01 (1H, m, C(8)indolyC(5)H), 7.03–7.08 (1H, m, C(8)indolyC(6)H), 7.45 (1H, dd, *J* 3.3, 1.7, C(9)furanC(5)H), 7.47–7.50 (1H, m, C(8)indolyC(7)H), 7.48–7.50 (1H, m, C(8)indolyC(4)H), 7.61 (1H, d, *J* 3.3, C(8)indolyC(2)H), 7.78–7.84 (1H, m, ArC(3)H), 7.91–7.96 (1H, m, ArC(2)H), 8.17–8.20 (1H, m, ArC(4)H), 8.30–8.35 (1H, m, ArC(1)H); ¹³C{¹H} NMR (126 MHz, DMSO) δ_C: 35.4 (C(9)H), 58.1

(C(8)H), 102.6 (C(8)indolyC(3)H), 105.6 (C(10)H), 107.3 (C(9)furanC(3)H), 109.7 (C(8)indolyC(7)H), 110.5 (C(9)furanC(4)H), 119.3 (C(8)indolyC(5)H), 120.31 (C(8)indolyC(4)H), 121.7 (C(8)indolyC(6)H), 122.9 (ArC(4)H), 126.0 (ArC(1)H), 127.0 (C(8)indolyC(2)H), 127.7 (C(8)indolyC(3a)), 128.2 (C(10a)), 131.7 (ArC(3)H), 131.9 (C(4a)), 135.0 (ArC(2)H), 137.1 (C(8)indolyC(7a)), 142.6 (C(9)furanC(5)H), 151.6 (C(9)furanC(2)), 164.2 (ArC(7)); HRMS (ESI⁺) C₂₃H₁₆N₂NaO₃S [M+Na]⁺, found 439.0713, requires 439.0728 (-3.4 ppm).

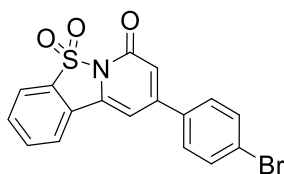
9-Phenyl-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (360)



2-(1*H*-Pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.) was dissolved in anhydrous MeCN (2.5 mL, 0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.) and pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) were added. The reaction was stirred at 0 °C for 20 min before warmed up to rt. HyperBTM **93** (3.9 mg, 10 mol%), saccharin-derived ketimine **339** (33.7 mg, 0.125 mmol, 1.0 eq.), and *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.) were added sequentially and the reaction stirred at rt. for 24 h. The reaction mixture was concentrated under reduced pressure to give the crude product that was purified by column chromatography (50:50 EtOAc/petrol) to give the titled compound as a yellow solid (25.1 mg, 65%). Spectroscopic data were in accordance with the literature.¹⁸ mp >300 °C {Lit.¹⁸ >300 °C}; ¹H NMR (500 MHz, DMSO) δ_H: 6.94 (1H, d, *J* 1.4, C(8)*H*), 7.54–7.61 (3H, m, C(9)PhC(2,6)*H*+C(9)PhC(4)*H*), 7.77 (1H, d, *J* 1.5, C(10)*H*), 7.85–7.90 (1H, m, ArC(3)*H*), 7.91–7.94 (2H, m, C(9)PhC(3,5)*H*), 7.99–8.03 (1H, m, ArC(2)*H*), 8.29 (1H, d, *J* 7.8, ArC(1)*H*), 8.50 (1H, d, *J* 7.9, ArC(4)*H*).

9-(Furan-2-yl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (372)

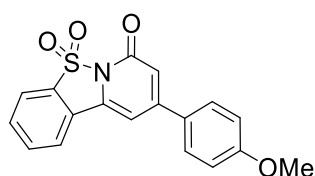
2-(1*H*-Indol-1-yl)acetic acid **223** (50.0 mg, 0.29 mmol, 1.5 eq.) was dissolved in anhydrous MeCN (2.9 mL, 0.07 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (65 μL, 0.39 mmol, 2 eq.) and pivaloyl chloride (47 μL, 0.39 mmol, 2 eq.) were added. The reaction was stirred at 0 °C for 20 min before warmed to rt. *rac.* HyperBTM **93** (11.9 mg, 0.04 mmol, 20 mol%), saccharin-derived ketimine **342** (50.0 mg, 0.19 mmol, 1 eq.), and *i*-Pr₂NEt (81 μL, 0.48 mmol, 2.5 eq.) were added sequentially and the reaction stirred at rt. for 24 h. The reaction mixture was concentrated under reduced pressure to give the crude product that was purified by recrystallization in EtOAc to give the titled compound as a brown solid (10 mg, 17%). mp 284 °C; ν_{\max} (film, cm⁻¹) 1661 (C=O), 1624 (C=C), 1578 (S=O); ¹H NMR (500 MHz, DMSO) δ_{H} : 6.73 (1H, s, C(8)*H*), 6.79–6.82 (1H, m, C(9)furanC(5)*H*), 7.53 (1H, d, *J* 3.4, C(9)furanC(4)*H*), 7.73 (1H, s, C(10)*H*), 7.87 (1H, t, *J* 7.6, ArC(3)*H*), 7.98–7.03 (1H, m, ArC(2)*H*), 8.02–8.05 (1H, m, C(9)furanC(5)*H*), 8.27 (1H, d, *J* 7.8, ArC(1)*H*), 8.41 (1H, d, *J* 7.8, ArC(4)*H*); ¹³C{¹H} NMR (126 MHz, DMSO) δ_{C} : 98.9 (C(10)*H*), 112.3 (C(8)*H*), 113.3 (C(9)furanC(3)*H*), 114.5 (C(9)furanC(4)*H*), 122.3 (ArC(1)*H*), 123.7 (ArC(4)*H*), 124.9 (ArC(10b)*H*), 131.7 (ArC(4a)*H*), 133.1 (ArC(3)*H*), 135.5 (ArC(2)*H*), 135.9 (C(10a)), 141.7 (C(9)furanC(2)*H*), 147.0 (C(9)furanC(5)*H*), 149.1 (C(9)), 158.4 (C(7)); HRMS (ESI⁺) C₁₅H₉NO₄SNa [M+Na]⁺ found 322.0134, requires 322.0145 (-3.4 ppm).

9-(4-Bromophenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (370)

2-(1*H*-Pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.) was dissolved in anhydrous MeCN (2.5 mL, 0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.) and pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) were added. The reaction was stirred at 0 °C for 20 min before warmed up to rt. HyperBTM **93** (3.9 mg, 10 mol%), saccharin-derived ketimine **340** (43.5 mg, 0.125 mmol, 1.0 eq.), and *i*-Pr₂NEt (0.044 mL, 0.25

mmol, 2.0 eq.) were added sequentially and the reaction stirred at rt. for 24 h. The reaction mixture was concentrated under reduced pressure to give the crude product that purified by recrystallization in Et₂O/pentane to give the titled compound as a yellow solid (9.7 mg, 20%). Spectroscopic data were in accordance with the literature.¹⁸ mp >300 °C {Lit.¹⁸ >300 °C}; ¹H NMR (500 MHz, DMSO) δ_H: 6.97 (1H, d, *J* 1.5, C(8)*H*), 7.73–7.79 (3H, m C(9)ArC(2,6)*H* + C(10)*H*), 7.85–7.88 (3H, m, Ar*H*), 8.00 (1H, t, *J* 7.7, Ar*H*), 8.28 (1H, d, *J* 7.8, Ar*H*), 8.47 (1H, d, *J* 7.9, Ar*H*).

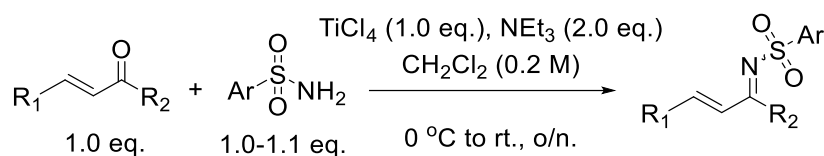
9-(4-Methoxyphenyl)-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide (371)



2-(1*H*-Pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 2.0 eq.) was dissolved in anhydrous MeCN (2.5 mL, 0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.) and pivaloyl chloride (0.031 mL, 0.25 mmol, 2.0 eq.) were added. The reaction was stirred at 0 °C for 20 min before warmed up to rt. HyperBTM **93** (3.9 mg, 10 mol%), saccharin-derived ketimine **341** (37.4 mg, 0.125 mmol, 1.0 eq.), and *i*-Pr₂NEt (0.044 mL, 0.25 mmol, 2.0 eq.) were added sequentially and the reaction stirred at rt. for 24 h. The reaction mixture was concentrated under reduced pressure to give the crude product that purified by recrystallization in Et₂O/pentane to give the titled compound as a yellow solid (6.4 mg, 15%). Spectroscopic data were in accordance with the literature.¹⁸ mp >300 °C {Lit.¹⁸ >300 °C}; ¹H NMR (400 MHz, CDCl₃) δ_H: 3.91 (3H, s, OCH₃), 6.78 (1H, d, *J* 1.5, C(8)*H*), 6.97 (1H, d, *J* 1.5, C(10)*H*), 7.02–7.07 (2H, m, C(9)ArC(3,5)*H*), 7.59–7.63 (2H, m, C(9)ArC(2,6)*H*), 7.75 (1H, td, *J* 7.6, 1.1, Ar*CH*), 7.83 (1H, td, *J* 7.6, 1.2, Ar*CH*), 7.91–7.97 (2H, m, Ar*CH*).

8.6. Experimentals for Chapter 6

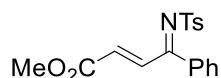
General Procedure A: Synthesis of unsaturated ketimines



To a solution of the corresponding unsaturated ketone (1.0 eq.) and ArSO_2NH_2 (1.0-1.1 eq.) in dry CH_2Cl_2 (0.2 M) was added NEt_3 (2.0 eq.) followed by titanium tetrachloride (1.0 eq., dropwise) at 0°C under an atmosphere of N_2 . The reaction mixture was further stirred at rt. for 16 h. Then it was quenched with H_2O (20 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried with MgSO_4 and concentrated under reduced pressure to give the crude mixture.

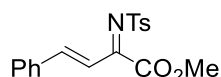
Generally, ketimines within the ester series were troublesome to purify, unless a solid was obtained. These were judged to be >90% pure by ^1H NMR and suitable for use in this protocol.

(1E)-3-Phenyl-3-(tosylimino)prop-1-en-1-yl acetate (402)



Following general procedure A: methyl (*E*)-4-oxo-4-phenylbut-2-enoate¹⁹ (4.70 g, 24.7 mmol), TsNH_2 (4.23 g, 24.7 mmol, 1.0 eq.), Et_3N (6.89 mL, 49.4 mmol, 2.0 eq.) and TiCl_4 (2.71 mL, 24.8 mmol) in CH_2Cl_2 (100 mL) gave crude **402** as a yellow oil which was used as a crude without further purification. Spectroscopic data were in accordance with the literature.¹⁹ ^1H NMR (400 MHz, CDCl_3) δ_{H} : 2.43 (3 H, s, CH_3), 3.83 (3 H, s, OCH_3), 6.21 (1 H, d, J 16.0, PhCCH), 7.19–7.60 (7 H, m, ArH), 7.86–7.92 (2 H, m, ArH), 8.22 (1 H, d, J 15.9, PhCH=CH).

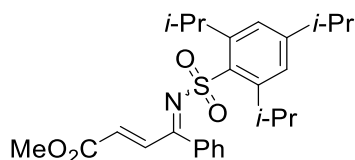
Methyl (3E)-4-phenyl-2-(tosylimino)but-3-enoate (412)



Following general procedure A: methyl (*E*)-2-oxo-4-phenylbut-3-enoate **132** (1.18 g, 6.18 mmol), TsNH_2 (1.06 g, 6.18 mmol, 1.0 eq.), Et_3N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl_4 (0.68 mL, 6.18 mmol) in CH_2Cl_2 (30 mL) gave, after chromatographic purification (20:80

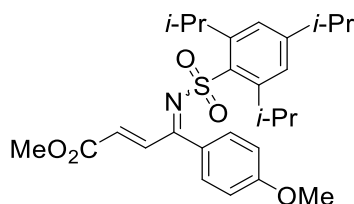
EtOAc/petrol), the titled compound as a sticky yellow oil (850 mg, 40%). Spectroscopic data were in accordance with the literature.¹⁹ ¹H NMR (400 MHz, CDCl₃) δ_H: 2.44 (3 H, s, CH₃), 4.12 (3 H, s, OCH₃), 6.88 (1 H, d, *J* 16.1, C(3)*H*), 7.34–7.58 (8 H, m, Ar*H* and C(4)*H*), 7.94 (2 H, d, *J* 8.1, NSO₂ArC(2,6)*H*).

Methyl (2*E*)-4-phenyl-4-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-2-enoate (425)



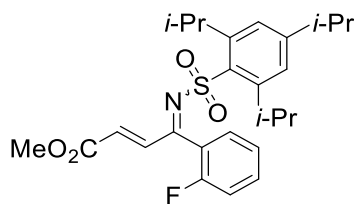
Following general procedure **A**: methyl (*E*)-4-oxo-4-phenylbut-2-enoate¹⁹ (1.18 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after chromatographic purification (30:70 Et₂O/petrol) and recrystallization in EtOAc/petrol, the titled compound as a white crystalline solid (1.75 g, 62 %). mp 112–114 °C; ν_{max} (film, cm⁻¹) 2957 (C-H), 2928 (C-H), 1730 (C=O), 1721 (C=C), 1626, 1599, 1531, 1244; ¹H NMR (500 MHz, CDCl₃) δ_H: 1.25 (18H, *J* 6.7, CH₃), 2.90 (1H, hept, *J* 6.9, CH), 3.79 (3H, s, OCH₃), 4.14–4.25 (2H, m, 2 x CH), 6.09 (1H, d, *J* 16.3, C(2)*H*), 7.16 (2H, s, ArCH), 7.42 (2H, t, *J* 7.7, C(4)ArCH), 7.55 (1H, t, *J* 7.6, C(4)ArCH), 7.74–7.78 (2H, m, C(4)ArCH), 8.05 (1H, d, *J* 16.3, C(3)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 23.7 (CH₃), 24.8 (CH₃), 30.2 (CH), 34.4 (CH), 52.5 (OCH₃), 123.7 (ArCH), 128.8 (ArCH), 130.3 (ArCH), 131.8 (ArC), 133.4 (ArC), 134.1 (ArC), 136.1 (ArC), 137.0 (ArC), 150.0 (ArC), 153.4 (ArC), 165.1 (C=N), 173.7 (CO₂Me); HRMS (ESI⁺) C₂₆H₃₃NO₄SNa [M+Na]⁺ found 478.2009, requires 478.2023 (-2.8 ppm).

Methyl (2E)-4-(4-methoxyphenyl)-4-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-2-enoate (496)

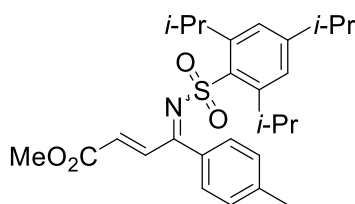


Following general procedure **A**: methyl (E)-4-(4-methoxyphenyl)-4-oxobut-2-enoate²⁰ (1.36 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after filtering through a pad of silica (30:70 Et₂O/petrol), the titled compound as a viscous yellow oil (>90% purity, 13:87 mixture of isomers) which was used as crude without further purification. ¹H NMR (500 MHz, CDCl₃) δ_H: 1.24 (9H, d, *J* 6.7, CH₃), 1.24 (9H, d, *J* 6.7, CH₃), 2.81–2.96 (1H, m, CH), 3.77 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 4.22 (2H, hept, *J* 6.8, CH), 6.00 (1H, d, *J* 16.4, C(2)H), 6.87–6.92 (2H, m, C(1)ArC(3,5)H), 7.14 (2H, s, SO₂ArCH), 7.74–7.83 (2H, m, C(1)ArC(2,4)H), 7.90 (1H, d, *J* 16.3, C(3)H). Selected data for the minor isomer: ¹H NMR (500 MHz, CDCl₃) δ_H (selected): 1.28 (18H, d, *J* 6.7, CH₃), 4.06–4.14 (2H, m, CH), 7.16 (1H, s, SO₂ArCH).

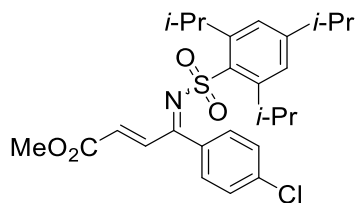
Methyl (2E)-4-(2-fluorophenyl)-4-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-2-enoate (497)



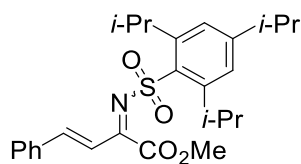
Following general procedure **A**: methyl (E)-4-(2-fluorophenyl)-4-oxobut-2-enoate¹⁹ (1.29 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after filtering through a pad of silica (30:70 Et₂O/petrol), the titled compound as a viscous deep red oil (>85% purity) which was used as crude without further purification. ¹H NMR (400 MHz, CDCl₃) δ_H: 1.23 (9H, d, *J* 6.7, CH₃), 1.27 (9H, d, *J* 6.9, CH₃), 2.91 (1H, h, *J* 6.9, CH), 3.79 (3H, s, OCH₃), 4.03 (1H, p, *J* 6.8, CH), 4.15–4.24 (1H, m, CH), 6.08–6.20 (1H, m, C(2)H), 7.09–7.26 (4H, m, ArCH), 7.43–7.52 (3H, m, ArCH + C(3)H); ¹⁹F{¹H} NMR (377 MHz, CDCl₃) δ_F: -111.5.

Methyl (2E)-4-(p-tolyl)-4-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-2-enoate (498)

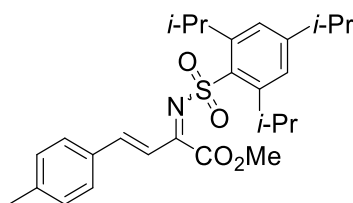
Following general procedure **A**: methyl (*E*)-4-oxo-4-(*p*-tolyl)but-2-enoate¹⁹ (1.26 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after filtering through a pad of silica (30:70 Et₂O/petrol), the titled compound as a yellow oil (>90% purity) which was used as crude without further purification. ¹H NMR δ_H (500 MHz, CDCl₃): 1.13–1.16 (18H, d, *J* 6.7, CH₃), 2.31 (3H, s, C(4)ArC(4)CH₃), 2.79 (1H, hept, *J* 6.9, CH), 3.68 (3H, s, OCH₃), 4.10 (2H, s, CH), 5.94 (1H, d, *J* 16.3, C(2)H), 7.05 (2H, s, NSO₂ArCH), 7.12 (2H, d, *J* 7.9, C(4)ArC(3,5)H), 7.58 (2H, d, *J* 7.6, C(4)ArC(2,6)H), 7.84–7.92 (1H, m, C(3)H).

Methyl (2E)-4-(4-chlorophenyl)-4-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-2-enoate (499)

Following general procedure **A**: methyl (*E*)-4-(4-chlorophenyl)-4-oxobut-2-enoate¹⁹ (1.39 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after filtering through a pad of silica (30:70 Et₂O/petrol), the titled compound as a yellow oil (>90% purity) which was used as crude without further purification. ¹H NMR (400 MHz, CDCl₃) δ_H: 1.24 (9H, d, *J* 6.9, CH₃), 1.25 (9H, d, *J* 6.9, CH₃), 2.90 (1H, hept, *J* 6.9, CH), 3.79 (3H, s, OCH₃), 4.10–4.24 (2H, m, CH), 6.07 (1H, d, *J* 16.4, C(2)H), 7.16 (2H, s, NSO₂ArCH), 7.40 (2H, d, *J* 8.3, C(4)ArC(2,6)H), 7.72 (2H, d, *J* 8.3, C(4)ArC(3,5)H), 8.00 (1H, d, *J* 16.4, C(3)H).

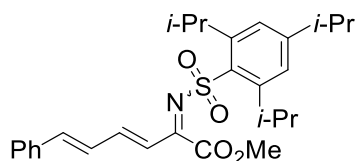
Methyl (3E)-4-phenyl-2-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-3-enoate (424)

Following general procedure **A**: methyl (E)-2-oxo-4-phenylbut-3-enoate **132** (1.18 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after chromatographic purification (30:70 Et₂O/petrol), the titled compound as a white crystalline solid (62:38 mixture of isomers, 2.11 g, 75%). Spectroscopic data were in accordance with the literature.²¹ mp 98–99 °C; ¹H NMR (500 MHz, CDCl₃) δ_H: 1.31 (18H, d, *J* 6.7, major + minor CH₃), 2.88–2.94 (1H, m, major + minor CH), 3.92 (3H, s, minor OCH₃), 4.02 (3H, s, major OCH₃), 4.11–4.26 (2H, m, major + minor CH), 6.82 (1H, d, *J* 16.4, C(2)H), 7.19 (2H, s, major + minor NSO₂ArCH), 7.32–7.59 (6H, m, major + minor ArH + C(3)H), 7.73 (1H, d, *J* 16.2, minor C(3)H).

Methyl (3E)-4-(*p*-tolyl)-2-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-3-enoate (500)

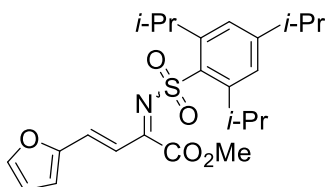
Following general procedure **A**: methyl (E)-2-oxo-4-(*p*-tolyl)but-3-enoate **488** (1.26 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after chromatographic purification (30:70 Et₂O/petrol), the titled compound as a yellow solid (62:38 mixture of isomers, 1.68 g, 58%). Spectroscopic data were in accordance with the literature.²¹ mp 87–89 °C; ¹H NMR (500 MHz, CDCl₃) δ_H: 1.31 (18H, d, *J* 6.7, major + minor CH₃), 2.37 (3H, s, major + minor CH₃), 2.87–2.93 (1H, m, major + minor CH), 3.91 (3H, s, minor OCH₃), 4.01 (3H, s, major OCH₃), 4.14–4.32 (2H, m, major + minor CH), 6.79 (1H, d, *J* 16.3, major C(2)H), 7.19 (2H, s, major + minor NSO₂ArCH), 7.30–7.48 (5H, m, major + minor, ArH + C(3)H), 7.68 (1H, *J* 16.2, minor C(3)H).

Methyl (3E,5E)-6-phenyl-2-(((2,4,6-triisopropylphenyl)sulfonyl)imino)hexa-3,5-dienoate (501)



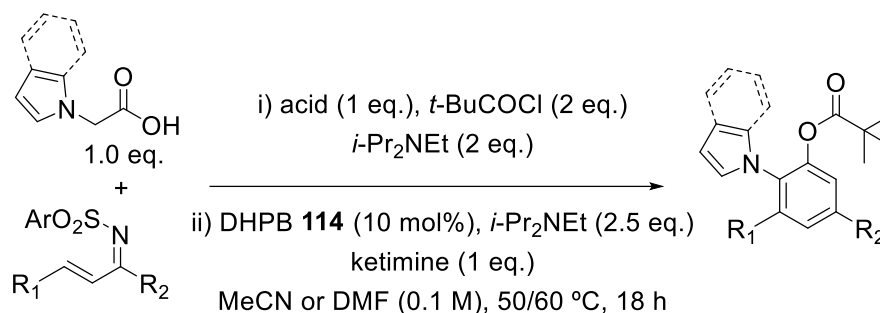
Following general procedure **A**: methyl (3E,5E)-2-oxo-6-phenylhexa-3,5-dienoate **285** (1.34 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after chromatographic purification (30:70 Et₂O/petrol), the titled compound as a yellow solid (56:44 mixture of isomers, 2.14 g, 62%). Spectroscopic data were in accordance with the literature.²¹ mp 63–65 °C; ¹H NMR (500 MHz, CDCl₃) δ_H: 1.31 (18H, d, *J* 6.7, major + minor CH₃), 2.87–2.94 (1H, m, major + minor CH), 3.90 (3H, s, minor OCH₃), 4.01 (3H, s, major OCH₃), 4.07–4.32 (2H, m, major + minor CH), 6.38 (1H, d, *J* 15.6, major C(2)H), 6.91–7.52 (10H, m, major + minor ArCH and CH^A=CH^B).

Methyl (3E)-4-(furan-2-yl)-2-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-3-enoate (502)



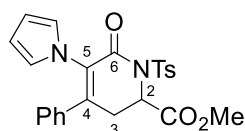
Following general procedure **A**: methyl (*E*)-4-(furan-2-yl)-2-oxobut-3-enoate **495** (1.11 g, 6.18 mmol), 2,4,6-triisopropylbenzenesulfonamide (1.93 g, 6.80 mmol, 1.1 eq.), Et₃N (1.72 mL, 12.4 mmol, 2.0 eq.) and TiCl₄ (0.68 mL, 6.18 mmol) in CH₂Cl₂ (30 mL) gave, after chromatographic purification (30:70 Et₂O/petrol), the titled compound as a yellow solid (61:39 mixture of isomers, 1.35 g, 49%). Spectroscopic data were in accordance with the literature.²¹ mp 56–58 °C; ¹H NMR (500 MHz, CDCl₃) δ_H: 1.17–1.43 (18H, m, major + minor CH₃), 2.87–2.96 (1H, m, major + minor CH), 3.90 (3H, s, minor OCH₃), 4.01 (3H, s, major OCH₃), 4.09–4.31 (2H, m, major + minor CH), 6.54–7.61 (7H, major + minor ArCH and CH=CH).

General Procedure B: Synthesis of pyridines



Acid (1.0 eq.) was dissolved in anhydrous MeCN or DMF (0.1 M) under an atmosphere of N₂ and cooled to 0 °C before *i*-Pr₂NEt (2 eq.) and pivaloyl chloride (2 eq.) were added. The reaction was stirred at 0 °C for 20 min before heating to 50 or 60 °C. DHPB **114** (10 mol%), the required unsaturated ketimine (1 eq.), and *i*-Pr₂NEt (2.5 eq.) were added sequentially and the reaction stirred at 50 or 60 °C for 18 h. After that, the reaction mixture was concentrated under reduced pressure to give the crude product which was purified by flash silica column chromatography.

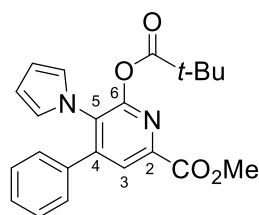
Methyl 6-oxo-4-phenyl-5-(1H-pyrrol-1-yl)-1,2,3,6-tetrahydropyridine-2-carboxylate (414)



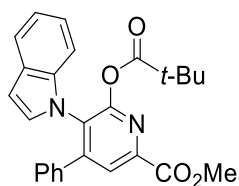
Following **General Procedure B**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **412** (85.9 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 60 °C for 4 h gave crude product that was purified by column chromatography (30:70 Et₂O/petrol, R_f 0.40) to give the titled compound as a yellow oil (30 mg, 27%). ν_{\max} (film, cm⁻¹) 2961 (C-H), 1744 (C=O), 1692 (C=O), 1597 (C=C), 1352; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.43 (3H, s, NSO₂PhCH₃), 3.42 (1H, dd, *J* 17.9, 5.7, C(3)*H^AH^B*), 3.49 (1H, dd, *J* 17.9, 2.6, C(3)*H^AH^B*), 3.70 (3H, s, OCH₃), 5.56 (1H, dd, *J* 5.7, 2.5, C(2)*H*), 6.04 (2H, t, *J* 2.2, C(5)Ar(3,4)*H*), 6.34 (2H, t, *J* 2.2, C(5)Ar(2,5)*H*), 6.90–6.93 (2H, m, C(4)ArC(2,6)*H*), 7.21–7.32 (5H, m, NSO₂ArC(3,5)*H* + C(4)ArC(3,4,5)*H*), 8.00–8.03 (2H, m, NSO₂ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 21.9 (NSO₂PhCH₃), 33.4 (C(3)), 53.4 (OCH₃),

55.7 (C(2)), 109.5 (C(5)ArC(3,4)H), 122.5 (C(5)ArC(2,5)H), 127.4 (C(4)ArC(2,6)H), 128.4 (C(4)ArC(4)H), 128.7 (C(4)ArC(3,5)H), 129.2 (NSO₂ArC(3,5)H), 129.9 (NSO₂ArC(1)), 130.1 (NSO₂ArC(2,6)H), 135.0 (NSO₂ArC(4)), 135.2 (C(4)ArC(1)), 144.6 (C(4)), 145.4 (C(5)), 160.4 (C(6)), 170.2 (C(2)CO₂Me); HRMS (ESI⁺) C₂₄H₂₃N₂O₅S [M+H]⁺ found 451.1322, requires 451.1322 (-0.1 ppm).

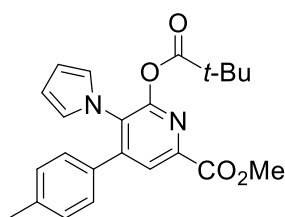
Methyl 4-phenyl-6-(pivaloyloxy)-5-(1*H*-pyrrol-1-yl)picolinate (413)



Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in DMF (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **424** (113.9 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 60 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a yellow solid (62.4 mg, 66%). mp 108–110 °C; ν_{\max} (film, cm⁻¹) 2968 (C-H), 2955 (C-H), 2928 (C-H), 1763 (C=O), 1724 (C=O), 1489 (ArC=C), 1362, 1263; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.16 (9H, s, 3 x CH₃), 4.02 (3H, s, OCH₃), 6.16 (2H, t, *J* 2.1, C(5)Ar(3,4)H), 6.48 (2H, t, *J* 2.1, C(5)Ar(2,5)H), 7.08–7.10 (2H, m, C(4)ArC(2,6)H), 7.29–7.37 (3H, m, C(4)ArC(3,4,5)H), 8.23 (1H, s, C(3)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 27.0 (CH₃), 39.2 (C(CH₃)₃), 53.4 (OCH₃), 110.2 (C(5)ArC(3,4)H), 122.5 (C(5)ArC(2,5)H), 126.0 (C(3)), 127.9 (C(4)ArC(2,6)H), 128.8 (C(4)ArC(3,5)H), 129.5 (C(4)ArC(4)H), 131.0 (C(4)), 134.8 (C(4)ArC(1)), 145.3 (C(6)), 150.8 (C(5)), 155.2 (C(2)), 164.6 (C(2)CO₂Me), 176.4 (C(6)OCO); HRMS (ESI⁺) C₂₂H₂₃N₂O₄ [M+H]⁺ found 379.1644, requires 379.1652 (-2.2 ppm).

Methyl 5-(1*H*-indol-1-yl)-4-phenyl-6-(pivaloyloxy)picolinate (432)

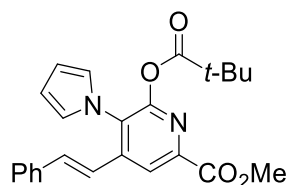
Following **General Procedure B**, 2-(1*H*-indol-1-yl)acetic acid **223** (43.8 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in DMF (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **424** (113.9 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 60 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a yellow oil (50.3 mg, 47%). ν_{\max} (film, cm⁻¹) 2958 (C-H), 1734 (C=O), 1645 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.26 (9H, s, 3 x CH₃), 4.05 (3H, s, OCH₃), 6.47 (1H, dd, *J* 3.3, 0.9, C(5)ArH), 6.65 (1H, d, *J* 3.3, C(5)ArH), 6.98–7.00 (2H, m, C(5)ArH), 7.04–7.21 (6H, m, C(5)ArH + C(4)ArCH), 7.58 (1H, dt, *J* 7.6, 1.0, C(5)ArH), 8.32 (1H, s, C(3)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 26.6 (CH₃), 38.9 (C(CH₃)₃), 53.4 (OCH₃), 104.7 (ArCH), 110.7 (ArCH), 120.8 (ArCH), 121.1 (ArCH), 122.9 (ArCH), 123.8 (ArCH), 126.2 (C(3)), 127.9 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 128.9 (C(5)ArC), 129.6 (C(4)), 134.7 (C(4)ArC(1)), 136.7 (C(5)ArC), 145.9 (C(6)), 152.1 (C(5)), 156.3 (C(2)), 164.7 (C(2)CO₂Me), 176.2 (C(6)OCO); HRMS (ESI⁺) C₂₆H₂₅N₂O₄ [M+H]⁺ found 429.1804, requires 429.1809 (-1.1 ppm).

Methyl 6-(pivaloyloxy)-5-(1*H*-pyrrol-1-yl)-4-(*p*-tolyl)picolinate (433)

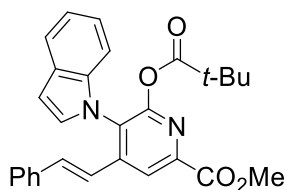
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in DMF (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **500** (117.4 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 60 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the

titled compound as a yellow oil (62.4 mg, 59%). ν_{\max} (film, cm^{-1}) 2959 (C-H), 1732 (C=O), 1695 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 1.24 (9H, s, 3 x CH_3), 2.33 (3H, s, CH_3), 4.02 (3H, s, OCH_3), 6.18 (2H, t, J 2.1, C(5)Ar(3,4)H), 6.48 (2H, t, J 2.1, C(5)Ar(2,5)H), 6.95–6.98 (2H, m, C(4)ArC(3,5)H), 7.11 (2H, d, J 8.0, C(4)ArC(2,6)H), 8.22 (1H, s, C(3)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 21.4 (CH_3), 27.2 (CH_3), 39.2 ($\text{C}(\text{CH}_3)_3$), 53.3 (OCH_3), 110.2 (C(5)ArC(3,4)H), 122.5 (C(5)ArC(2,5)H), 125.9 (C(3)), 127.8 (C(4)ArC(3,5)H), 129.6 (C(4)ArC(2,6)H), 130.9 (C(4)), 131.9 (C(4)ArC(1)), 139.8 (C(4)ArC(4)), 145.3 (C(6)), 150.8 (C(5)), 155.3 (C(2)), 164.7 (C(2)CO₂Me), 176.5 (C(6)OCO); HRMS (ESI⁺) $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4\text{Na}$ [M+Na]⁺ found 415.1624, requires 415.1628 (-1.0 ppm).

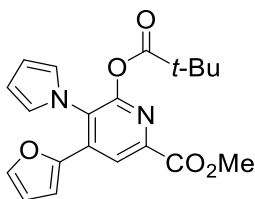
Methyl (*E*)-6-(pivaloyloxy)-5-(1*H*-pyrrol-1-yl)-4-styrylpicolinate (**435**)



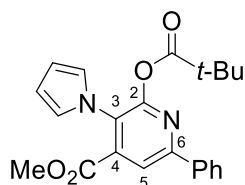
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in DMF (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **501** (120.4 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 60 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a yellow oil (57.6 mg, 57%). ν_{\max} (film, cm^{-1}) 2958 (C-H), 1732 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 1.23 (9H, s, 3 x CH_3), 4.04 (3H, s, OCH_3), 6.36 (2H, t, J 2.1, C(5)Ar(3,4)H), 6.51 (1H, d, J 16.4, C(4)CH=CHPh), 6.68 (2H, t, J 2.1, C(5)Ar(2,5)H), 7.30–7.45 (6H, m, ArCH + C(4)CH=CHPh), 8.45 (1H, s, C(3)); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 27.1 (CH_3), 39.0 ($\text{C}(\text{CH}_3)_3$), 53.3 (OCH_3), 110.2 (C(5)ArC(2,6)H), 119.7 (C(4)CH=CHPh), 120.4 (C(3)), 123.0 (C(5)ArC(3,5)H), 127.5 (PhC(2,6)H), 128.9 (PhC(3,5)H), 129.6 (PhC(4)H), 130.9 (C(4)), 135.5 (PhC(1)), 137.1 (C(4)CH=CHPh), 145.3 (C(6)), 147.4 (C(5)), 155.6 (C(2)), 164.8 (C(2)CO₂Me), 176.4 (C(6)OCO); HRMS (ESI⁺) $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4\text{Na}$ [M+Na]⁺ found 427.1622, requires 427.1628 (-1.5 ppm).

Methyl (E)-5-(1H-indol-1-yl)-6-(pivaloyloxy)-4-styrylpicolinate (436)

Following **General Procedure B**, 2-(1H-indol-1-yl)acetic acid **223** (43.8 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in DMF (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **501** (120.4 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 60 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a red oil (62.5 mg, 55%). ν_{\max} (film, cm⁻¹) 2961 (C-H), 1734 (C=O), 1634 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.24 (9H, s, 3 x CH₃), 4.07 (3H, s, OCH₃), 6.52 (1H, d, *J* 16.3, C(4)CH=CHPh), 6.74 (1H, dd, *J* 3.2, 0.9, C(5)ArH), 6.97–7.00 (1H, m, C(5)ArH), 7.07 (1H, d, *J* 3.2, C(5)ArH), 7.15–7.21 (3H, m, C(5)ArH + PhH), 7.25–7.28 (4H, m, PhH), 7.40 (1H, d, *J* 16.3, C(4)CH=CHPh), 7.67–7.70 (1H, m, C(5)ArH), 8.55 (1H, s, C(3)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 26.6 (CH₃), 38.9 (C(CH₃)₃), 53.5 (OCH₃), 104.7 (ArCH), 110.8 (ArCH), 119.8 (C(4)CH=CHPh), 120.7 (C(3)), 121.0 (ArCH), 121.1 (ArCH), 123.1 (ArCH), 127.6 (ArCH), 129.0 (C(5)ArC), 129.7 (C(4)), 135.4 (PhC(1)), 137.1 (C(4)CH=CHPh), 137.4 (C(5)ArC), 145.8 (C(6)), 148.1 (C(5)), 156.6 (C(2)), 165.0 (C(2)CO₂Me), 176.2 (C(6)OCO); HRMS (ESI⁺) C₂₈H₂₆N₂O₄Na [M+Na]⁺ found 477.1779, requires 477.1785 (-1.2 ppm).

Methyl 4-(furan-2-yl)-6-(pivaloyloxy)-5-(1H-pyrrol-1-yl)picolinate (434)

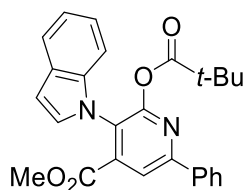
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in DMF (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **502** (111.4 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 60 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a yellow oil (48.8 mg, 53%). ν_{\max} (film, cm⁻¹) 2959 (C-H), 1732 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.26 (9H, s, 3 x CH₃), 4.06 (3H, s, OCH₃), 5.25 (1H, d, *J* 3.6, C(4)ArC(3)H), 6.37–6.38 (1H, m, C(3)ArC(4)H), 6.40 (2H, t, *J* 2.1, C(5)Ar(3,4)H), 6.57 (2H, t, *J* 2.1, C(5)Ar(2,5)H), 7.57 (1H, d, *J* 1.7, C(3)ArC(5)H), 8.66 (1H, s, C(3)); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 27.0 (CH₃), 39.0 (C(CH₃)₃), 53.3 (OCH₃), 110.7 (C(5)ArC(2,6)H), 113.3 (C(4)ArC(4)H), 114.4 (C(4)ArC(3)H), 120.3 (C(3)), 120.5 (C(5)ArC(3,5)H), 126.8 (C(4)), 144.7 (C(4)ArC(5)H), 146.0 (C(6)), 149.2 (C(5)), 152.8 (C(4)ArC(2)) 156.6 (C(2)), 164.5 (C(2)CO₂Me), 176.5 (C(6)OCO); HRMS (ESI⁺) C₂₀H₂₀N₂O₅Na [M+Na]⁺ found 391.1260, requires 391.1264 (-1.1 ppm).

Methyl 6-phenyl-2-(pivaloyloxy)-3-(1H-pyrrol-1-yl)isonicotinate (403)

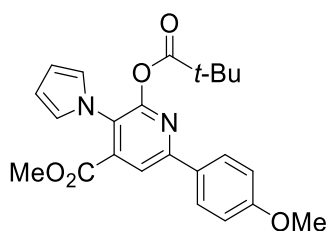
Following **General Procedure B**, 2-(1*H*-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **425** (113.9 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 50 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a yellow solid (60.5 mg, 64%). mp 106–109 °C; ν_{\max} (film, cm⁻¹) 2959 (C-H), 2932 (C-H), 2870 (C-H), 1765 (C=O), 1720 (C=O), 1487 (Ar C=C), 1441 (Ar C=C), 1356, 1258,

1233, 1098, 1070, 1059; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 1.19 (9H, s, 3 x CH_3), 3.73 (3H, s, OCH_3), 6.28 (2H, t, J 2.1, $\text{C}(3)\text{Ar}(3,4)\text{H}$), 6.68 (2H, t, J 2.1, $\text{C}(3)\text{Ar}(2,5)\text{H}$), 7.44–7.52 (3H, m, $\text{C}(6)\text{ArC}(3,4,5)\text{H}$), 8.04–8.06 (3H, m, $\text{C}(6)\text{ArC}(2,6)\text{H} + \text{C}(5)\text{H}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 26.9 (CH_3), 39.2 ($\text{C}(\text{CH}_3)_3$), 53.2 (OCH_3), 109.7 ($\text{C}(3)\text{ArC}(3,4)\text{H}$), 118.7 ($\text{C}(5)$), 123.0 ($\text{C}(3)\text{ArC}(2,5)\text{H}$), 126.7 ($\text{C}(6)$), 127.4 ($\text{C}(6)\text{ArC}(2,6)\text{H}$), 129.0 ($\text{C}(6)\text{ArC}(4)\text{H}$), 130.2 ($\text{C}(6)\text{ArC}(3,5)\text{H}$), 136.8 ($\text{C}(6)\text{ArC}(1)$), 140.7 ($\text{C}(2)$), 155.3 ($\text{C}(4)$), 156.4 ($\text{C}(3)$), 165.0 ($\text{C}(4)\text{CO}_2\text{Me}$), 176.5 ($\text{C}(2)\text{OCO}$); HRMS (ESI^+) $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ found 401.1460, requires 401.1472 (-2.9 ppm).

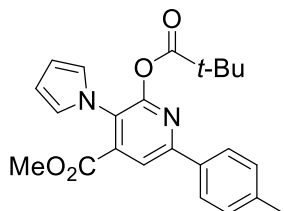
Methyl 3-(1*H*-indol-1-yl)-6-phenyl-2-(pivaloyloxy)isonicotinate (**427**)



Following **General Procedure B**, 2-(1*H*-indol-1-yl)acetic acid **223** (43.8 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **425** (113.9 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 50 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a light yellow solid (57.8 mg, 54%). mp 128–130 °C; ν_{max} (film, cm^{-1}) 2967 (C-H), 2955 (C-H), 1761 (C=O), 1721 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 0.90 (9H, s, 3 x CH_3), 3.53 (3H, s, OCH_3), 6.66 (1H, dd, J 3.3, 0.9, $\text{C}(3)\text{ArH}$), 7.00–7.03 (1H, m, $\text{C}(3)\text{ArH}$), 7.08 (1H, d, J 3.3, $\text{C}(3)\text{ArH}$), 7.11–7.19 (2H, m, $\text{C}(6)\text{ArCH}$), 7.48–7.54 (3H, m, $\text{C}(6)\text{ArCH}$), 7.63 (1H, dt, J 7.7, 0.9, $\text{C}(3)\text{ArH}$), 8.08–8.11 (2H, m, $\text{C}(3)\text{ArH}$), 8.18 (1H, s, $\text{C}(5)\text{H}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 26.6 (CH_3), 39.0 ($\text{C}(\text{CH}_3)_3$), 53.1 (OCH_3), 103.9 (ArCH), 110.2 (ArCH), 119.3 ($\text{C}(5)$), 120.5 (ArCH), 121.0 (ArCH), 122.7 (ArCH), 124.7 (ArCH), 127.4 (ArCH), 128.6 ($\text{C}(3)\text{ArC}$), 129.1 (ArCH), 129.3 (ArCH), 130.3 ($\text{C}(2)$), 136.9 ($\text{C}(6)\text{ArC}(1)$), 137.6 ($\text{C}(3)\text{ArC}$), 141.2 ($\text{C}(6)$), 156.4 ($\text{C}(3)$), 156.9 ($\text{C}(4)$), 164.7 ($\text{C}(2)\text{CO}_2\text{Me}$), 176.2 ($\text{C}(2)\text{OCO}$); HRMS (ESI^+) $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ found 429.1803, requires 429.1809 (-1.4 ppm).

Methyl 6-(4-methoxyphenyl)-2-(1H-pyrrol-1-yl)isonicotinate (428)

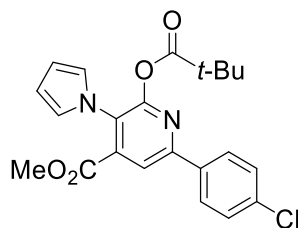
Following **General Procedure B**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **496** (121.4 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 50 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a yellow solid (38.8 mg, 38%). mp 74–78 °C; ν_{\max} (film, cm⁻¹) 2961 (C-H), 1763 (C=O), 1721 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.17 (9H, s, 3 x CH₃), 3.72 (3H, s, COOCH₃), 3.88 (3H, s, OCH₃), 6.26 (2H, t, *J* 2.1, C(3)Ar(3,4)*H*), 6.66 (2H, t, *J* 2.1, C(3)Ar(2,5)*H*), 6.98–7.01 (2H, m, C(6)ArC(3,5)*H*), 7.97 (1H, s, C(5)*H*), 7.99–8.02 (2H, m, C(6)ArC(2,6)*H*); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 26.9 (CH₃), 39.1 (C(CH₃)₃), 53.1 (COOCH₃), 55.6 (OCH₃), 109.6 (C(3)ArC(3,4)*H*), 114.4 (C(6)ArC(3,5)*H*), 117.8 (C(5)), 123.1 (C(3)ArC(2,5)*H*), 125.8 (C(6)), 128.8 (C(6)ArC(2,6)*H*), 129.4 (C(6)ArC(1)), 140.6 (C(2)), 155.2 (C(4)), 156.2 (C(3)), 161.4 (C(6)ArC(4)), 165.1 (C(4)CO₂Me), 176.6 (C(2)OCO); HRMS (ESI⁺) C₂₃H₂₄N₂O₅Na [M+Na]⁺ found 431.1570, requires 431.1577 (-1.7 ppm).

Methyl 2-(pivaloyloxy)-3-(1H-pyrrol-1-yl)-6-(*p*-tolyl)isonicotinate (429)

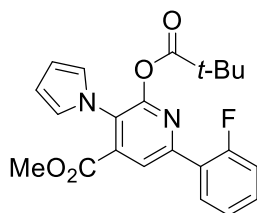
Following **General Procedure B**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **498** (117.4 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 50 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the

titled compound as a yellow solid (56.9 mg, 58%). mp 96–100 °C; ν_{\max} (film, cm^{-1}) 2968 (C-H), 1765 (C=O), 1719 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 1.18 (9H, s, 3 x CH_3), 2.42 (3H, s, CH_3), 3.73 (3H, s, COOCH_3), 6.27 (2H, t, J 2.2, C(3)Ar(3,4)H), 6.67 (2H, t, J 2.1, C(3)Ar(2,5)H), 7.27–7.31 (2H, m, C(6)ArC(3,5)H), 7.92–7.96 (2H, m, C(6)ArC(2,6)H), 8.00 (1H, s, C(5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 21.5 (CH_3), 26.9 (CH_3), 39.1 ($\text{C}(\text{CH}_3)_3$), 53.1 (OCH_3), 109.6 (C(3)ArC(3,4)H), 118.3 (C(5)), 123.1 (C(3)ArC(2,5)H), 126.3 (C(6)), 127.2 (C(6)ArC(3,5)H), 129.8 (C(6)ArC(2,6)H), 134.1 (C(6)ArC(1)), 140.5 (C(2)), 140.6 (C(6)ArC(4)), 155.3 (C(4)), 156.5 (C(3)), 165.0 (C(4) CO_2Me), 176.5 (C(2)OCO); HRMS (ESI⁺) $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4\text{Na}$ [$\text{M}+\text{Na}$]⁺ found 415.1619, requires 415.1628 (-2.2 ppm).

Methyl 6-(4-chlorophenyl)-2-(pivaloyloxy)-3-(1H-pyrrol-1-yl)isonicotinate (430)



Following **General Procedure B**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **499** (122.5 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 50 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as a yellow solid (64.0 mg, 62%). mp 88–90 °C; ν_{\max} (film, cm^{-1}) 2972 (C-H), 1761 (C=O), 1721 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 1.18 (9H, s, 3 x CH_3), 3.73 (3H, s, CH_3), 6.28 (2H, t, J 2.1, C(3)Ar(3,4)H), 6.67 (2H, t, J 2.1, C(3)Ar(2,5)H), 7.44–7.47 (2H, m, C(6)ArC(2,6)H), 7.98–8.01 (3H, m, C(6)ArC(3,5)H + C(5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 26.9 (CH_3), 39.2 ($\text{C}(\text{CH}_3)_3$), 53.2 (OCH_3), 109.8 (C(3)ArC(3,4)H), 118.5 (C(5)), 123.0 (C(3)ArC(2,5)H), 127.0 (C(6)), 128.6 (C(6)ArC(3,5)H), 129.3 (C(6)ArC(2,6)H), 135.2 (C(6)ArC(4)), 136.5 (C(6)ArC(1)), 140.8 (C(2)), 155.1 (C(4)), 155.4 (C(3)), 164.8 (C(4) CO_2Me), 176.5 (C(2)OCO); HRMS (ESI⁺) $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_4\text{Na}^{35}\text{Cl}$ [$\text{M}+\text{Na}$]⁺ found 435.1075, requires 435.1082 (-1.6 ppm).

Methyl 6-(2-fluorophenyl)-2-(pivaloyloxy)-3-(1H-pyrrol-1-yl)isonicotinate (431)

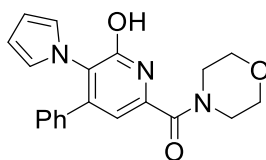
Following **General Procedure B**, 2-(1H-pyrrol-1-yl)acetic acid **155** (31.3 mg, 0.25 mmol, 1.0 eq.), *i*-Pr₂NEt (0.087 mL, 0.5 mmol, 2.0 eq.), pivaloyl chloride (0.062 mL, 0.5 mmol, 2.0 eq.) in MeCN (2.5 mL) at 0 °C for 20 min followed by DHPB **114** (4.8 mg, 10 mol%), ketimine **497** (118.4 mg, 0.25 mmol, 1.0 eq.) and *i*-Pr₂NEt (0.11 mL, 0.63 mmol, 2.5 eq.) at 50 °C for 18 h gave crude product that was purified by column chromatography (15:85 to 20:80 Et₂O/petrol) to give the titled compound as an orange solid (46.6 mg, 47%). mp 112–114 °C; ν_{\max} (film, cm⁻¹) 2974 (C-H), 1757 (C=O), 1719 (C=O); ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.18 (9H, s, 3 x CH₃), 3.74 (3H, s, CH₃), 6.28 (2H, t, *J* 2.1, C(3)Ar(3,4)H), 6.69 (2H, t, *J* 2.1, C(3)Ar(2,5)H), 7.19 (1H, ddd, *J* 11.5, 8.2, 1.1, C(6)ArC(6)H), 7.28 (1H, td, *J* 7.6, 1.2, C(6)ArC(4)H), 7.40–7.45 (1H, m, C(6)ArC(5)H), 8.07 (1H, td, *J* 7.9, 1.9, C(6)ArC(3)H), 8.14 (1H, d, *J* 1.2, C(5)H); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 26.9 (CH₃), 39.2 (C(CH₃)₃), 53.2 (OCH₃), 109.8 (C(3)ArC(3,4)H), 116.5 (d, *J* 22.7, C(6)ArC(3)H), 122.8 (d, *J* 11.7, C(5)), 123.0 (C(3)ArC(2,5)H), 124.9 (d, *J* 3.6, C(6)ArC(5)H), 125.0 (d, *J* 10.7, C(6)ArC(1)), 127.0 (C(6)), 131.4 (d, *J* 2.2, C(6)ArC(6)), 131.8 (d, *J* 8.6, C(6)ArC(4)H), 140.6 (C(2)), 152.0 (d, *J* 1.9, C(4)), 155.2 (C(3)), 160.8 (d, *J* 251.4, C(6)ArC(2)), 164.8 (C(4)CO₂Me), 176.5 (C(2)OCO); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -115.8; HRMS (ESI⁺) C₂₂H₂₁N₂O₄FNa [M+Na]⁺ found 419.1369, requires 435.1378 (-2.0 ppm).

Methyl 2-hydroxy-6-phenyl-3-(1H-pyrrol-1-yl)isonicotinate (439)

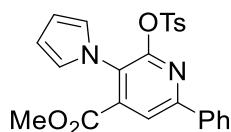
Following the procedure by Volochnyuk,²² a solution of **403** (90.8 mg, 0.24 mmol), morpholine (0.21 mL, 2.4 mmol, 10 eq.), Et₃N (67 μ L, 0.48 mmol, 2 eq.) were stirred in toluene (2 mL) in a sealed vial at 110 °C for 16 h. Once cooled, the resulting solid was collected by filtration and washed with petrol to give the titled compound as a yellow solid (41.0 mg, 58%). mp 76–78 °C;

ν_{\max} (film, cm^{-1}) 2951 (C-H), 2911 (C-H), 1719 (C=O), 1638 (Ar C=C), 1612 (Ar C=C), 1487, 1454; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 3.73 (3H, s, CH_3), 6.33 (2H, t, J 2.1, C(3)Ar(3,4)H), 6.72 (1H, s, C(5)H), 6.87 (2H, t, J 2.1, C(3)Ar(2,5)H), 7.46–7.51 (3H, m, C(6)ArC(3,4,5)H), 7.73–7.76 (2H, m, C(6)ArC(2,6)H), 11.79 (1H, s, OH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 52.9 (OCH₃), 103.0 (C(5)), 109.6 (C(3)ArC(3,4)H), 122.2 (C(3)ArC(2,5)H), 126.4 (C(6)ArC(2,6)H), 128.1 (C(6)), 129.5 (C(6)ArC(3,5)H), 130.7 (C(6)ArC(4)H), 132.1 (C(4)), 137.8 (C(2)), 144.8 (C(6)ArC(1)), 161.0 (C(3)), 166.4 (C=O); HRMS (ESI⁺) $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ found 317.0890, requires 317.0896 (-2.1 ppm).

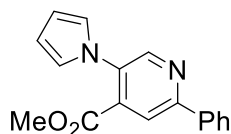
(6-Hydroxy-4-phenyl-5-(1H-pyrrol-1-yl)pyridin-2-yl)(morpholino)methanone (441)



Following the procedure by Volochnyuk,²² a solution of **413** (90.8 mg, 0.24 mmol), morpholine (0.21 mL, 2.4 mmol, 10 eq.), Et₃N (67 μL , 0.48 mmol, 2 eq.) were stirred in toluene (2 mL) in a sealed vial at 110 °C for 16 h. Once cooled, the resulting solid was collected by filtration and washed with petrol to give the titled compound as a white solid (42.8 mg, 51%). mp 241–242 °C; ν_{\max} (film, cm^{-1}) 3117 (C-H), 1639 (C=O), 1589 (C=O); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 3.22 (4H, t, J 4.8, morpholineC-H), 3.90 (4H, t, J 4.8, morpholineC-H), 6.13 (2H, t, J 2.1, C(5)Ar(3,4)H), 6.56 (2H, t, J 2.2, C(5)Ar(2,5)H), 7.11–7.14 (2H, m, C(4)ArC(2,6)H), 7.23 (1H, s, C(3)H), 7.27–7.31 (3H, m, C(4)ArC(3,4,5)H), 12.57 (1H, s, OH); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 43.0 (2 x CH₂), 64.3 (2 x CH₂), 108.9 (C(5)ArC(3,4)H), 110.7 (C(3)), 122.4 (C(5)ArC(2,5)H), 127.9 (C(4)ArC(2,6)H), 128.6 (C(4)ArC(3,5)H), 129.0 (C(4)ArC(4)H), 129.4 (C(6)), 136.5(C(4)ArC(1)), 136.7 (C(4)), 140.9 (C(5))147.9 (C(2)), 161.0 (C(2)CO); Characterization was not carried out further due to low solubility.

Methyl 6-phenyl-3-(1*H*-pyrrol-1-yl)-2-(tosyloxy)isonicotinate (442)

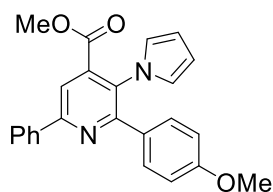
Stirred solution of **439** (30 mg, 0.10 mmol, 1 eq.) in anhydrous THF (1.5 mL) at $-78\text{ }^{\circ}\text{C}$ under an N_2 atmosphere was treated with NaH (6 mg, 60% wt, 0.15 mmol, 1.5 eq) followed by a solution of tosyl chloride (29.2 mg, 0.153 mmol, 1.5 eq) in anhydrous THF (1.5 mL). After 1 h, the reaction mixture was allowed to warm to rt, then heated to $60\text{ }^{\circ}\text{C}$ for 3 h. The reaction was then poured into ice water (10 mL), neutralized with K_2CO_3 and extracted with CHCl_3 (3 x 10 mL). The crude material was purified by flash chromatography (15:85 EtOAc/petrol) to afford the titled compound as a yellow solid (39.3 mg, 86%). mp $98\text{--}102\text{ }^{\circ}\text{C}$; ν_{max} (film, cm^{-1}) 2926 (C-H), 2851 (C-H), 1734 (C=O), 1491 (Ar C=C); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.50 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 6.37 (2H, t, J 2.1, C(3)Ar(3,4)H), 6.81 (2H, t, J 2.2, C(3)Ar(2,5)H), 7.32–7.37 (2H, m, ArCH), 7.44–7.50 (3H, m, ArCH), 7.81–7.87 (4H, m, ArCH), 7.99 (1H, s, C(5)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 21.9 (CH_3), 53.3 (OCH_3), 110.5 (C(3)ArC(3,4)H), 118.5 (C(5)), 122.9 (C(3)ArC(2,5)H), 125.3 (C(6)), 127.2 (ArCH), 128.9 (ArCH), 129.0 (ArCH), 129.8 (ArCH), 130.4 (ArCH), 134.5 (C(6)ArC(1)), 136.1 (C(2)), 141.0 (ArC), 145.4 (ArC), 152.4 (C(3)), 154.8 (C(4)), 165.2 (C(4)CO₂Me); HRMS (ESI⁺) $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_5\text{NaS}$ $[\text{M}+\text{Na}]^+$ found 471.0978, requires 471.0985 (-1.5 ppm).

Methyl 2-phenyl-5-(1*H*-pyrrol-1-yl)isonicotinate (445)

Following the procedure of Yoshida,²³ to a solution of **442** (52 mg, 0.12 mmol), $\text{Pd}(\text{OAc})_2$ (1.3 mg, 0.006 mmol, 5 mol%), DPPP (2.4 mg, 0.006 mmol, 5 mol%) and Et_3N (0.081 mL, 0.6 mmol, 5.0 eq.) in DMF (1.2 mL) was added formic acid (13 μL , 0.36 mmol, 3.0 eq.). The reaction was heated in a sealed vial for 1 h at $60\text{ }^{\circ}\text{C}$ under N_2 . Once cooled, the reaction mixture was quenched with brine (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were dried over MgSO_4 , filtered and concentrated under reduced pressure. Chromatographic

purification (5:95 EtOAc/Petrol) gave the title compound as a yellow gum (26.0 mg, 78%). ν_{\max} (film, cm^{-1}) 3103 (C-H), 2953 (C-H), 1721 (C=O), 1487; ^1H NMR (500 MHz, CDCl_3) δ_{H} : 3.80 (3H, s, CH_3), 6.39 (2H, t, J 2.2, C(5)Ar(3,4)H), 6.87 (2H, t, J 2.1, C(5)Ar(2,5)H), 7.44–7.54 (3H, m, C(2)ArC(3,4,5)H), 8.03–8.06 (3H, m, C(2)ArC(2,6)H + C(3)H), 8.78 (1H, s, C(6)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 53.1 (CH_3), 110.7 (C(5)ArC(3,4)H), 120.0 (C(3)), 122.2 (C(5)ArC(2,5)H), 127.1 (C(2)ArC(3,5)H), 129.1 (C(2)ArC(2,6)H), 129.8 (C(2)ArC(4)H), 133.8 (C(5)), 135.2 (C(2)), 137.7 (C(2)ArC(1)), 147.7 (C(6)), 156.6 (C(4)), 166.1 (C(4)COOMe); HRMS (ESI⁺) $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ found 279.1119, requires 279.1128 (-3.2 ppm).

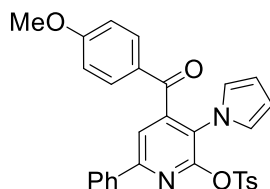
Methyl 2-(4-methoxyphenyl)-6-phenyl-3-(1H-pyrrol-1-yl)isonicotinate (446)



To a screw cap vial was charged $\text{Pd}(\text{dba})_2$ (1.6 mg, 0.003 mmol, 2.5 mol%), 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide (1.0 mg, 0.006 mmol, 5 mol%) and anhydrous 1,4-dioxane (1 mL). The reaction mixture was stirred at rt for 5 mins. 4-Methoxyphenylmagnesium bromide solution (0.5 M in THF, 0.17 mL, 0.17 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 5 minutes. **442** (50 mg, 0.11 mmol, 1.0 eq.) was added and the reaction was heated at 80 °C for 16 h before being cooled to rt. Then the reaction mixture was quenched with 1 M aq. HCl and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. Chromatographic purification (Et_2O /petrol 10:90) gave the titled compound as a light yellow oil (8.5 mg, 20%). ν_{\max} (film, cm^{-1}) 2953 (C-H), 1724 (C=O), 1609 (Ar C=C); ^1H NMR (500 MHz, CDCl_3) δ_{H} : 3.73 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.27 (2H, t, J 2.1, C(3)Ar(3,4)H), 6.62 (2H, t, J 2.1, C(3)Ar(2,5)H), 6.80–6.84 (2H, m, C(2)ArC(3,5)H), 7.30–7.34 (2H, m, C(6)ArC(2,6)H), 7.44–7.53 (3H, m, C(6)ArC(3,4,5)H), 7.92 (1H, s, C(5)H), 8.12–8.16 (2H, m, C(2)ArC(2,4)H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 53.1 (CH_3), 55.4 (CH_3), 110.2 (C(3)ArC(3,4)H), 113.7 (C(2)ArC(3,5)H), 117.4 (C(5)), 122.6 (C(3)ArC(2,5)H), 127.2 (C(2)ArC(2,4)H), 129.0 (C(2)ArC(3,5)H), 129.8 (C(6)ArC(3,5)H), 129.9 (C(6)ArC(4)H), 130.1 (C(6)ArC(2,6)H), 130.7 (C(3)), 138.0 (C(6)), 139.8 (C(6)ArC(1)), 155.6 (C(2)), 156.5 (C(2)ArC(4)),

160.4 (C(4)), 166.5 (C(4)COOMe); HRMS (ESI⁺) C₂₄H₂₁N₂O₃ [M+H]⁺ found 385.1538, requires 385.1547 (-2.3 ppm).

4-(4-Methoxybenzoyl)-6-phenyl-3-(1H-pyrrol-1-yl)pyridin-2-yl 4-methylbenzenesulfonate (447)



To a screw cap vial was charged Pd(dba)₂ (1.6 mg, 0.003 mmol, 2.5 mol%), 4,4,5,5-tetramethyl-1,3,2-dioxaphospholane 2-oxide (1.0 mg, 0.006 mmol, 5 mol%) and anhydrous 1,4-dioxane (1 mL). The reaction mixture was stirred at rt for 5 mins. 4-Methoxyphenylmagnesium bromide solution (0.5 M in THF, 0.17 mL, 0.17 mmol, 1.5 eq.) was added and the reaction mixture was stirred at rt for 5 minutes. **442** (50 mg, 0.11 mmol, 1.0 eq.) was added and the reaction was heated at 80 °C for 16 h before being cooled to rt. Then the reaction mixture was quenched with 1 M aq. HCl and extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Chromatographic purification (Et₂O/petrol 10:90) gave the titled compound as a white solid (31.2 mg, 54%). mp 164–166 °C; ν_{\max} (film, cm⁻¹) 3157 (C-H), 1661 (C=O), 1603 (Ar C=C), 1576 (S=O), 1489; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.48 (3H, s, CH₃), 3.83 (3H, s, OCH₃), 6.07 (2H, t, *J* 2.2, C(3)Ar(3,4)H), 6.72 (2H, t, *J* 2.1, C(3)Ar(2,5)H), 6.80–6.84 (2H, m, ArH), 7.31–7.35 (2H, m, ArH), 7.40–7.46 (3H, m, ArH), 7.60–7.64 (2H, m, ArH), 7.71 (1H, s, C(5)H), 7.78–7.81 (2H, m, ArH), 7.83–7.88 (2H, m, ArH); ¹³C{¹H} NMR (126 MHz, CDCl₃) δ_{C} : 21.9 (CH₃), 55.7 (OCH₃), 110.8 (C(3)ArC(3,4)H), 114.0 (ArCH), 117.8 (C(5)), 123.0 (C(3)ArC(2,5)H), 124.2 (ArC), 127.2 (ArCH), 128.0 (ArC), 128.9 (ArCH), 129.0 (ArCH), 129.8 (ArCH), 130.3 (ArC), 131.9 (ArCH), 134.6 (C(2)), 136.3 (ArC), 145.4 (C(6)), 148.4 (C(3)), 151.3 (ArC), 154.3 (C(4)), 164.6 (C(4)COArC(4)), 191.9 (C(4)CO); HRMS (ESI⁺) C₃₀H₂₅N₂O₅S [M+H]⁺ found 525.1473, requires 525.1479 (-1.1 ppm).

8.7. References

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