Development and application of bifunctional iminophosphorane organocatalysts

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A thesis submitted for the degree of
Doctor of Philosophy
2016

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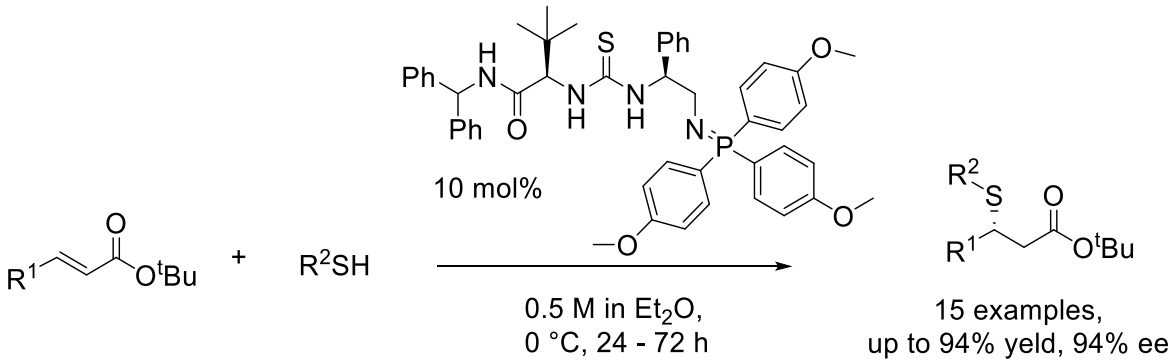
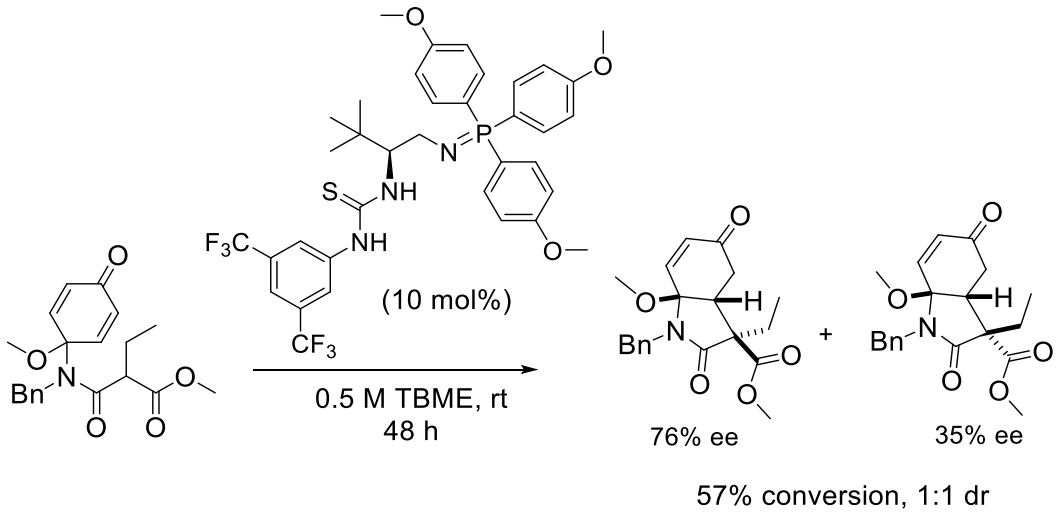
Abstract

This thesis presents the development and application of bifunctional iminophosphorane (BIMP) organocatalysts, incorporating a triaryl-substituted iminophosphorane organosuperbase for organocatalytic enantioselective reactions.

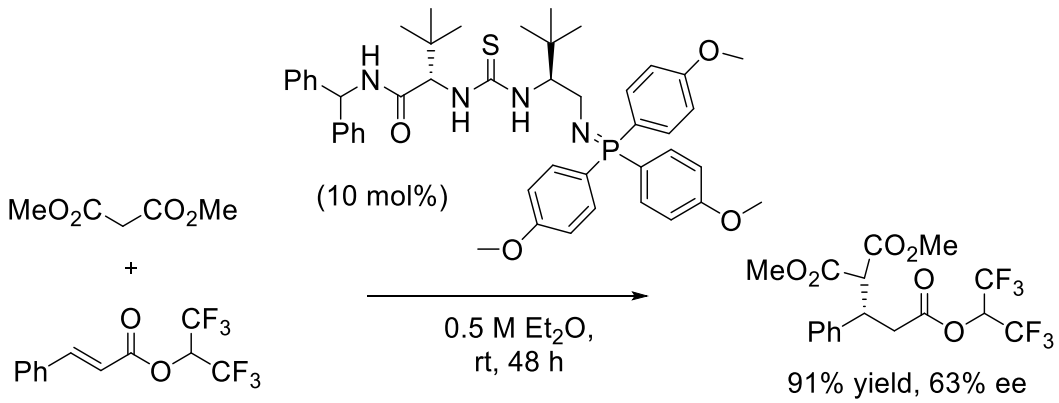
Chapter 2 describes the design and synthesis of a new class of BIMP catalysts and its application in the first organocatalytic enantioselective sulfa-Michael reaction of alkyl thiols to unactivated β-substituted α,β-unsaturated esters. The conjugate adducts were obtained in up to 94% yield and 94% ee. In addition, the reaction was performed on a 1 gram preparative scale with 1 mol% catalyst.



Chapter 3 describes the application of BIMP catalysts in the enantioselective desymmetrisation reaction *via* an intramolecular Michael addition of a pendant pronucleophile to prochiral cyclohexadienone. The high Brønsted basicity of BIMP catalysts was demonstrated in the Michael addition of high pKa pronucleophiles, such as α-substituted malonamate and amide.



Chapter 4 describes the application of BIMP catalysts in the challenging Michael addition of malonates to crotonates, cinnamates and methacrylates. For example, the conjugate adduct of malonate and hexafluoroisopropyl cinnamate was achieved in 91% yield and 63% ee in 48 h.



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I declare that thesis has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree at this or any other university or institute of learning. Work that was done as part of a collaboration with a research colleague has been fully acknowledged and referenced within the text.

I was admitted as a probationary research student in October 2012 and as a candidate for the degree of Doctor of Philosophy in October 2013; the higher study for which this is a record was carried out in the University of Oxford between 2012 and 2015.

Jinchao Yang

Date **Signature of candidate**

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Acknowledgements

First and foremost, I would like to thank Darren for giving me the opportunity to work in this group. Thank you for your enthusiasm and guidance during my three years of research.

Special thanks to Alistair for your help when I first joined the group and for all the invaluable discussions about the project and chemistry.

Thank you to all the NMR staff, especially to Barbara for her help with the NMR spectroscopy.

I would also like to thank all the Dixon members for making my three years in Oxford a memorable experience, especially Lucas, Chris, Tao, Matt, Vaibhav, Yao, Gerard, Ruben, Angel, Yusuke, Alex.

A big thank you to my proofreaders: Yao, Ruben, Angel, Alistair, Tao, Gerard, Pablo, Mahendra for your time and suggestions.

I must thank my parents for their love and support throughout all the years I am away from home.

Finally, I would like to thank Yijun for your support in my life; without you, none of these would be possible.

Abbreviations

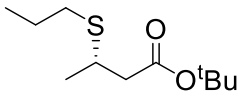
Å	Angstrom
Ac	Acetyl
aq.	Aqueous
Ar	Aryl
BEMP	2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
BIMP	Bifunctional Iminophosphorane
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bu	Butyl
°C	Degree Celsius
cat	Catalyst
d	Doublet
dd	Doublet of doublets
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	N,N-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
dq	Doublet of quartets
dr	Diastereomeric ratio
dt	Doublet of triplets
EDC•HCl	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
Et_3N	Triethylamine
ee	Enantiomeric excess
eq	Equivalents
Et	Ethyl
ESI	Electrospray ionization
EWG	Electron Withdrawing Group

FCC	Flash Column Chromatography
GC	Gas Chromatography
H	Hour
H-bond	Hydrogen bond
HOBt	1-Hydroxybenzotriazole hydrate
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HOSEY	Heteroatom Nuclear Overhauser effect spectroscopy
Hz	Hertz
Im	Imidazole
iPr	*iso*-Propyl
IR	Infrared
J	Coupling constant
LiHMDS	Lithium bis(trimethylsilyl)amide
M	Molar
M	Multiplet
M	Meta
m/z	Mass per charge ratio
Me	Methyl
Min	Minutes
mL	Millilitres
Mmol	Millimole
Mol	Mole
m.p.	Melting point
MS	Molecular sieves
n. d.	Not determined
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Np	Naphthyl
Ph	Phenyl
Phth	Phthalimido
p*Ka*	-log(*Ka*)
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
Pr	Propyl

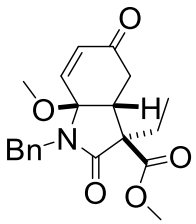
PS-BEMP	Polystyryl 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
q	Quartet
quin	Quintet
rt	Room temperature
SMA	Sulfa-Michael Addition
sext	Sextet
TMS	Trimethylsilyl
TBDPS	tert-Butyldiphenylsilyl
TBME	*tert*-Butyl methyl ether
TBS	tert-Butyldimethylsilyl
tBu	tert-Butyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMG	N,N,N′,N′-Tetramethylguanidine
t_R	Retention time
TS	Transition state
Ts	Tosylate

A Note on Stereochemistry

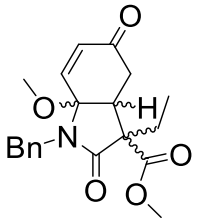
Throughout this thesis, the graphic presentations of absolute and relative stereochemical configurations are in accord with the conventions proposed by Maehr [i]. (a) Solid and broken wedges are used to indicate the absolute stereochemical configuration of enantioenriched compounds. (b) Solid and broken bold lines indicate the relative stereochemical configuration of diastereoenriched compounds. (c) Wavy bonds are used for enantioenriched compounds with unknown stereochemical configuration.

(a) 

An enantioenriched compound with known absolute stereochemical configuration

(b) 

A diastereoenriched compound with known relative stereochemical configuration

(c) 

A diastereoenriched and/or enantioenriched compound with unkown stereochemical configuration

[i] Maehr, H. J., *Chem. Educ.*, **1985**, *62*, 114.

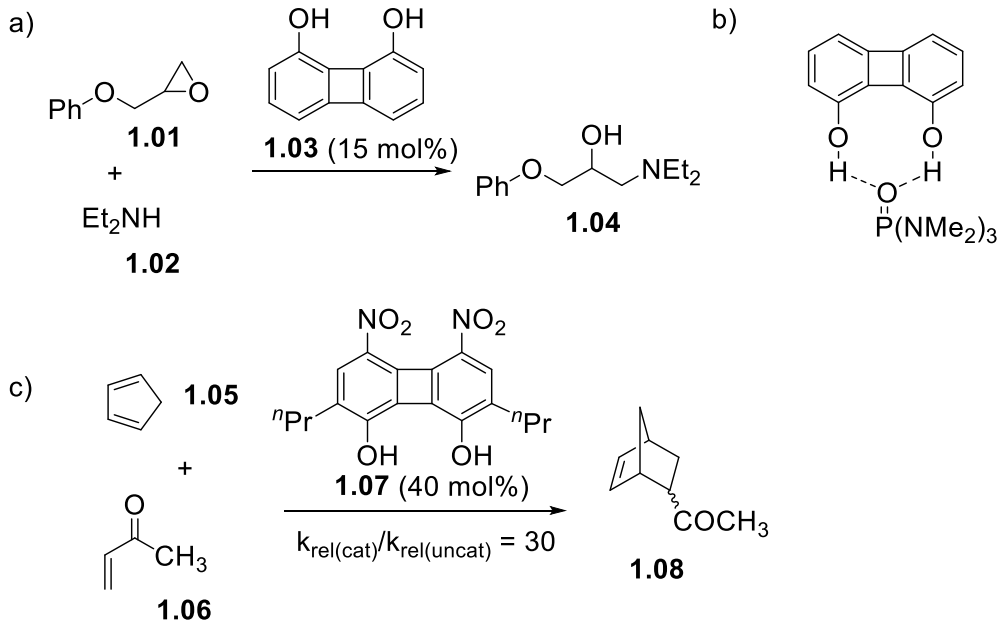
Chapter 1 Introduction

Asymmetric organocatalysis has emerged as a powerful tool for accessing enantioenriched molecules since the beginning of the 21st century.[1,2,3,4] Numerous asymmetric organocatalytic systems have been developed based on different activation modes, for example, iminium catalysis[5], enamine catalysis[6], phase transfer catalysis[7], Brønsted acid catalysis[8], Brønsted base catalysis[9] and asymmetric bifunctional organocatalysis[10,11,12]. Of these classes, asymmetric bifunctional organocatalysis has received much attention due to its capability of displaying two simultaneous modes of activation. This chapter will concentrate on the development of chiral bifunctional organocatalysts possessing hydrogen bond (abbreviated as H-bond) donor moiety and Brønsted base moiety which can simultaneously activate the electrophile and the nucleophile in a reaction.

1.1 H-bond Donor Development for Organocatalysis

H-bond donor groups play a crucial role in activating/organising the electrophiles and/or nucleophiles in organocatalysis.[13,14] In 1985, early work on H-bond catalysis by Hine showed that 1,8-biphenylenediol **1.03** was able to catalyse the ring opening reaction of epoxide **1.01** (Scheme 1.01a). Hine also demonstrated that 1,8-biphenylenediol was capable of forming two H-bonds with the same basic oxygen atom simultaneously by X-ray studies (Scheme 1.01b).[15,16] Based on this observation, Kelly introduced biphenylenediol catalyst **1.07** to study the Diels-Alder reaction of various dienes and dienophiles.[17] Rate enhancement of 30 fold

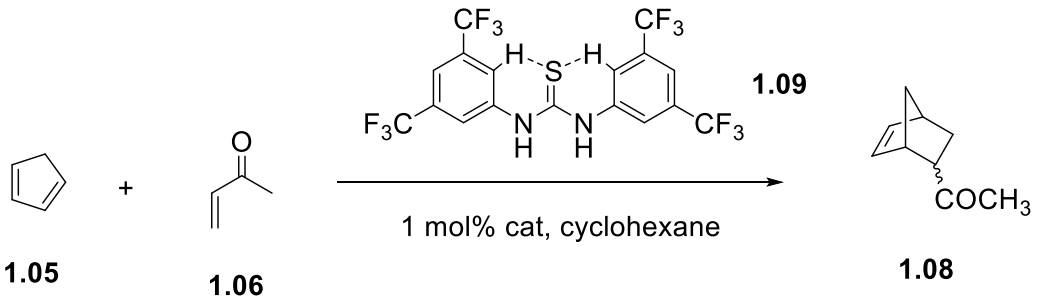
was achieved using 40 mol% catalyst loading (Scheme 1.01c).



Scheme1.01. a) Epoxide ring opening reactions catalysed by 1,8-biphenylenediol 1.03; b) Dual H-bonding mode of biphenylenediol with phosphoramide; c) Rate acceleration promoted by biphenylenediol 1.07 in Diels-Alder reaction.

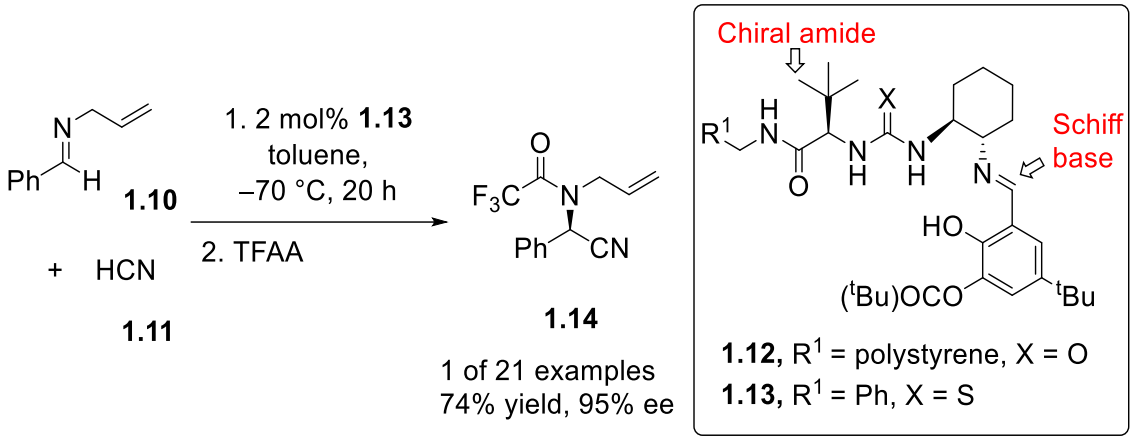
Based on Hine's and Kelly's work, Schreiner investigated thiourea derivatives as catalysts. These are excellent H-bond donors due to their enhanced acidity compared with urea (p*Ka* thiourea = 21.0 in DMSO; p*Ka* urea = 26.9 in DMSO).[18] A range of thiourea derivatives bearing different alkyl and/or aryl groups on thiourea were synthesised for the systematic study of the Diels-Alder reaction between cyclopentadiene **1.05** and methyl vinyl ketone **1.06**. It was shown that *N,N*-bis [3,5-bis(trifluoromethyl) phenyl] thiourea **1.09** was most effective, enhancing the reaction rate by a factor of 9 to aliphatic thioureas (Scheme 1.02).[19] It is noteworthy that the rate enhancement of the reaction was achieved with 1 mol% catalyst loading. Schreiner explained that the complexation between carbonyl functionalities and thioureas is likely controlled by entropic effects; therefore, the efficacy of H-bonding between the thioureas and the carbonyl functionalities is dependent on the rigidity of the thiourea. The thioureas bearing

m- and *p*-substituted aryls possess the highest rigidity due to the internal interaction between the more polarised *o*-hydrogen and sulfur. In addition, the electron withdrawing inductive effect arising from the trifluoromethyl groups at the *m*-position of the aromatic ring increases the acidity of the protons of the thiourea.[19]



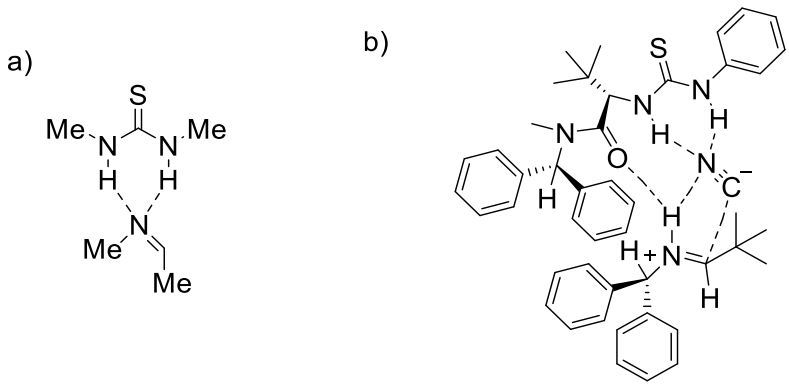
Scheme 1.02. Diels-Alder reaction catalysed by Schreiner's thiourea catalyst 1.09.

In 1998, Jacobsen reported a new class of chiral H-bond donor catalysts utilising urea/thiourea groups to link chiral amide and Schiff base moieties (amido-thiourea catalyst, Scheme 1.03). Catalyst **1.13** was used to catalyse the asymmetric Strecker reaction of HCN to various aldimines in high yields and ee's (Scheme 1.03).[20, 21] The use of the resin-bound catalyst **1.12** could also afford the reaction in 97% yield and 92% ee. In particular, the resin-bound catalyst could be recycled after the reaction by filtration and reused for more than 10 cycles without loss of either activity or stereocontrol over the reaction. Since this initial work on the Strecker reaction, a family of structurally related amido-thiourea catalysts has been developed by Jacobsen and successfully used in a range of enantioselective reactions, such as the Strecker reaction of HCN to ketimines[22], the Mannich reaction[23] and hydrophosphonylation of imines[24].



Scheme 1.03. Enantioselective addition of HCN to aldimines catalysed by thiourea derivatives.

Preliminary mechanistic studies showed that the catalytic activity arose from the formation of ground-state dual H-bonds between the thiourea protons on the catalyst and the imine substrate (Scheme 1.04a).[25] However, the exact form of H-bond interactions was unclear in the rate- or enantio- determining transition state. In a later mechanistic study of amido-thiourea catalysed enantioselective imine hydrocyanation, Jacobsen rationalised the mechanism of the reaction and transition state H-bond interactions *via* detailed experimental and computational studies. It was shown that the reaction involves an initial catalyst-promoted proton transfer from hydrogen isocyanide to the imine to generate iminium/cyanide ion pairs. This key species was then bound by the catalyst in the transition structure, where the thiourea of the catalyst formed a dual H-bond with nitrogen on the cyanide (Scheme 1.04b).[26]

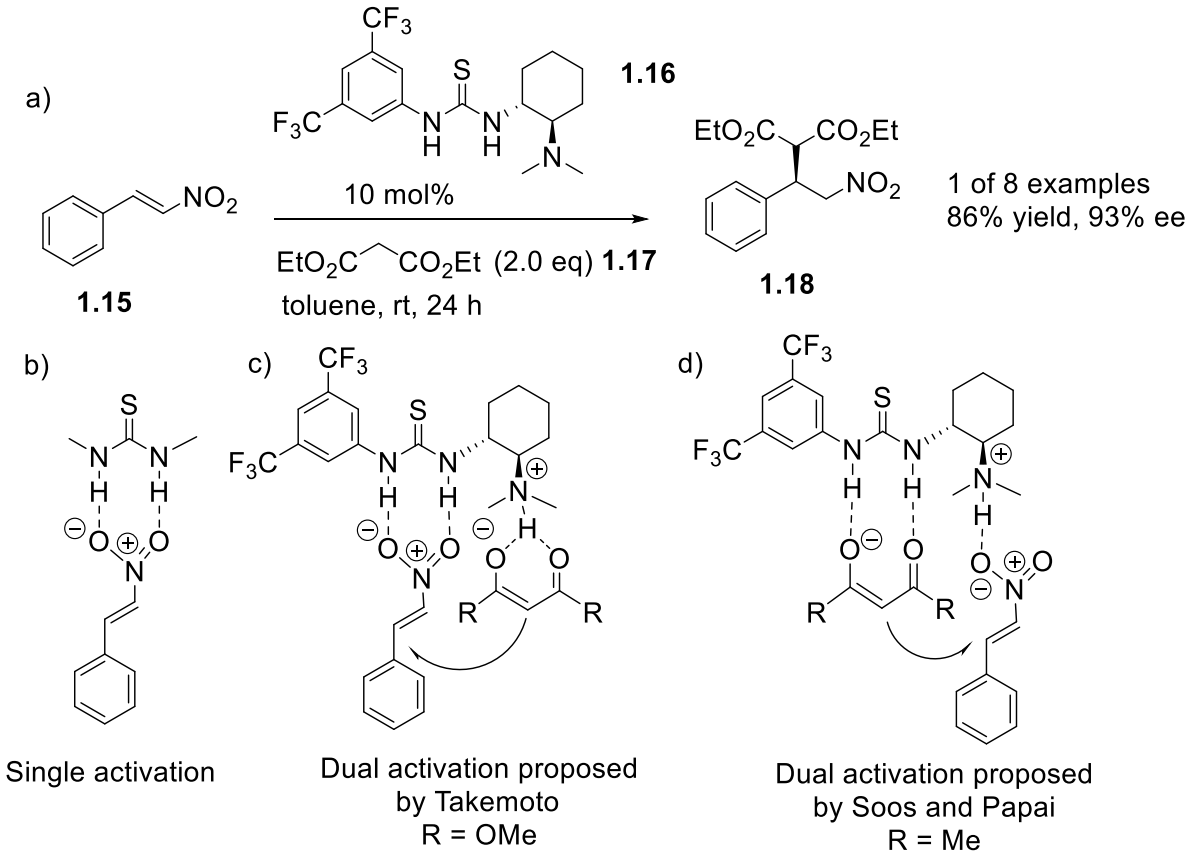


Scheme 1.04. a) Ground state interactions between thiourea and aldemine; b) Calculated transition state for the Strecker reaction of HCN with (*E*)-N-benzhydryl-2,2-dimethylpropan-1-imine.

1.2 Brønsted Base/H-bond Donor Bifunctional Organocatalysts

Recognising the superior ability of H-bond donor catalysts to enhance reactivity and deliver high enantiocontrol, Takemoto developed a new class of bifunctional organocatalyst that adopted a thiourea H-bond donor moiety and an additional nucleophile-activating Brønsted base group; this catalyst was used in the enantioselective Michael addition of malonates to nitroolefins (Scheme 1.05a).[27] In initial work, Takemoto proposed that the Brønsted base and the H-bond donor could simultaneously activate both the nucleophile and electrophile in the reaction. Based on this idea, a H-bond donating thiourea moiety was used to link a highly electron deficient arene, namely 3,5-$(CF_3)_2C_6H_3$, with cyclohexyldiamine chiral scaffold to form the bifunctional catalyst **1.16**. Control experiments demonstrated that high reactivity and enantioselectivity were only achievable when both the thiourea and tertiary amino group were present in the catalyst. This led the authors to postulate a dual activation mechanism, where the thiourea moiety bound to the nitro group, and the dimethylamino group deprotonated the malonate to form the enolate. The enolate form of the malonate then attacked the electrophile

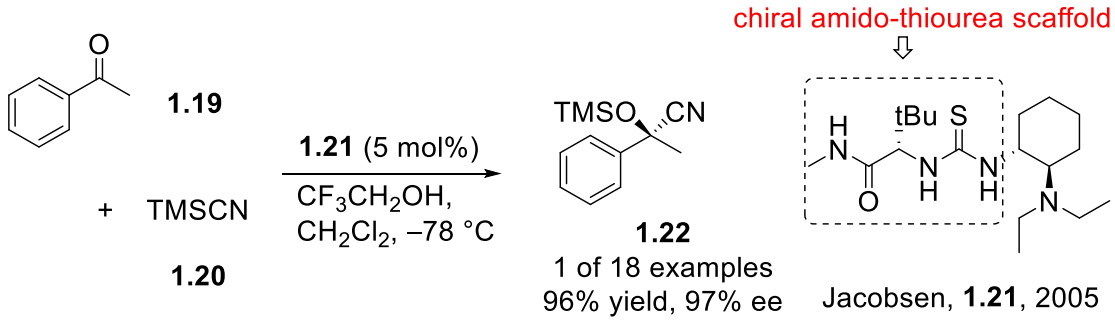
preferentially from one face to give the product in high enantioselectivity (Scheme 1.05c).



Scheme 1.05. a) Takemoto's catalyst 1.16 in the enantioselective Michael addition of malonate to nitroolefin; b) Single activation mode; c) Dual activation proposed by Takemoto; d) Dual activation proposed by Soos and Papai.

Building on Takemoto's experimental work and proposed transition state model, Soos and Papai proposed a different transition state after detailed computational studies.[28] In their proposition, the enolate of the pronucleophile was stabilised by forming two H-bonds with both protons on the thiourea, while the protonated dimethylamine group form a H-bond with the nitro group of the electrophile (Scheme 1.05d).

Both mechanisms (Scheme 1.05c and d) are considered to be plausible and have accounted for the observed enantioselectivity of the product.



Scheme 1.06. Jacobsen's chiral amido-thiourea bifunctional organocatalyst and its application in the enantioselective cyanosilylation of ketones.

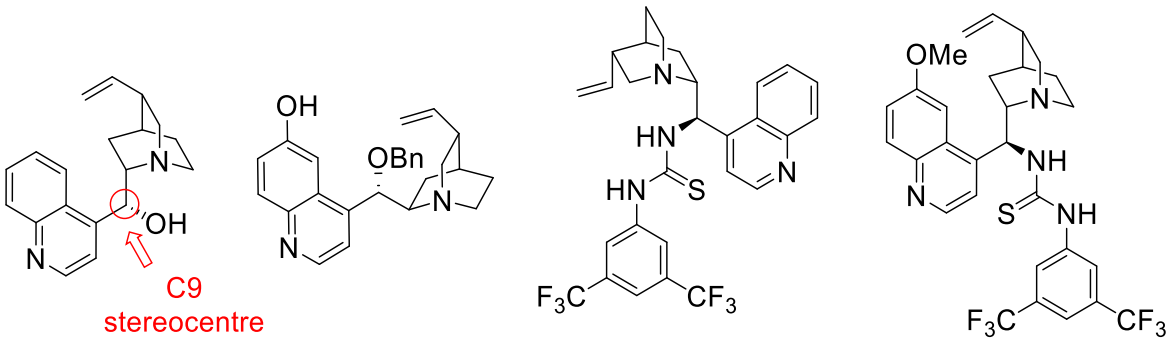
Since the development of Takemoto's bifunctional organocatalyst and its application in Michael addition of malonates to nitroolefins, various bifunctional organocatalysts have been synthesised by other groups and applied successfully to a range of enantioselective reactions.

One type of bifunctional organocatalyst is the Jacobsen's amido-thiourea bifunctional catalyst, which is derived from chiral amido-thiourea Schiff base catalysts (Scheme 1.03) by replacing the Schiff base moiety with a Brønsted base. For instance, cyclohexyldiamine group was coupled to the modified Jacobsen's chiral amido-thiourea scaffold to generate bifunctional catalyst **1.21** (Scheme 1.06), which was used in the enantioselective cyanosilylation of ketones.[29] This family of catalyst has also been used in a range of enantioselective reactions, such as the conjugate addition of ketones to nitroalkenes[30] and the nitro-Mannich reaction[31].

Another important family of bifunctional organocatalysts are those derived from cinchona alkaloids.[10,32] This class of natural products are inexpensive and readily available in both *pseudo*enantiomeric forms. In addition, cinchona alkaloids possess a basic bridgehead quinuclidine group attached to a complex chiral scaffold; along with a hydroxyl group attached to the C-9 stereocentre that could

be transformed into other functional groups, such as, urea and thioureas (Scheme 1.07). In 2004, Deng[33] reported cinchona alkaloid derivative **1.24** bearing a 6′-hydroxy-quinoline in place of a 6′-methoxyquinoline or quinoline ring (Scheme 1.07), which was applied very successfully to the Michael addition of malonate to nitroolefins with high yields and ee's.

In 2005, four groups individually reported the use of cinchona alkaloid derived bifunctional thiourea organocatalysts (Scheme 1.07) in asymmetric catalysis. Chen[34] reported the sulfa-Michael addition of aryl thiols to α,β-unsaturated imides using **1.25** as the catalyst, although the enantioselectivity of the reaction was low. Connon[35] and Dixon[36] both successfully developed and applied catalyst **1.25** to the highly enantioselective Michael addition of malonate to nitroolefins. Soos[37] presented the Michael addition of nitromethane to chalcones catalysed by **1.26** with high yields and ee's.



Cinchonidine, **1.23**

Deng,**1.24**, 2004

Chen, Dixon, Connon, **1.25**, 2005

Soos, **1.26**, 2005

Scheme 1.07. Cinchona alkaloids derived bifunctional organocatalysts.

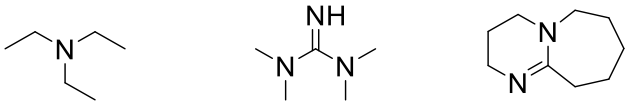
The synthetic utility of cinchona alkaloids derived bifunctional organocatalysts has been quickly recognised by various groups and numerous enantioselective reactions have been developed based on these catalysts, such as conjugate addition of thiols[38], nitromethane[37] and enol species (e.g. malonate esters,

malononitriles and β-ketoesters) [39] to chalcones, the Diels-Alder reaction[40], the Mannich reaction[41] and the aza-Henry reaction[42].

1.3 Organocatalysts Incorporating Superbases

Although Brønsted base/H-bond donor bifunctional organocatalysts have been demonstrated as successful in promoting a wide range of enantioselective reactions, there are limitations, i.e. the low reactivity of organocatalysts.[43]

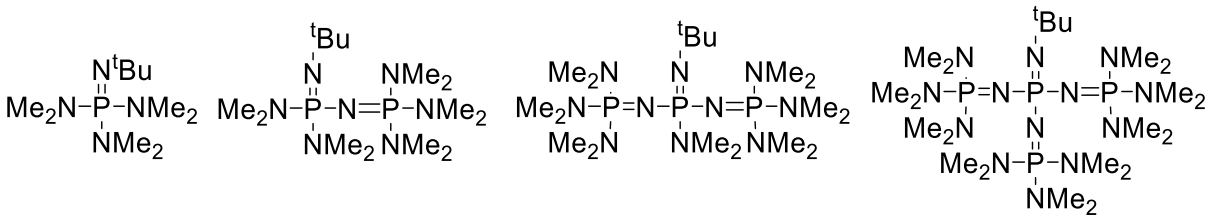
One solution for the reactivity problem mentioned above is to incorporate a stronger organic base into the catalyst. The Brønsted base moieties used in the bifunctional organocatalysts are typically amine functional groups, which have a relatively low p*Ka* (for example, p*Ka* = 18.8 in MeCN for triethylamine (Et_3N), **1.27**, Scheme 1.08) compared with other stronger Brønsted bases.[44] For instance, the introduction of an imine functionality (=NH) to the α-carbon of an amine gives amidine. A commonly used amidine reagent is DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene, **1.29**, Scheme 1.08).[44] Another example of strong base is the guanidine moiety, which contains two amines and one imine connected to the same carbon. A commonly used guanidine reagent is TMG (1,1,3,3-tetramethylguanidine, **1.28**, Scheme 1.08). [45] The basicity of these compounds arises from the highly conjugated electron rich system which allows positive charge in the conjugate acid to be delocalised in the molecule. As the number of nitrogen atoms increases in the base, there are more isoelectronic forms of the protonated molecule; thus the basicity increases.[45]



triethylamine **1.27** pK_{BH+} : 18.8 (in MeCN) | TMG **1.28** 23.3 (in MeCN) | DBU **1.29** 24.34 (in MeCN)

Scheme 1.08. Comparison of superbases and their basicity.

Another family of strong organic bases is the phosphazenes (iminophosphoranes), first introduced by Schwesinger in 1985. It contains a phosphorus atom bonded to four nitrogens belonging to three amines and one imine group ($R\text{-}N{=}P(NR_2)_3$).[46] These compounds are highly basic, chemically stable, and kinetically active because their structure contains large number of sterically hindered nitrogens. They are classified as P_n bases (n denotes the number of phosphorus atoms in the molecule)[47,48] (Scheme 1.09).



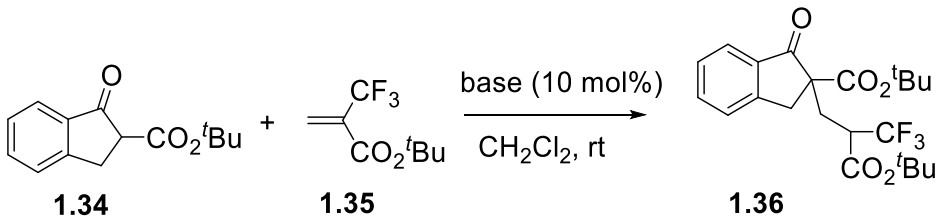
P1, **1.30** 26.98 | P2, **1.31** 33.49 | P3, **1.32** 38.6 | P4, **1.33** 42.7

Scheme 1.09. Comparison of Pn bases and their basicity (pK_{BH+} in MeCN).

The high p*Ka* of these strong organic bases (superbase)[ii] are directly associated with their reactivity in catalytic reactions. An example of the rate comparison in the Michael addition of β-ketoester **1.34** to acrylate **1.35** catalysed by tertiary amine and stronger organic bases is shown below (Table 1.1). The use of TMG as

[ii] The superbase in this thesis refers to bases with p*Ka* values comparable to, or greater than, that of TMG (pK_{BH+} 23.3 in MeCN).

catalyst enhanced the reaction rate by a factor of 300 compared to Et_3N.[49]



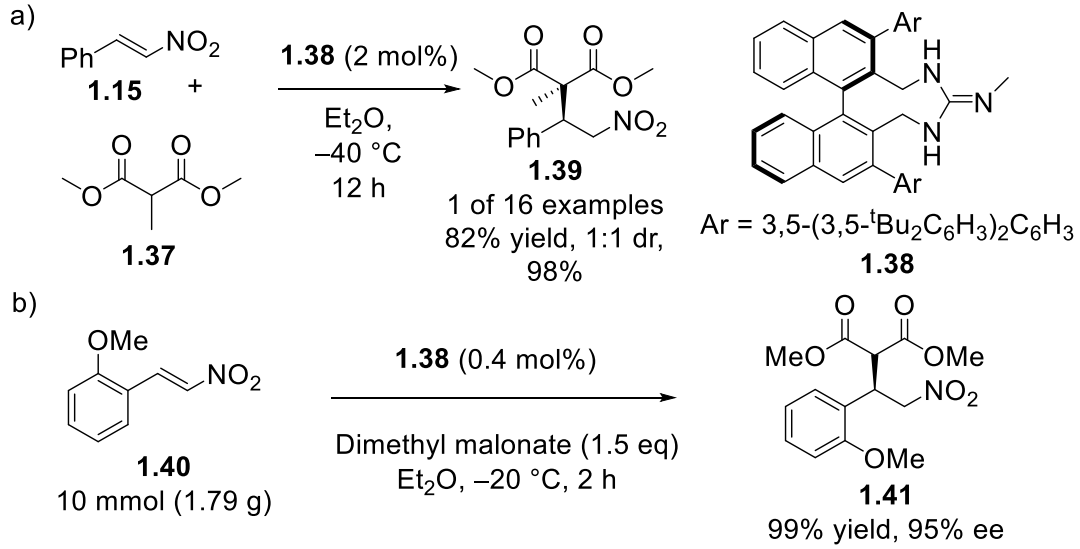
1.34 **1.35** **1.36**

Table 1.1 Michael addition of β-ketoester 1.34 to acrylate 1.35 catalysed by achiral bases

Entry	Base	Time	Yield
1	Et_3N	48 h	47
2	DBU	15 min	84
3	TMG	10 min	85

Therefore, if superbases could be applied as the Brønsted basic moiety in bifunctional organocatalysts, the catalytic ability of such catalysts could be greatly improved in terms of reaction rate, and possibly catalyst loading. The higher catalytic ability would also allow the use of more challenging pronucleophiles and electrophiles in enantioselective reactions.

Recognising the preeminent role superbases play in organocatalysis, several groups synthesised a variety of chiral superbase organocatalysts and applied these catalysts to a range of enantioselective reactions. Representative examples are shown below.

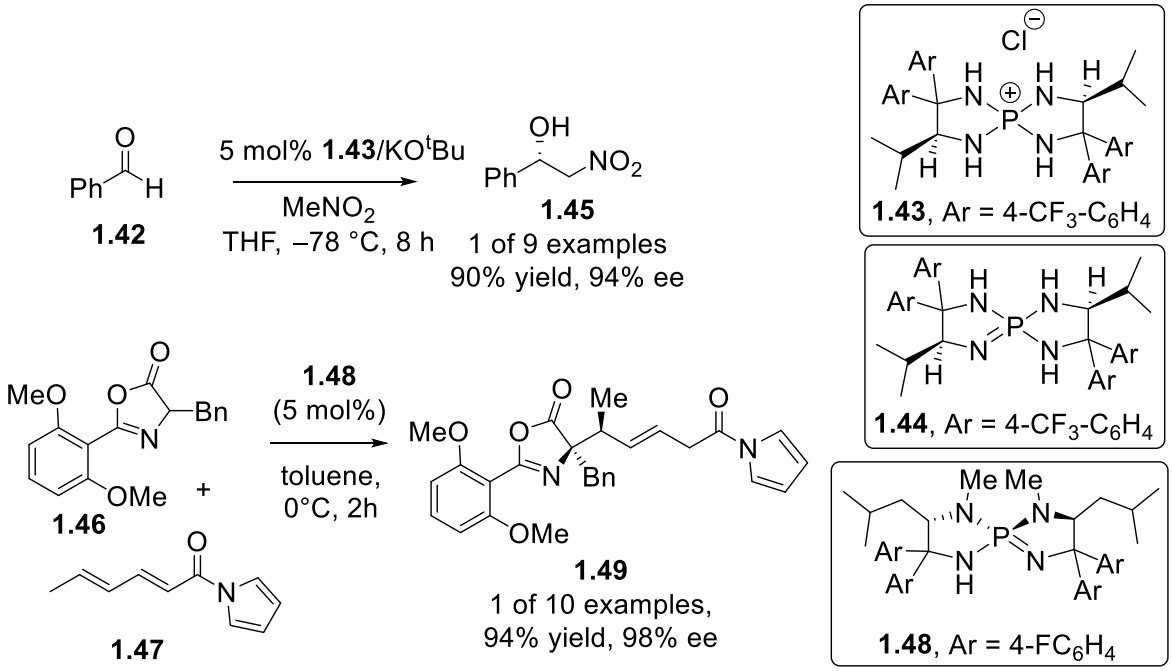


Scheme 1.10. Terada's chiral guanidine superbase organocatalyst in the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes.

One important family of chiral superbase organocatalysts are the guanidines.[50] In 2006, Terada[51] designed a chiral guanidine catalyst **1.38** by incorporating an axially chiral binaphthyl backbone to the guanidine. This catalyst was applied to the enantioselective Michael addition of 1,3-dicarbonyl compounds into a broad range of conjugated nitroalkenes. Moreover, the reaction was tolerant of the steric hindered α-substituted malonate **1.37** (Scheme 1.10a). High catalytic efficiency was also demonstrated in the preparative scale (10 mmol) synthesis of **1.41** with low catalyst loading (0.4 mol%) and fast reaction time (2 h). (Scheme 1.10b)

Another important family of chiral superbase organocatalysts are the chiral phosphazenes (iminophosphoranes, Scheme 1.09).[52] In 2007, Ooi first reported a chiral tetraaminophosphonium chloride salt **1.43** possessing a P-spirocyclic structure (Scheme 1.11). A Henry reaction with simple substrates was used to test the efficacy of this catalyst and high yields and enantioselectivities were obtained for a range of substrates.[53] The authors postulated that catalyst **1.43** was initially deprotonated by a strong base such as KO^{t}Bu to generate the active catalyst triamino-iminophosphorane **1.44** *in situ*. The group later developed the free

triamino-iminophosphorane **1.48** which was used directly as a strong base in the highly diastereo- and enantioselective 1,6-addition of azlactones **1.46** to simple δ-monosubstituted dienyl N-acylpyrroles **1.47**.[54] This class of superbase catalysts was applied in several enantioselective reactions, for example, hydrophosphonylation of aldehydes[55] and ynones[56], amination of ketones[57].



Scheme 1.11. Ooi's chiral triamino-iminophosphorane catalysts and its application in the Henry reaction and the Michael reaction.

A recent development of chiral superbase organocatalysts is the chiral cyclopropenimine organocatalysts. Cyclopropenimine is well appreciated as a strong base but no data of its basicity has been reported until Lambert's measurement in 2012 showed that the pK_{BH+} of cyclopropenimine is 26.9 (in MeCN)[58], which is comparable to that of P$_1$-^{t}Bu **1.30** (26.98 in MeCN, Scheme 1.09). The authors rationalised that the conjugate acid of the cyclopropenimine is stabilised by the aromatic cyclopropenium ion plus 3 nitrogen lone pairs; therefore, leads to high Brønsted basicity of cyclopropenimine. Recognising its strong basicity, the group designed chiral cyclopropenimine **1.52** and tested it in the

Michael reaction of glycine imine **1.50** with methyl acrylate **1.51**. Remarkably, the product was obtained in quantitative yield and 91% ee in 5 min with 10% catalyst loading, much more effective than the reported chiral guanidine catalyst **1.52** which took 3 days for the reaction to go to completion (Table 1.2).[59] This class of catalysts was also successfully applied to the enantioselective Mannich reaction.[60]

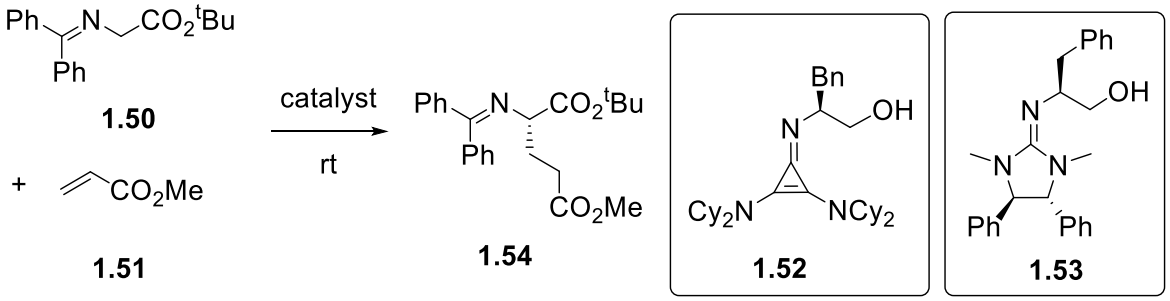
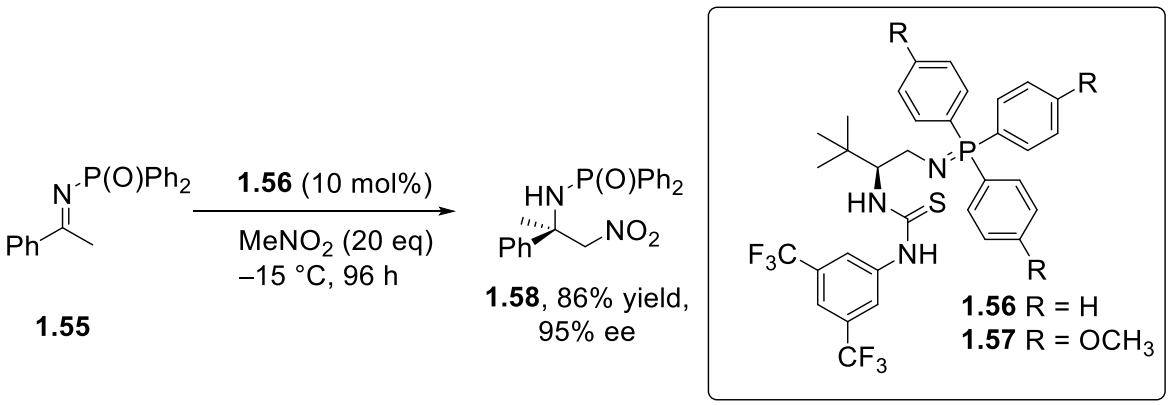


Table 1.2 Comparison of cyclopropenimine catalyst 1.52 and guanidine catalyst 1.53 in the Michael addition of glycine imine with methyl acrylate

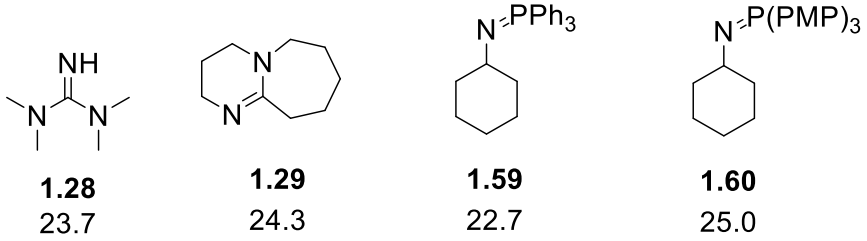
Entry	Catalyst	Loading	Time	Yield	ee
1	**1.52**	10	5 min	99	91
2	**1.53**	20	3 days	98	93

Finally, the Dixon group has developed a new family of strongly basic bifunctional iminophosphorane (BIMP) thiourea catalysts derived from chiral amino acids, including *L*-*tert*-leucine, *D*-phenyl glycine, *L*-serine and *L*-valine. The BIMP catalyst derived from *L*-*tert*-leucine **1.56** was successfully applied to the first enantioselective organocatalytic addition of nitromethane to ketimines (Scheme 1.12).



Scheme 1.12. Asymmetric nitro-Mannich reaction of $MeNO_2$ with ketimines catalysed by bifunctional iminophosphoranes.

Furthermore, the pK_{BH+} (MeCN) of the iminophosphorane **1.59** derived from cyclohexyl azide and triphenylphosphine was measured to be 22.7. The pK_{BH+} (MeCN) of the iminophosphorane **1.60** derived from cyclohexyl azide and tris(4-methoxyphenyl)phosphine (abbreviated as $P(PMP)_3$) was measured to be 25.0, which is comparable to other superbases such as guanidines and amidines (Scheme 1.13).[61]



Scheme 1.13. Comparison of pK_{BH+} values of TMG, DBU and iminophosphorane 1.59 and 1.60 in MeCN.

1.4 DPhil Aims

Given the excellent reactivity of and the high enantiocontrol demonstrated by BIMP catalysts, we envisaged that this class of catalysts could promote organocatalytic reactions involving more challenging pronucleophiles and electrophiles.

The broad aims of this D.Phil. were to expand the reaction scope of BIMP catalysts

family and to uncover new methodologies *via* the development of new classes of BIMP catalysts; this will be achieved through fine-tuning of each modular component of the catalyst.

Initially, we planned to investigate the Michael reactions of crotonate and cinnamate esters, as these are known to be low reactivity electrophiles, and their use in enantioselective Michael reaction has never been reported before. We speculated that the reluctance of these esters to undergo organocatalytic Michael reactions could be overcome using BIMP catalysts. To exemplify this we chose the sulfa-Michael addition of thiols to crotonate and cinnamate esters as this reaction is of central importance for the asymmetric construction of chiral sulfides possessing a β -stereogenic centre. The results are presented in Chapter 2.

Next, we decided to study the asymmetric desymmetrisation of cyclohexadienones *via* an enantioselective intramolecular Michael addition of high p*Ka* pronucleophiles, such as malonamate and amide. This reaction could afford complex bicyclic ring systems that are useful building blocks for natural products and pharmaceuticals. The results are presented in Chapter 3.

Finally, we planned to investigate the challenging enantioselective Michael addition of malonate esters to α,β-unsaturated esters. This unprecedented reaction is a fundamental method of building carbon-carbon bond stereo-specifically at the β-carbon of an ester. The results are presented in Chapter 4.

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Chapter 2 BIMP Catalyst Development and Enantioselective Sulfa-Michael Addition of Thiols to β-Substituted α,β-Unsaturated Esters

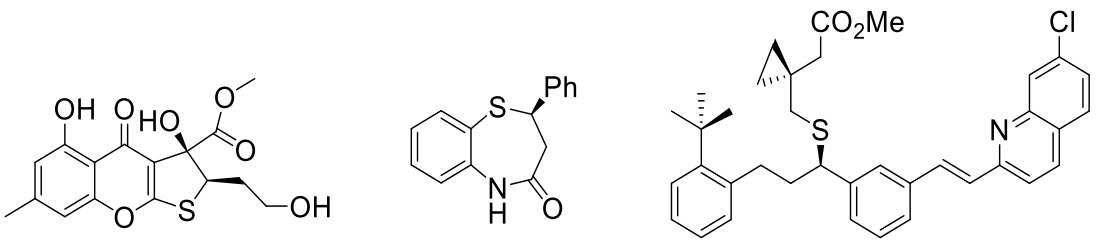
2.1 Chapter Overview

This chapter describes the BIMP catalyst development and its application in the first highly organocatalytic enantioselective sulfa-Michael addition (SMA) of thiol pronucleophiles to unactivated β-substituted α,β-unsaturated esters.[1] Good reactivity and poor enantioselectivity were obtained initially with existing BIMP family catalyst members. Different chiral scaffolds were introduced to the iminophosphorane moiety and new generations of BIMP catalysts were synthesised and applied to the SMA. BIMP catalyst incorporating a chiral amido-thiourea scaffold was found to give high yield and ee for the reaction. A broad range of alkyl thiols and alkyl substituted α,β-unsaturated esters were well tolerated in this reaction. Catalyst loading studies were performed and the catalytic reaction was carried out at 1% catalyst loading on a preparative scale. Various derivatives of conjugate adducts were synthesised to demonstrate the application of the methodology. NMR experiments have also been performed to study the mechanism of the reaction.

2.2 Introduction

2.2.1 Sulfur-containing Compounds

The sulfa-Michael addition (SMA) of thiol pronucleophiles to conjugated β-substituted electron deficient alkenes is a fundamental way to construct chiral sulfides bearing a stereogenic centre at the β-position of the molecule.[2,3] Such adducts are versatile precursors for the synthesis of biological interesting natural products (Coniothienol A[4]) and pharmaceuticals (*(R)*-thiazesim[5,6] and Singulair[7]) (Scheme 2.01).



Coniothienol A, **2.01** (R)-thiazesim, **2.02** Singulair, **2.03**

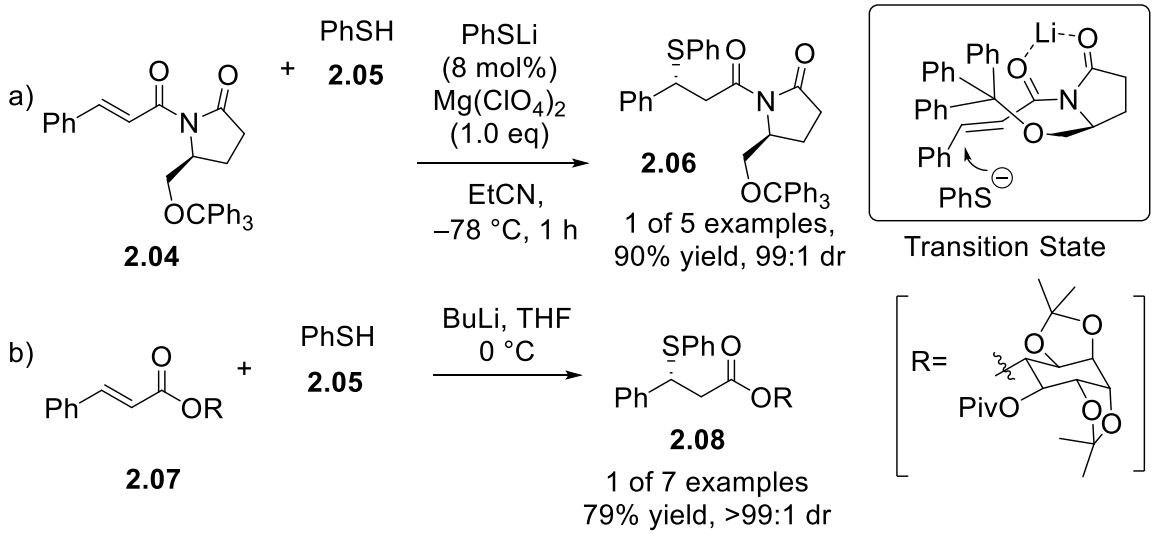
Scheme 2.01. Representatives of biologically significant molecules containing chiral sulfides.

2.2.2 SMA Reactions Catalysed by Metal Containing Catalyst Systems

Early SMAs were mainly catalysed by strong bases, and chiral auxiliaries attached to either thiol pronucleophile or electrophile were used for the induction of asymmetry at the β position of the conjugate adduct. For example, Tomioka[8] reported the synthesis of β-(phenylthio)carboxylate derivatives **2.06** using catalytic amount of lithium thiophenolate (PhSLi), accompanied by stoichiometric Lewis acid magnesium perchlorate and excess thiophenol (Scheme 2.02a). The lithium cation coordinates with the two carbonyl oxygens of **2.04** to form the *syn*-chelate.

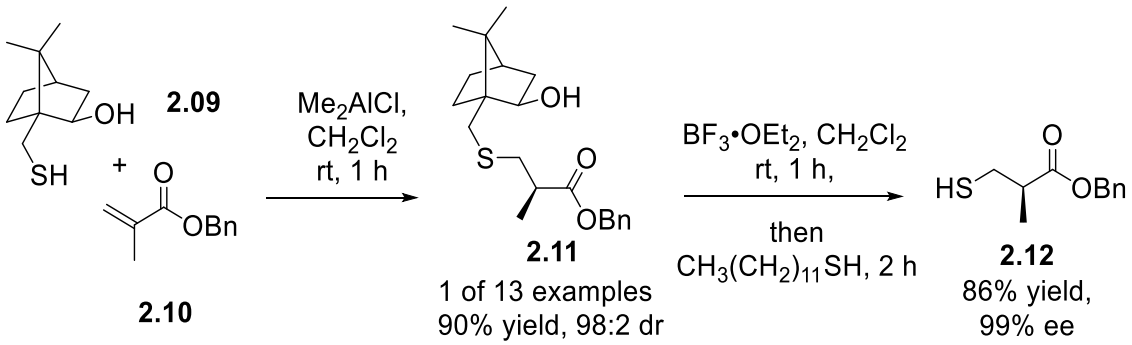
Lithium thiophenolate attacks preferentially from the *si*-face as the top face is blocked by the (trityloxy)methyl group attached to the pyrrolidinone (see transition state). Excellent yields and dr's were achieved in this reaction.

In addition, Hoberg[9] demonstrated the efficacy of inositol as a chiral template in the SMA of thiols to inositol cinnamate **2.07**, in the presence of BuLi (Scheme 2.02b). High levels of diastereocontrol were observed and further cleavage of the chiral auxiliaries gave rise to free carboxylic acid derivatives in high ee's.



Scheme 2.02. a) Diastereoselective SMA using chiral pyrrolidinone auxiliary; b) Diastereoselective SMA using inositol as chiral auxiliary.

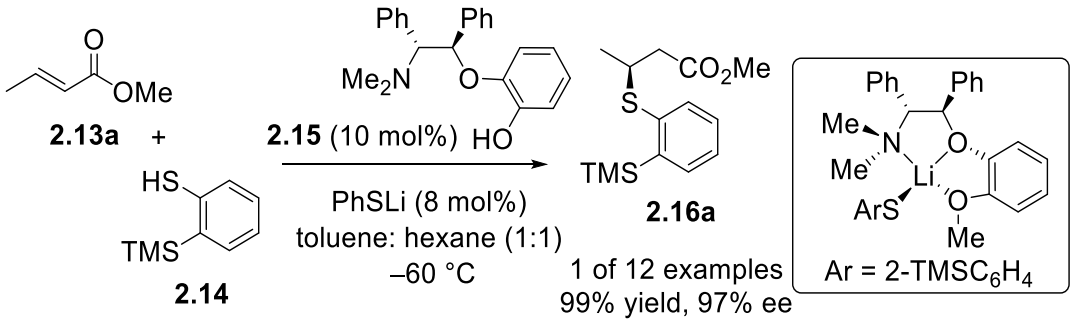
Asymmetric SMA could also be achieved using chiral thiols as the pronucleophiles. For example, Node[10] described dimethyl aluminium chloride promoted SMA using isoborneol-modified thiol pronucleophile **2.09**. The chiral auxiliary on sulfur was removed after the reaction *via* a boron trifluoride-diethyl etherate promoted Wagner-Meerwein rearrangement to provide β-thiocarbonyl products with good yields and maintained stereochemical information (Scheme 2.03).



Scheme 2.03. Chiral thiols acting as pronucleophiles in the SMA reaction.

Although high selectivities are achievable with chiral auxiliaries bound substrates, the reactions are not efficient in terms of atom economy, as at least an equal amount of chiral auxiliary is required for the reaction and removed after the reaction.

In 1997, Tomioka[11] presented the first highly enantioselective SMA of aryl thiols to simple unactivated α,β-unsaturated esters catalysed by lithium thiophenolate and chiral ligand **2.15**. It was postulated that the lithium cation coordinates with the chiral ligand to form a chiral chelate, that imparts asymmetry in the addition of thiol **2.14** to the substrate (Scheme 2.04).



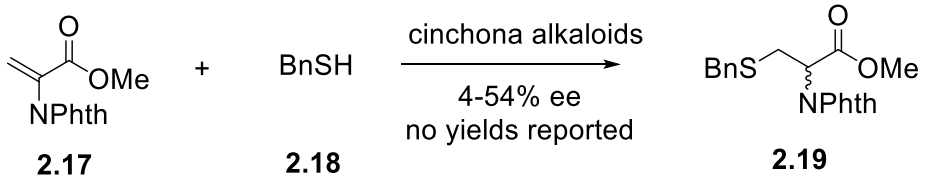
Scheme 2.04. SMA using lithium thiophenolate and chiral ligand.

The drawback of chiral auxiliary was overcome and simple α,β-unsaturated esters could be used for this reaction, although 2-(trimethylsilyl)thiophenol **2.14** was required as the pronucleophile to achieve high yield and enantioselectivity. On the

other hand, the use of thiophenol as pronucleophile only afforded the product in 71% ee. This is because 2-(trimethylsilyl)thiophenol **2.14** possesses the optimal size for the formation of the sterically defined monomeric chelated structure as shown above[11] (Scheme 2.04). In addition, it was necessary to perform the reactions at –60 °C for a period of 18 - 120 h to achieve high yields and enantioselectivities.

2.2.3 Organocatalytic Enantioselective SMA Reactions

The organocatalytic enantioselective SMA has also been studied extensively. The first organocatalytic enantioselective SMA was reported by Pracejus[12] in 1977, in which various cinchona alkaloids catalysed the addition between methyl α-phthalimidoacrylate **2.17** and benzyl thiol **2.18** (Scheme 2.05).

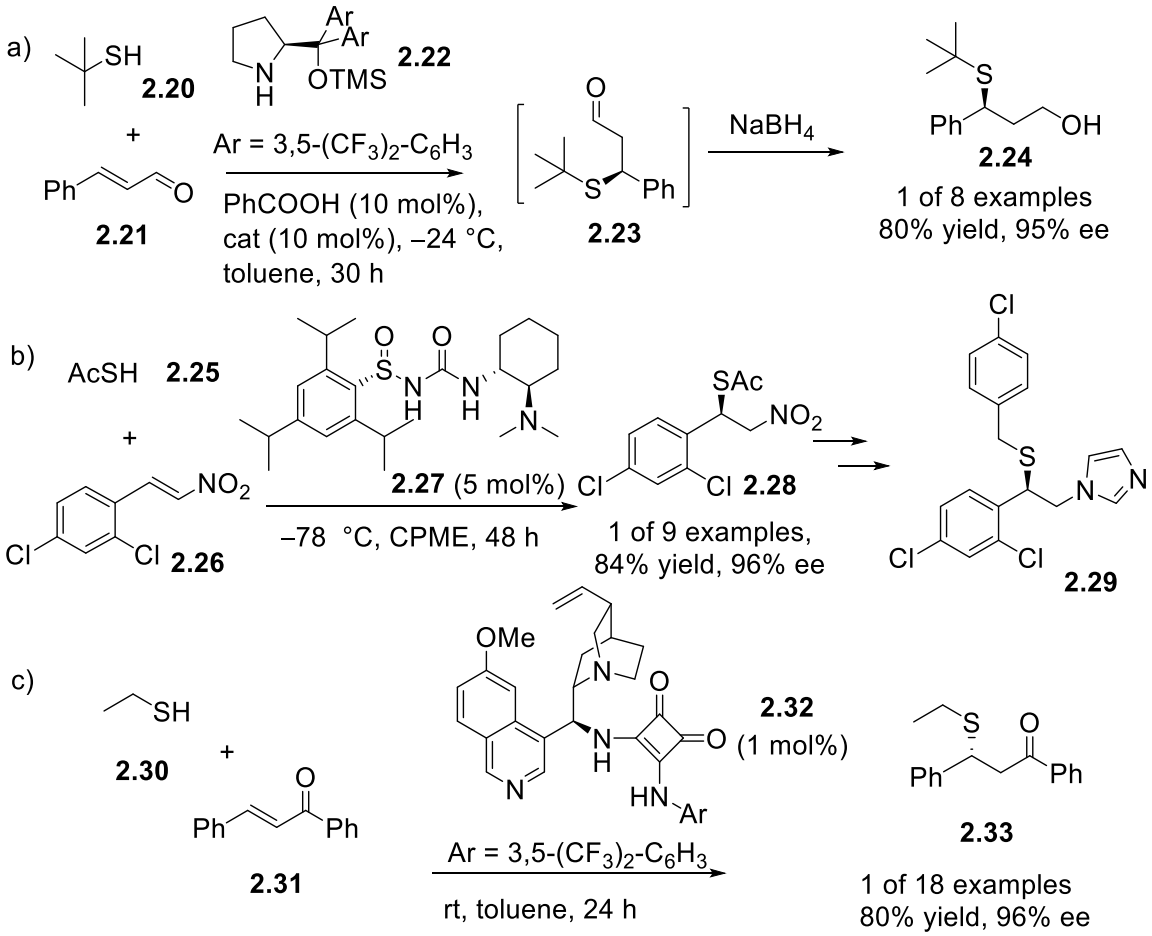


Scheme 2.05. First organocatalytic SMA reported by Pracejus.

In 2005, Jorgensen[13] reported an iminium ion promoted SMA of thiols to α,β-unsaturated aldehydes catalysed by diarylprolinol silyl ether catalyst **2.22**. The conjugate adducts were found to racemise rapidly. This could be prevented by either performing the reactions in the presence of an acid co-catalyst (PhCOOH) at low temperature (–24 °C) or by reducing the conjugate adducts *in situ* with sodium borohydride to give alcohols. Multicomponent 'domino' reactions were also introduced to make ring system by taking advantage of the reactive aldehyde (Scheme 2.06a).[14,15,16]

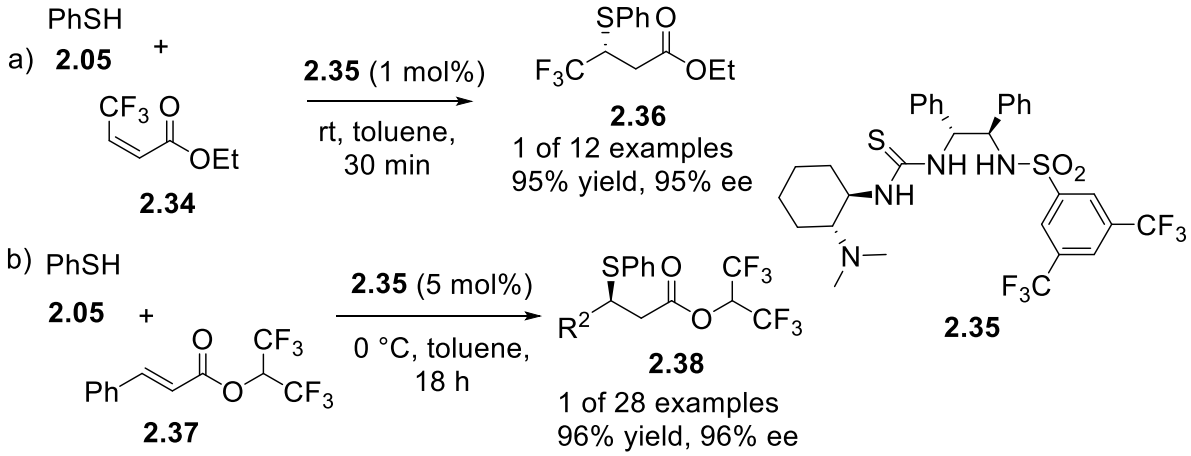
In 2009, Ellman[17] presented a sulfinyl urea organocatalyst **2.27** that promoted the first enantioselective SMA of thioacetic acid to nitroolefins in high yields and good to high enantioselectivities. Furthermore, the conjugate adduct bearing *o,p*-dichlorophenyl substituent was transformed to *(R)*-sulconazole **2.29**, an antifungul drug[18], in five steps with 96% ee (Scheme 2.06b).

Chen[19] described a bifunctional cinchona alkaloid squaramide catalyst **2.32** that promoted the SMA of aliphatic thiols to chalcone **2.31** in high yields and good to high enantioselectivities. When thiophenol was used as the pronucleophile, a higher reaction rate was observed, but lower enantioselectivity was achieved compared to aliphatic thiols (Scheme 2.06c).



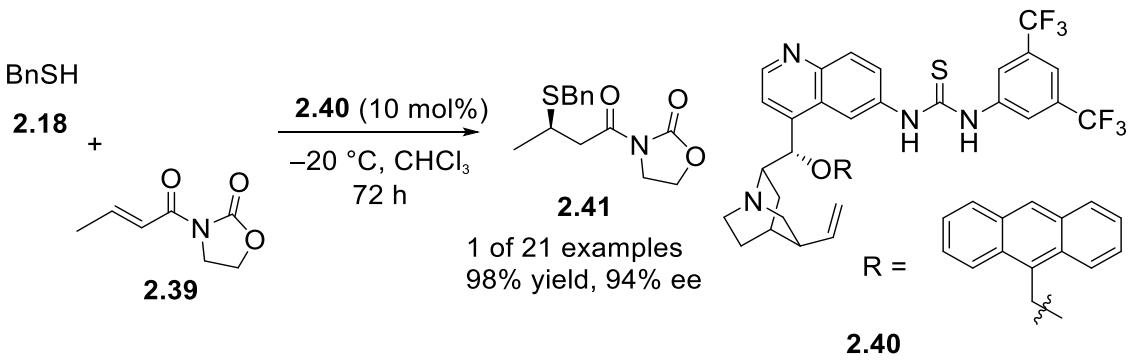
Scheme 2.06. a) SMA of thiols to α,β-unsaturated aldehydes; b) SMA of AcSH to nitroolefins; c) SMA of thiols to α,β-unsaturated ketones.

The SMA of thiols to activated β-substituted α,β-unsaturated esters has also been reported. Wang[20] described a tertiary amine-thiourea-sulfonamide catalyst **2.35** promoted highly enantioselective SMA of thiols to Z-configured 4,4,4-trifluorocrotonate[21] **2.34** (Scheme 2.07a). Interestingly, the use of E-configured substrate led to the formation of the opposite enantiomer with a lowered ee at 86%. The same group [22] later reported the SMA of thiols to α,β-unsaturated hexafluoroisopropyl esters **2.37** catalysed by **2.35** (Scheme 2.07b). In both cases, strongly electron withdrawing group CF_3 was incorporated into the α,β-unsaturated ester to make it more electrophilic, thus facilitating the SMA reaction.



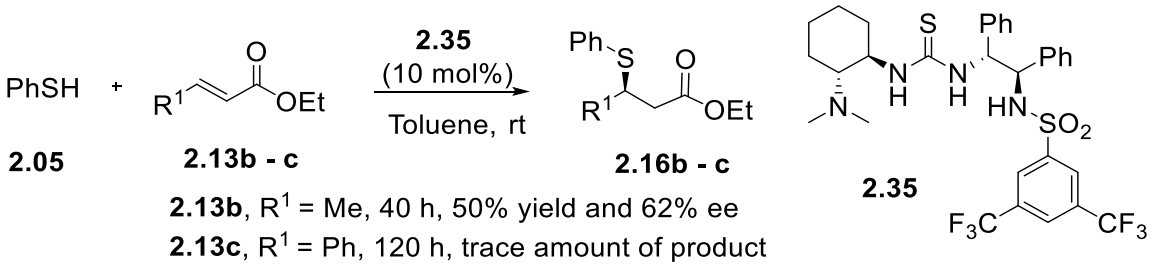
Scheme 2.07. a) SMA of thiols to Z-configured 4,4,4-trifluorocrotonate; b) SMA of thiols to α,β-unsaturated hexafluoroisopropyl esters.

The derivatives of β-substituted α,β-unsaturated ester has also been used as substrates for the SMA reaction. For instance, Deng[23] reported the SMA of thiols to α,β-unsaturated N-acylated oxazolidin-2-one **2.39**. The conjugate adducts were transformed to β-mercapto ester compounds in two steps (Scheme 2.08).



Scheme 2.08. SMA of thiols to α,β-unsaturated N-acylated oxazolidin-2-ones.

Although organocatalysts have achieved success on the SMA of thiols to reactive Michael acceptors, the use of unactivated β-substituted α,β-unsaturated esters remains a challenge. For instance, the reaction with unactivated crotonates, ethyl crotonate **2.13b** as an example, was slow and gave only 50% yield after 40 h and moderate enantioselectivity with tertiary amine-thiourea-sulfonylamide catalyst **2.35**.[20] The reaction was also carried out with ethyl cinnamate **2.13c** as electrophile and only trace amount of product was obtained after 120 h (Scheme 2.09).[22] Overall, the use of unactivated crotonate and cinnamate as electrophiles in SMA remains an unsolved problem.



Scheme 2.09. SMA of PhSH to ethyl crotonate and ethyl cinnamate catalysed by tertiary amine thiourea sulfonylamide catalyst 2.35.

2.3 Aims

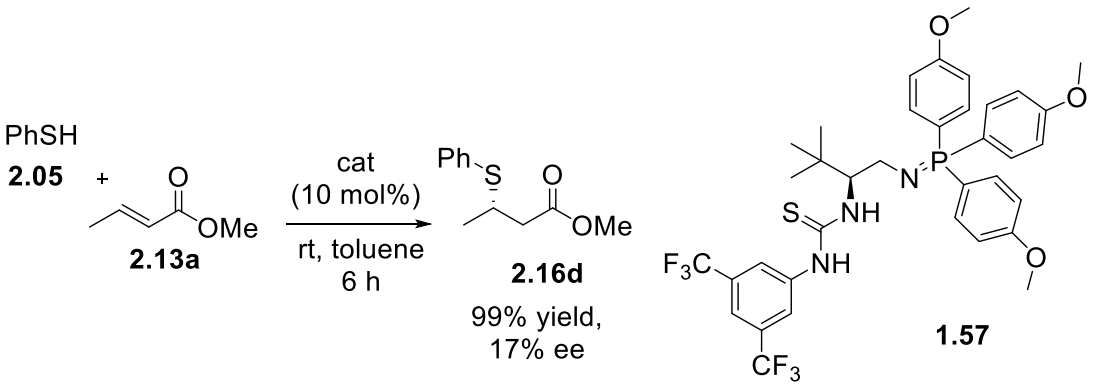
To the best of our knowledge, there is only one successful example of using unactivated β-substituted α,β-unsaturated esters as electrophiles in the SMA reactions. This reaction requires strong lithium base as the catalyst and the

reaction scope is limited to more acidic aryl thiols as oppose to less acidic aliphatic thiols (Scheme 2.04). In addition, there is no literature presence on the use of unactivated β-substituted α,β-unsaturated esters in the organocatalytic SMA reactions or any other Michael addition reactions. This is due to the low electrophilicity of such substrates. A proven strategy to overcome low substrate electrophilicity is to increase the concentration of the nucleophilic conjugate base in the pot – and therefore the rate of the nucleophilic addition reaction – by enhancing the Brønsted basicity of the catalyst to tertiary amine catalyst. We, therefore, envisaged that the reactivity issues with unactivated β-substituted α,β-unsaturated esters could be overcome using highly Brønsted basic BIMP catalysts (Chapter 1.3). The potential stereocontrol issues for this SMA reaction could be solved with fine tuning of each modular component of the existing BIMP catalyst.

2.4 Catalyst Development for the SMA Reaction

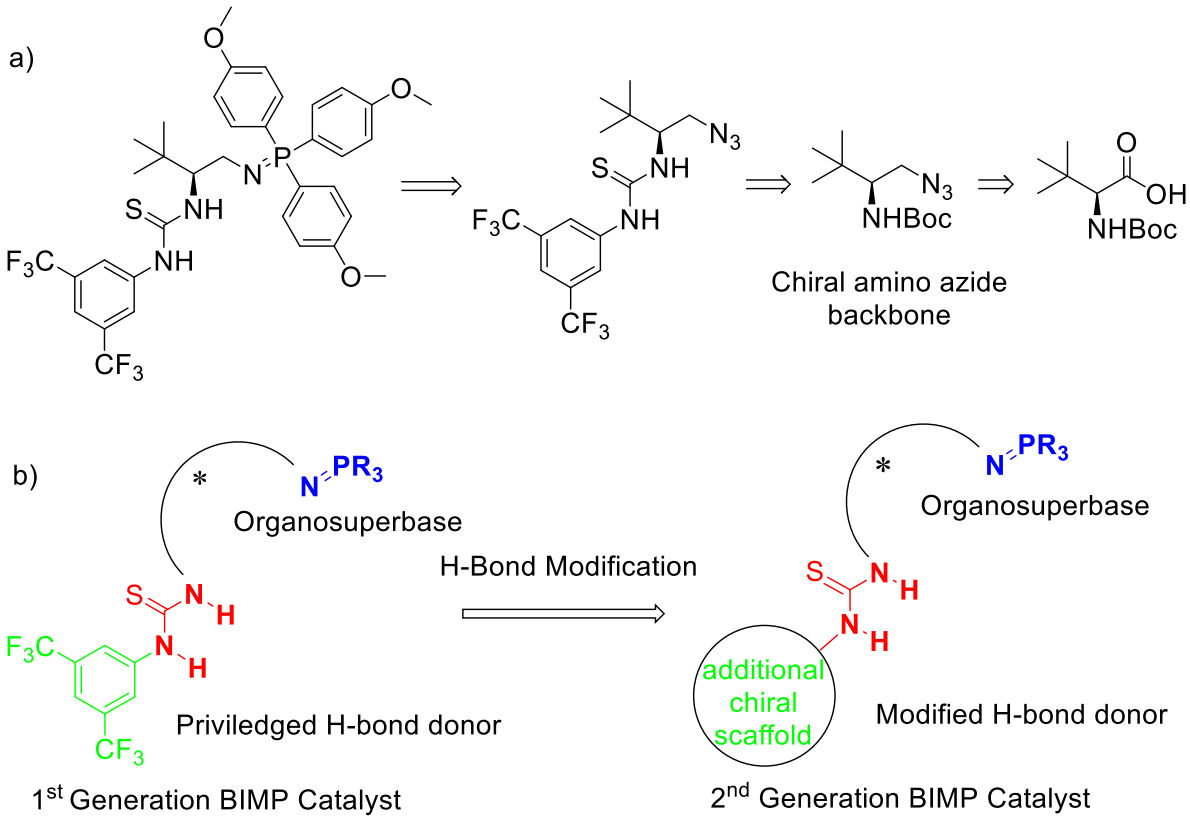
2.4.1 Proof of Principle and Concept of Catalyst Design

With the aims established, we set out to investigate the asymmetric SMA of thiols to unactivated β-substituted α,β-unsaturated ester with our BIMP catalysts. We first used BIMP catalyst **1.57** (chapter 1) for the SMA of thiophenol to methyl crotonate. To our delight, the reaction went to completion within 6 h, furthermore the ee was low, but significant at 17% (Scheme 2.10).



Scheme 2.10. SMA of thiophenol to methyl crotonate with BIMP catalyst 1.57. *The reaction was performed using 0.2 mmol methyl crotonate, 0.6 mmol PhSH and 10 mol% catalyst in 0.4 mL toluene.*

The BIMP catalyst can be prepared in one step from its catalyst precursor *via* the Staudinger reaction.[24,25] The catalyst precursor can be synthesised *via* a thiourea coupling using amino azide and isothiocyanate. The chiral amino azide backbone is derived from the corresponding amino acid, which have been used as chiral backbone for other organocatalysts (Scheme 2.11a).[26,27]

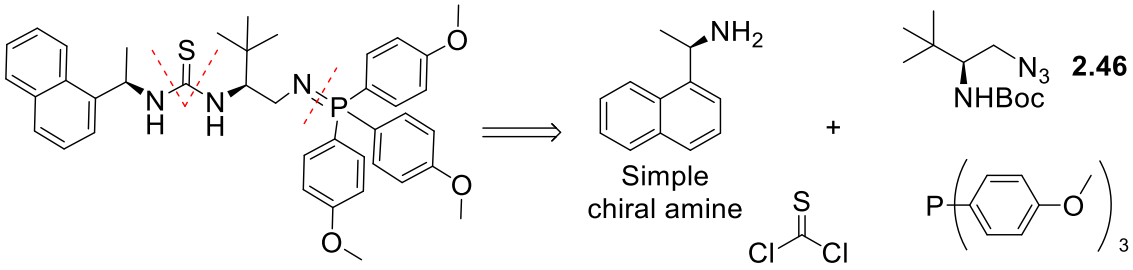


Scheme 2.11. a) Retrosynthesis of 1st generation BIMP catalyst; b) The conceptual design of 2nd generation BIMP catalyst.

As the chiral amino azide backbone and iminophosphorane moiety have demonstrated good reactivity and selectivity in the previous research conducted in our group[28], we decided to modify the BIMP catalyst by replacing the simple aryl thiourea with an additional chiral scaffold in order to achieve high enantiocontrol (Scheme 2.11b).

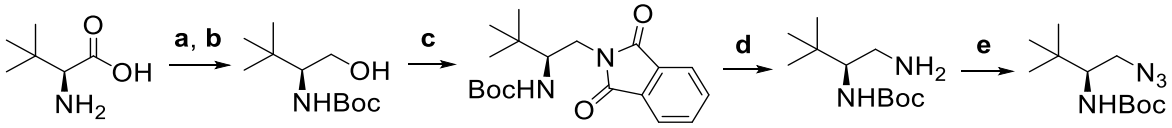
2.4.2 BIMP Catalysts with Simple Chiral Amine as the Additional Chiral Scaffold

Initially, we developed a series of catalysts that has one stereogenic centre on each side of the thiourea, with the hypothesis that the presence of an additional chiral centre next to the thiourea could enhance the enantioselectivity of the reaction (Scheme 2.12).



Scheme 2.12. Structure elucidation and retrosynthesis of BIMP catalyst with simple chiral amine as the additional chiral scaffold.

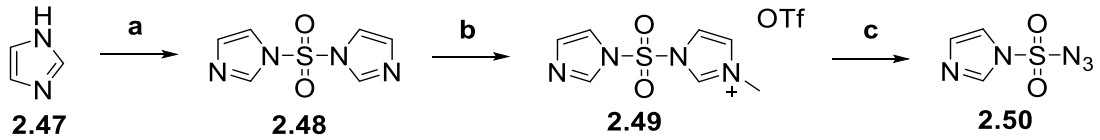
Both enantiomers of 1-(1-naphthyl) ethylamine and 3,3-dimethyl-2-butylamine were chosen as the additional chiral scaffold. *L-tert*-leucine derived N-Boc protected amino azide **2.46** was selected as the chiral backbone and $P(PMP)_3$ was used in the iminophosphorane moiety as they have demonstrated good enantiocontrol in the previous research conducted in our group.[28] A representative catalyst structure with *(R)*-1-(1-naphthyl)ethylamine as the additional chiral scaffold is shown above (Scheme 2.12).



2.42 **2.43** **2.44** **2.45** **2.46**

Scheme 2.13. Synthesis of *L-tert*-leucine amino azide. *a) $NaBH_4$ (2.4 eq), I_2 (1.0 eq), THF, 0 °C to reflux; b) Boc_2O (1.18 eq), NEt_3 (1.18 eq), CH_2Cl_2, overnight, 68% over two steps; c) DIAD (1.1 eq), PPh_3 (1.0 eq), phthalimide (1.0 eq), overnight, 80% yield; d) $N_2H_4.H_2O$ (1.5 eq), H_2O, EtOH, reflux, 2.5 h, 99% yield; e)* ***2.50*** *(1.2 eq), K_2CO_3 (1.8 eq), MeOH, overnight, 61% yield.*

The synthesis of *L-tert*-leucine derived Boc-amino azide **2.46** was first carried out and is shown above (Scheme 2.13). The amino azide **2.46** was synthesised from *L-tert*-leucine **2.42** in five steps. The amino acid was first reduced to amino alcohol, which was subsequently treated with $(Boc)_2O$ to give N-Boc protected amino alcohol **2.43** in 68% yield over two steps. This amino alcohol then underwent Mitsunobu reaction to substitute the hydroxyl group with phthalimide to afford **2.44** in 80% yield. The phthalimide protecting group was then removed by treatment with hydrazine monohydrate to give the free amine **2.45** in 99% yield. Treatment of the free amine with diazotransfer reagent[29] **2.50** afforded the amino azide **2.46** in 61% yield.

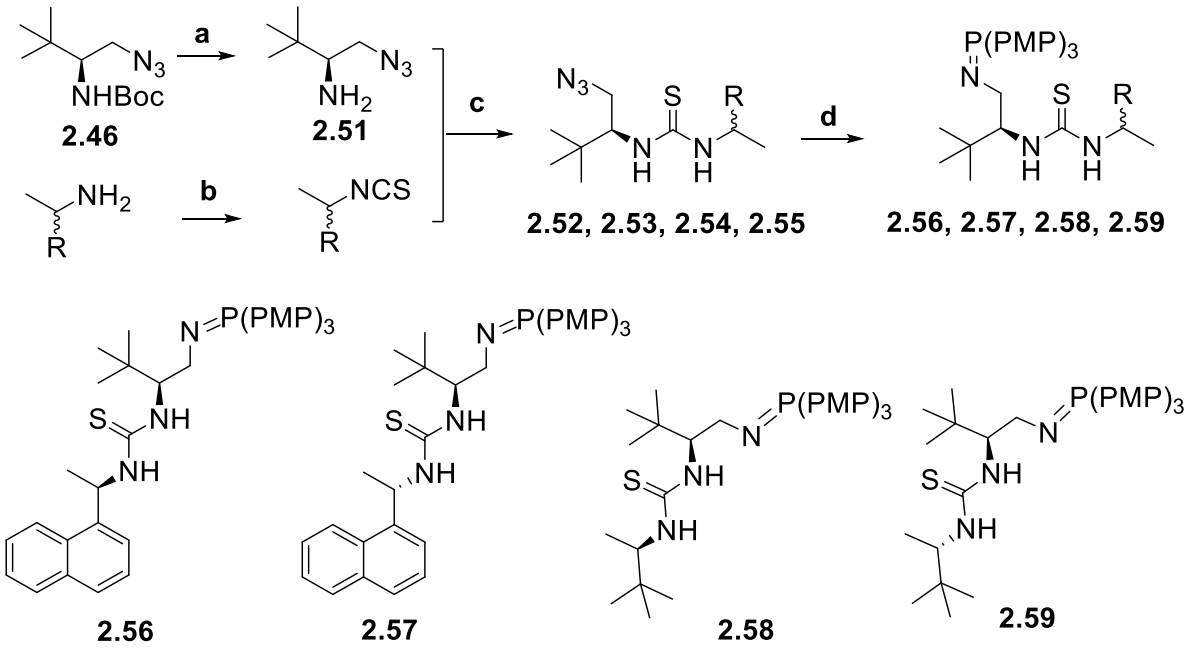


2.47 **2.48** **2.49** **2.50**

Scheme 2.14. Synthesis of diazotransfer reagent. *a) SO_2Cl_2 (1.0 eq), CH_2Cl_2, 0 °C to rt then overnight, 80% yield; b) MeOTf (0.9 eq), CH_2Cl_2, 0 °C, 2.5 h; c) NaN_3 (1.2 eq), H_2O, EtOAc, 0 °C, 2 h;*

The diazotransfer reagent was synthesized in three steps[29] (Scheme 2.14). Initial treatment of imidazole **2.47** with sulfuryl chloride afforded sulfuryl imidazole **2.48** in 80% yield. A subsequent treatment of sulfuryl imidazole **2.48** with methyl triflate afforded the triflate salt **2.49**, which was then reacted with NaN_3 to give the diazotransfer reagent **2.50**. It is a potentially explosive compound, and was used

in situ for the diazotransfer reaction.[30]



Scheme 2.15. Synthesis of BIMP catalysts with simple chiral amine as the additional chiral scaffold. *a) TFA, 0 °C to rt; b) $CSCl_2$ (2 eq), CH_2Cl_2: THF: sat aq. $NaHCO_3$ 10:1:10, 0 °C to rt, 2 h; c) isothiocyanate (1.0 eq), deprotected azide (1.1 eq), Et_2O, overnight, 56-79% over two steps; d) $P(PMP)_3$, Et_2O.*

The synthesis of BIMP catalysts was then carried out (Scheme 2.15). Both enantiomers of 1-(1-naphthyl) ethylamine and 3,3-dimethyl-2-butylamine were first reacted with thiophosgene in a biphasic solvent mixture to give the corresponding isothiocyanate derivatives, which were subsequently treated with the free amine **2.51** to give catalyst precursors **2.52**, **2.53**, **2.54**, **2.55** in 56 - 79% yield. Treatment of the catalyst precursors with $P(PMP)_3$ afforded the iminophosphoranes **2.56**, **2.57**, **2.58**, **2.59**. These catalysts were used *in situ* in the SMA of thiophenol to methyl crotonate (Table 2.1).

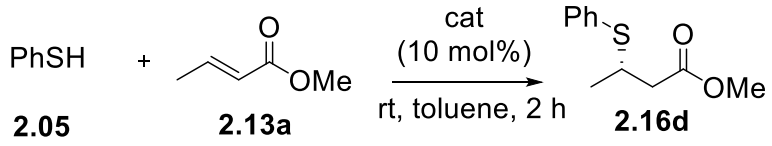


Table 2.1 SMA of PhSH to methyl crotonate

Entry[a]	catalyst	yield (%)	ee (%)
1	**2.56**	93	37
2	**2.57**	95	27
3	**2.58**	>99	32
4	**2.59**	>99	27

*a) Reactions were conducted using **2.13a** (0.2 mmol), **2.05** (0.6 mmol) and 10 mol% catalyst (0.02 mmol) in toluene (0.4 mL).*

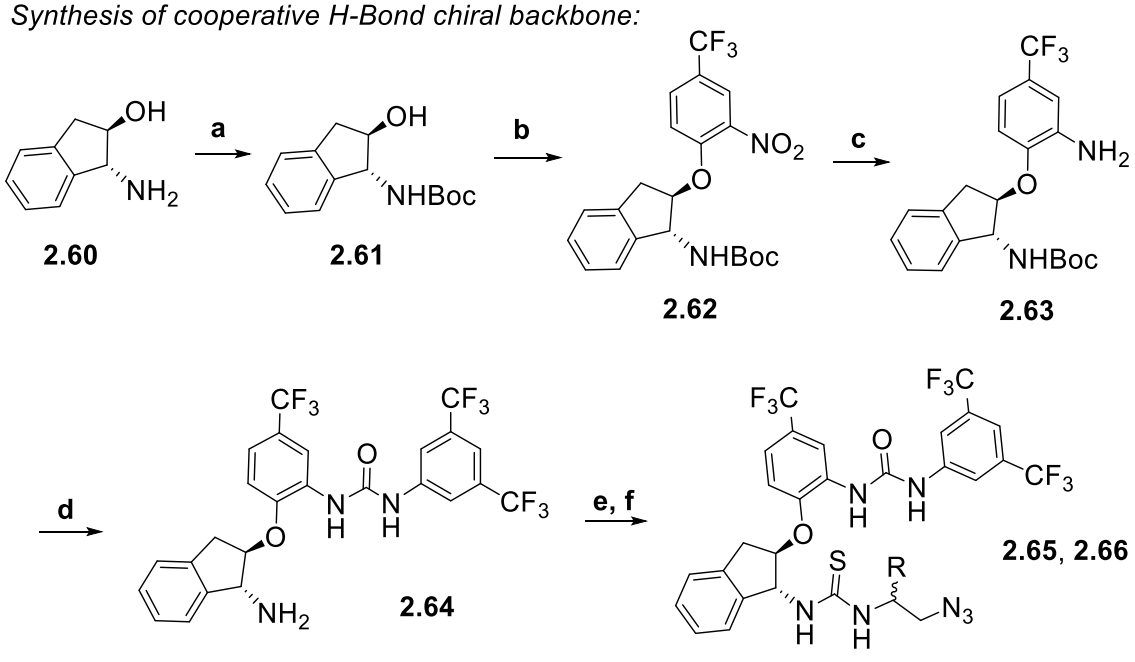
Although the reactivities of these catalysts were excellent, the enantioselectivities were generally low, ranging from 27% to 37% ee. The results obtained in the reactions catalysed by **2.56** and **2.58** showed that *(R)*-naphthylethylamine was slightly better than *(R)*-dimethyl-2-butylamine in terms of stereoselectivity (Table 2.1, entry 1 vs 3). However, the same ee's of the products obtained from the reactions catalysed by **2.57** and **2.59** (derived from *(S)*-naphthylethylamine and *(S)*-dimethyl-2-butylamine) showed there was no difference between these two chiral amine groups (Table 2.1, entry 2 vs 4). In addition, the reactions catalysed by the two pairs of diastereomers, i.e. **2.56** and **2.57**, **2.58** and **2.59**, gave the same major enantiomer and similar ee's, indicating that the simple chiral amine group on the catalyst has little effect in determining the stereochemical configuration of the final product (Table 2.1, entry 1 vs 2, entry 3 vs 4).

2.4.3 BIMP Catalysts with Cooperative H-Bond Donor as the Additional Chiral Scaffold

In the meantime, another series of BIMP catalysts possessing a cooperative H-bond donor scaffold were synthesised. The idea for the series of catalysts was to

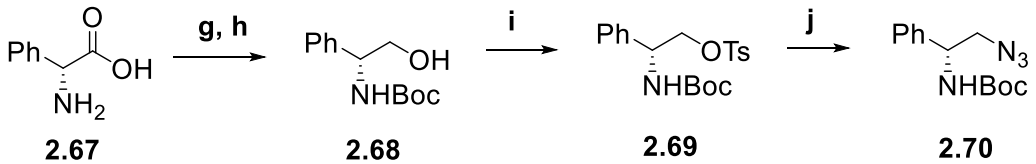
have both urea and thiourea moieties in the catalyst, in which the hydrogens of the urea could establish hydrogen bonds with the sulfur of the thiourea (see structures **2.65** and **2.66**). Smith[31] has demonstrated that hydrogens on the thiourea of this type of cooperative H-bond donor catalyst can make stronger hydrogen bonds to the substrate and increase the enantiocontrol over the reaction than an isolated thiourea does. Pihko[32] has later verified such cooperative binding in the catalyst by X-ray evidence. We envisaged that the incorporation of this conformationally well-defined chiral H-bond donor scaffold to BIMP catalysts might increase the enantiocontrol over the reaction. The synthesis of the catalysts precursors is shown below (Scheme 2.16).

Synthesis of cooperative H-Bond chiral backbone:



2.60 **2.61** **2.62** **2.63** **2.64** **2.65**, **2.66**

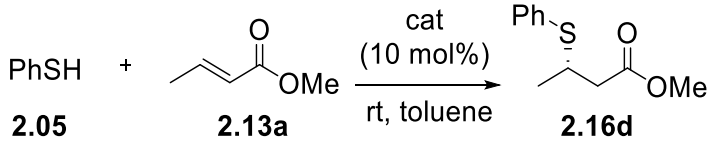
Synthesis of amino aizde derived from D-phenylglycine:



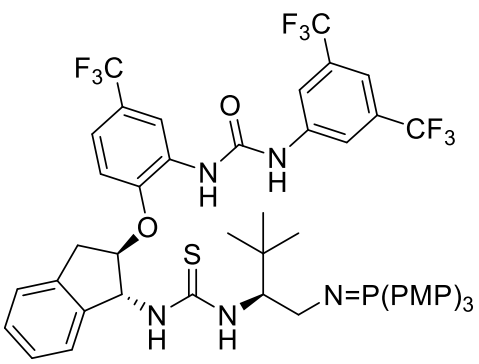
2.67 **2.68** **2.69** **2.70**

Scheme 2.16. Synthesis of BIMP catalysts with cooperative H-bond donor as the additional chiral scaffold. *a) $(Boc)_2O$ (1.3 eq), Na_2CO_3 (2.6 eq), THF: H_2O (7:3), overnight, 96%; b) 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (3 eq), LiHMDS (1.2 eq), THF, –40 °C to rt, 4 h, 96%; c) H_2, Pd/C, EtOAc, overnight, >99%; d) 3,5-Bis(trifluoromethyl)phenyl isocyanate (1.2 eq), THF, 45 min, then TFA, overnight, 93% over two steps; e) $CSCl_2$ (2 eq), CH_2Cl_2: THF: sat aq. $NaHCO_3$ 10: 1: 10, 0 °C to rt, 2 h; f) Boc-deprotected azides (1.1 eq), Et_2O, overnight, 67 - 77% over two steps. g) $NaBH_4$ (2.4 eq), I_2 (1.0 eq), THF, 0 °C to reflux; h) Boc_2O (1.18 eq), NEt_3 (1.18 eq), CH_2Cl_2, overnight, 38% over two steps; i) TsCl (1.1 eq), Et_3N (2.0 eq), CH_2Cl_2, overnight, 69% yield; j) NaN_3 (1.1 eq), DMF, 45 °C, overnight, 76% yield.*

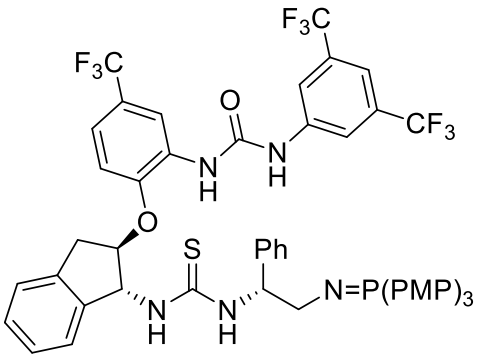
1,2-Amino alcohol **2.60** was N-Boc protected (96% yield) and then reacted with 1-fluoro-2-nitro-4-(trifluoromethyl)benzene to form **2.62** in 96% yield. The nitro group of **2.62** was then reduced to the free amine by hydrogenation in over 99% yield. This compound was then reacted with an isocyanate to generate the urea, which was subsequently Boc deprotected to give the chiral urea amine **2.64** in 93% yield over two steps. In parallel, we prepared amino azides **2.70**. *D*-phenyl glycine **2.67** underwent standard carboxylic acid reduction and Boc protection to give **2.68** in 38% yield over two steps. The hydroxyl group on **2.68** was then tosylated (69% yield) and substituted by azide (76% yield) to give the amino azide **2.70**. Finally, previously prepared chiral urea amine **2.64** was treated with $CSCl_2$ to give the corresponding isothiocyanates, which were subsequently treated with the N-Boc deprotected forms of amino azides **2.46** and **2.70** to afford catalyst precursors **2.65** and **2.66** (Scheme 2.16).



2.05 **2.13a** **2.16d**



2.71
>99% yield, 21% ee



2.72
94% yield, -27% ee

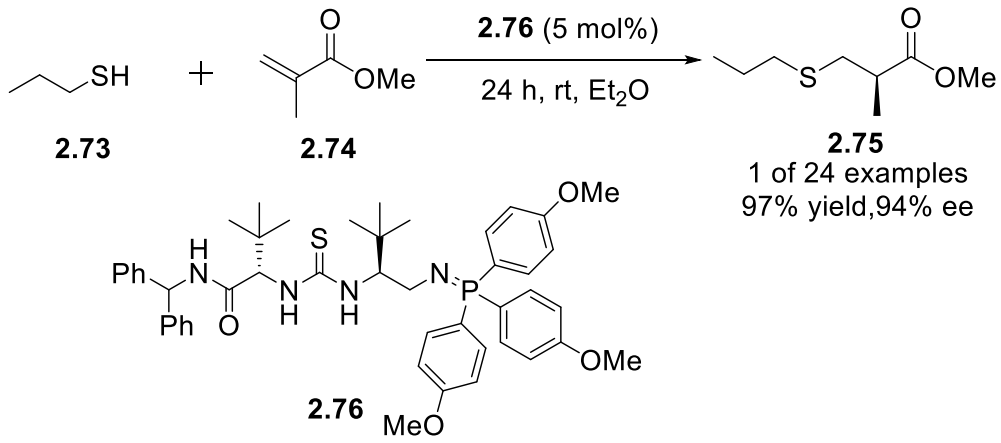
Scheme 2.17. SMA of PhSH to methyl crotonate catalysed by BIMP catalysts with cooperative H-bond donor as additional chiral scaffold. *Reactions were performed using **2.13a** (0.2 mmol), **2.05** (0.6 mmol) and 10 mol% catalyst (0.02 mmol) in toluene (0.4 mL) at rt. Ee's were determined by HPLC analysis on a chiral stationary phase.*

The catalysts **2.71** and **2.72** were generated from catalyst precursors via Staudinger reaction with $P(PMP)_3$ and used *in situ* for the SMA of thiophenol to methyl crotonate and the results are shown above (Scheme 2.17). Both reactions were finished within 24 h and afforded the products in good yields. The reaction promoted by catalyst **2.71** gave the product in 21% ee, while catalyst **2.72** gave the product in 27% ee with the opposite major enantiomer obtained. This slight increase of ee from 21% to 27% attracted our attention as *L-tert*-leucine derived azide had proved to be the best catalyst scaffold in the previous nitro-Mannich reaction.[28] The change in the major enantiomer of these reactions corresponds to the change in the stereochemical configuration of the amino azide moiety, suggesting that the amino azide moiety is dominant in determining the stereochemical configuration of the product.

2.4.4 BIMP Catalyst with Amido-Thiourea H-Bond Donor as the Additional Chiral Scaffold

2.4.4.1 Proof of Principle and Catalyst Synthesis

The Dixon group has recently developed BIMP catalyst **2.76** for the SMA of alkyl thiols to α-substituted α,β-unsaturated esters with excellent yields and enantioselectivities (Scheme 2.18).[33]

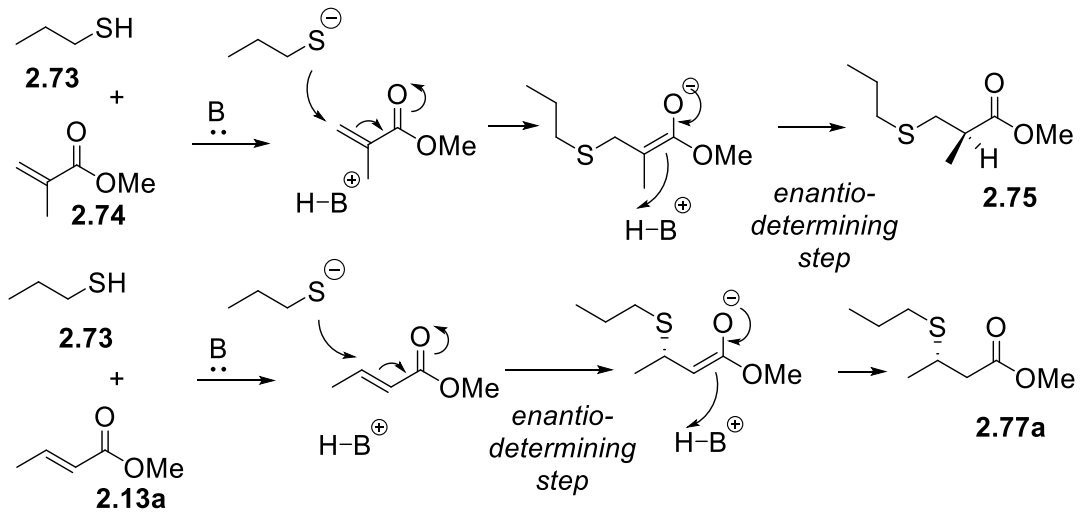


Scheme 2.18. Organocatalytic asymmetric sulfa-Michael/enantioselective protonation sequence. *Reactions were performed using **2.73** (0.2 mmol), **2.74** (1.0 mmol) and 10 mol% catalyst **2.76** (0.02 mmol) in Et_2O (0.4 mL) at rt.*

Based on the precedent, we examined catalyst **2.76** in our model reaction of thiophenol and methyl crotonate. After 3 h, the product was obtained in 50% yield[iii] and a disappointing 17% ee. At first glance, the SMA reactions using methacrylate and crotonate as electrophiles are very similar, these two reactions go through different reaction pathways and enantiodetermining steps to generate the final product. We propose that the SMA of 1-propanethiol **2.73** to methyl methacrylate **2.74** proceeds *via* non-selective conjugate attack by thiol at the β-position followed by enantioselective protonation to give the chiral product. In parallel, we postulate

[iii] Incomplete reaction

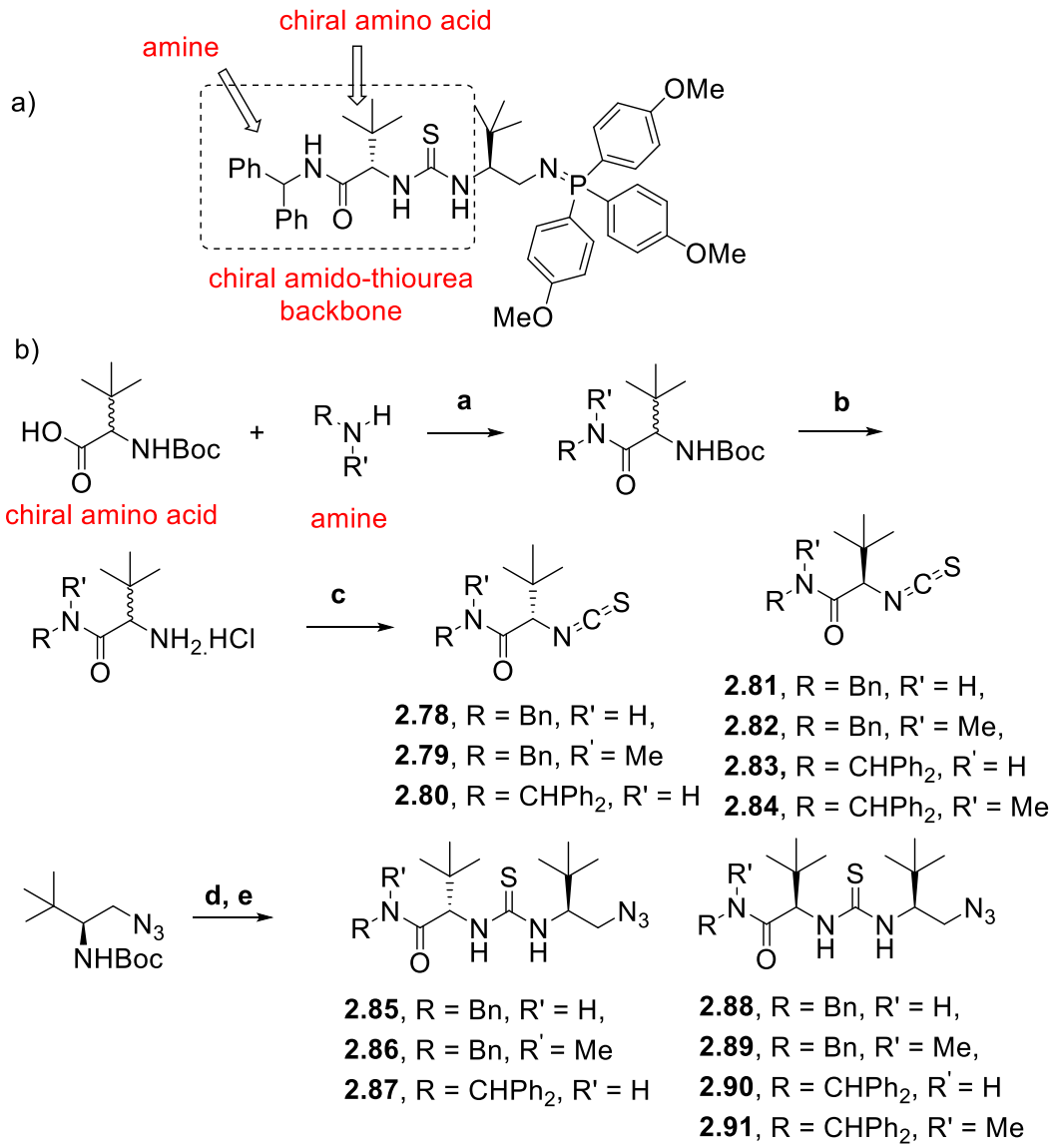
that the SMA of 1-propanethiol **2.73** to methyl crotonate **2.13a** proceeds *via* direct enantiodetermining conjugate attack by thiol to give chiral β-thiol enolate followed by non-enantiodetermining protonation to give the final product (Scheme 2.19).[34] In summary, the differences in the reaction pathways and enantiodetermining steps lead to the low ee in our first attempt.



Scheme 2.19. Representation of the stepwise mechanism of the SMA of 1-propanethiol to methyl methacrylate and methyl crotonate.

Although enantioselectivity was poor, reactivity of this reaction was promising based on this new generation of catalysts and we decided to further develop these catalysts. This family of catalysts was built on the Jacobsen's chiral amido thiourea scaffold consisting of an amine and a chiral amino acid linked by an amide bond (Scheme 2.20a). The *tert*-leucine had been proved to be superior in giving high stereoselectivity in the pioneering work by Jacobsen.[35,36,37] We thus decided to introduce different amines to the *tert* leucine amido-thiourea backbone, including benzylamine, benzylmethyl amine and benzhydryl amine, to form isothiocyanates **2.78**, **2.79** and **2.80** (Scheme 2.20b). These isothiocyanates were then reacted with *L-tert*-leucine derived amino azide **2.51** to form catalyst precursors **2.85**, **2.86**

and **2.87**. *D-tert*-Leucine was also used for the formation of isothiocyanates **2.81** to **2.84**, which were then reacted with amino azide **2.51** to give catalyst precursors **2.88** to **2.91**.



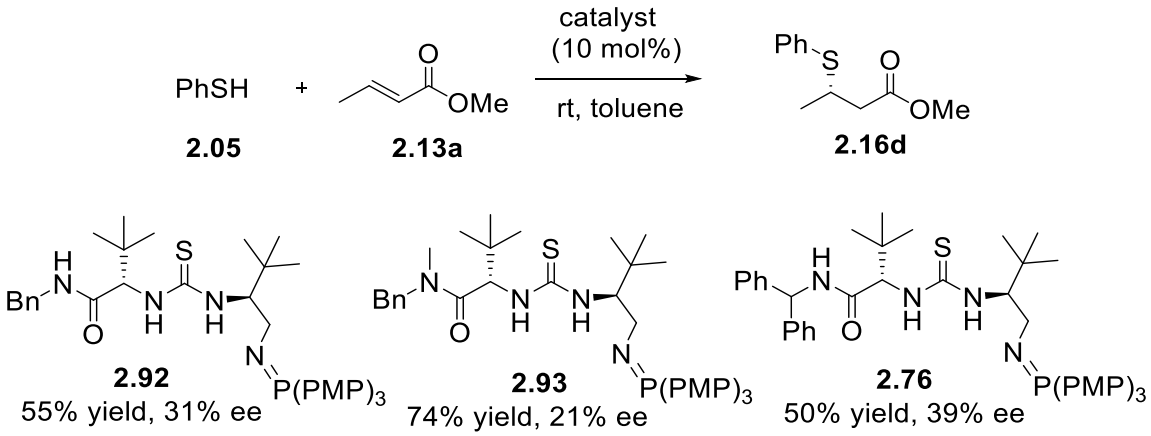
Scheme 2.20. Structure elucidation and synthesis of chiral amino-thiourea H-bond donor catalyst precursors. *a) EDC·HCl (1.1 eq), HOBt (1.1 eq), DIEA (1.5 eq), CH_2Cl_2, rt, overnight; b) 4N HCl (in 1,4-dioxane, 9.6 eq), CH_2Cl_2, rt, 4 h; c) $CSCl_2$ (1.5 eq), sat. aq. $NaHCO_3$ and CH_2Cl_2, 0 °C to rt, 23-95% over 3 steps; d) TFA, 0 °C to rt; e)* isothiocyanates*, Et_2O, 0 °C to rt, 55-69% yield.*

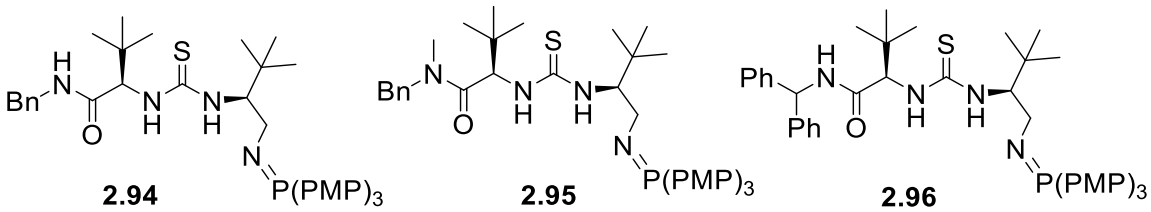
The detailed synthesis of the chiral amido-thiourea H-bond donor catalysts followed the strategy outlined in Scheme 2.20. According to a procedure

developed by Jacobsen,[38] amide coupling of benzhydryl amine and *N*-Boc-*tert*-leucine, *N*-Boc deprotection and treatment of the amine with thiophosgene afforded the isothiocyanates in 23-95% yield over three steps on gram scale. Addition of amino azide **2.51** to the isothiocyanate afforded the catalyst precursors in 55 - 69% yields (Scheme 2.20b).

2.4.4.2 Catalyst Design and Optimisation

BIMP catalysts were prepared from their catalyst precursors *via* Staudinger reaction with $P(PMP)_3$ and used *in situ* for the SMA of thiophenol to methyl crotonate (Scheme 2.21). The reactions catalysed by **2.92**, **2.93** and **2.76** were quenched after fixed time and the reactions catalysed by **2.94**, **2.95** and **2.96** were left to completion and gave excellent yields. Catalysts **2.92**, **2.93** and **2.76** bearing (*R*, *R*)-stereocentres on distal and proximal positions of thiourea gave similar ee's compared with their diastereomers **2.94**, **2.95** and **2.96**. The best enantiocontrol (41% ee) was obtained when catalyst **2.95** was used.





2.94 91% yield, 19% ee

2.95 90% yield, 41% ee

2.96 93% yield, 33% ee

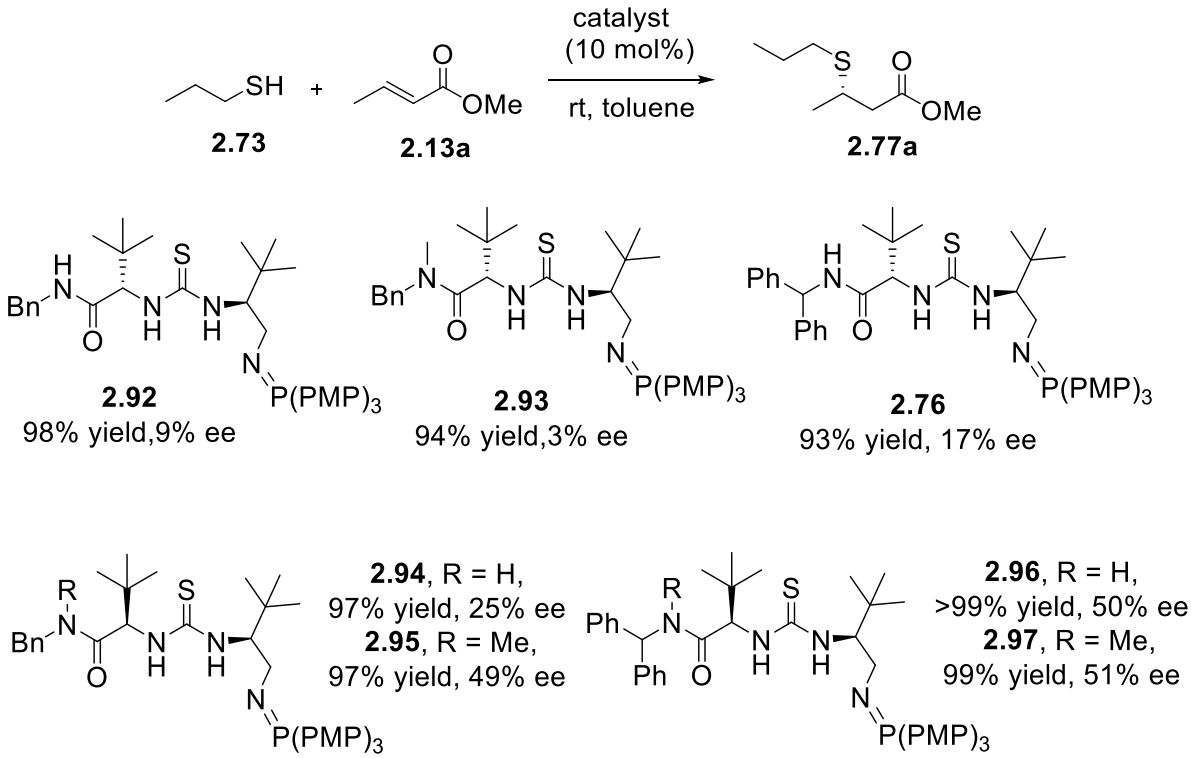
Scheme 2.21. SMA of PhSH and methyl crotonate catalysed by amido-thiourea BIMP catalysts. *Reactions were performed using 2.13a (0.2 mmol), 2.05 (0.6 mmol) and 10 mol% catalyst (0.02 mmol) in toluene (0.4 mL) at rt.*

We then performed a full catalyst screen on the SMA of 1-propanethiol to methyl crotonate (Scheme 2.22), and all the reactions were finished after 2 hours, faster than those reactions using thiophenol[iv]. These results have attracted our attention as thiophenol is more acidic than 1-propanethiol, and one would assume that SMA using thiophenol as pronucleophile would be faster than 1-propanethiol. The reasons for this interesting result are discussed later in the proposed reaction mechanism section. Catalysts, **2.92**, **2.93** and **2.76** generally afforded the products in poor ee's for this reaction. Catalysts **2.94**, **2.95** and **2.96** gave rise to products with better ee's than their diastereomers. The catalyst **2.95** with a distal tertiary amide group, gave conjugate adduct **2.77a** in 49% ee, which is higher than that of catalyst **2.94**, which bears a distal benzyl amine derived secondary amide group. Catalyst **2.96** bearing a distal benzhydryl secondary amide, also performed better than **2.94**, giving conjugate adduct **2.77a** in 50% ee. Therefore, catalyst **2.97** bearing a benzhydryl tertiary amide group was synthesised and tested in the reaction. To our disappointment, the product was obtained in only 51% ee, which

[iv] The SMA of 1-propnethiol to methyl crotonate catalysed by **2.101** was also performed using 1.5 eq 1-propanethol and took 6 h to complete. We therefore, decided to use 3.0 eq thiol for the reaction.

was comparable to the outcomes with catalysts **2.95** and **2.96**.

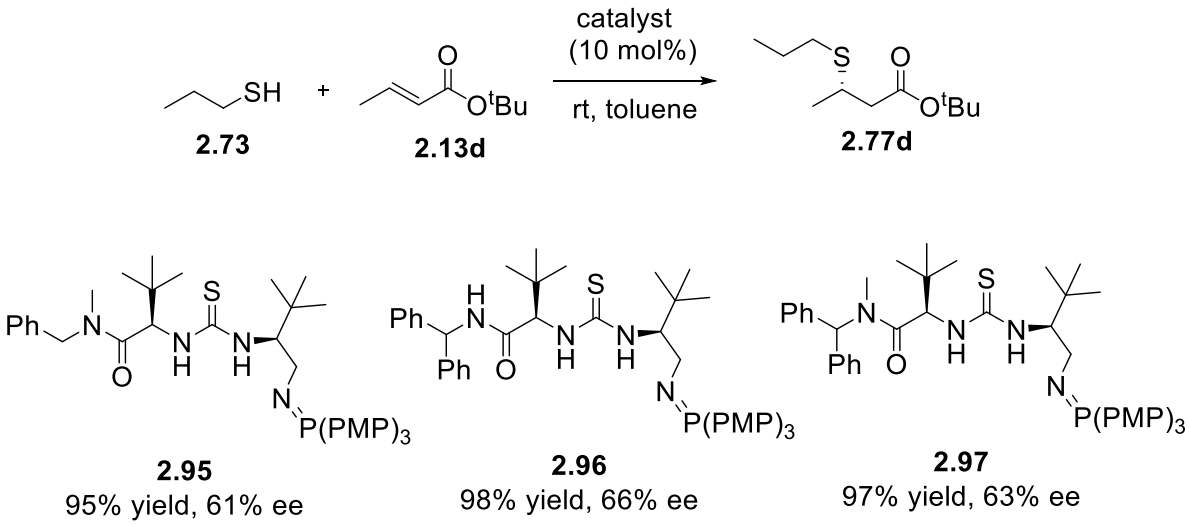
As a control experiment, we also performed this reaction using cinchona alkaloid derived bifunctional organocatalyst **1.25**; however, no reaction was observed after 168 h.



Scheme 2.22. SMA of 1-propanethiol and methyl coronate catalysed by amido-thiourea BIMP catalysts. *Reactions were performed using **2.13a** (0.2 mmol), **2.73** (0.6 mmol) and 10 mol% catalyst (0.02 mmol) in toluene (0.4 mL) at rt.*

Next, we turned our interest to the modification of the electrophile. *tert*-Butyl esters have shown better selectivities than methyl esters in some asymmetric reactions,[39,40] hence, our previously best catalysts **2.95**, **2.96**, **2.97** were tested for the SMA of 1-propanethiol to commercially available *tert*-butyl crotonate **2.13d** (Scheme 2.23). The reactions catalysed by **2.95** and **2.97** gave 61% ee and 63% ee and the reaction catalysed by **2.96** gave 66% ee, the highest ee to date. The reaction time had to be increased to 6 h, presumably due to increased steric interactions associated with the bulky *tert*-butyl ester on the electrophile (*vide infra*

for the transition state model). (Scheme 2.23)



Scheme 2.23. SMA of 1-propanethiol and *tert*-butyl crotonate. *Reactions were performed using tert-butyl crotonate **2.13d** (0.2 mmol), 1-propanethiol **2.74** (0.6 mmol) and 10 mol% catalyst (0.02 mmol) in toluene (0.4 mL) at rt.*

With these promising results in hand, we decided to perform a conditions screening (Table 2.2). Keeping all other conditions the same, the concentration of the reaction was decreased to 0.1 M from 0.5 M, and pleasingly, 96% yield and 75% ee was obtained, albeit with an increase in reaction time from 6 h to 24 h (Table 2.2, entry 2). A further decrease in concentration to 0.05 M decreased the reactivity significantly, giving 52% yield after 96 h and a disappointingly decreased ee of 61% (Table 2.2, entry 3). Next, we investigated the temperature effect on this reaction. Keeping a concentration of 0.5 M, temperature was decreased to 0 °C. A longer reaction time (18 h) and same ee (66%) were observed compared to room temperature example (Table 2.2, entry 1 vs 4). We then increased the reaction temperature to 40 °C. At 0.1 M concentration, the reaction gave a decreased yield of 65% and an eroded 69% ee compared to room temperature example (Table 2.2, entry 2 vs 5). Preliminary results showed room temperature

was the optimal temperature for the reaction. In parallel, the reaction was performed with 5% catalyst loading, and resulted in a decrease in both reactivity and ee (Table 2.2, entry 6). Finally, we changed the reaction solvent to Et_2O, as a previous similar reaction showed Et_2O was a better solvent in giving higher selectivity.[33] A slight increase in ee from 75% to 76% was observed (Table 2.2, entry 7).

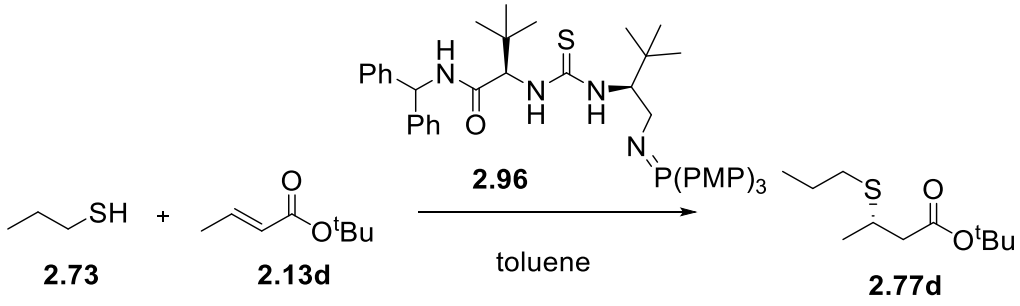


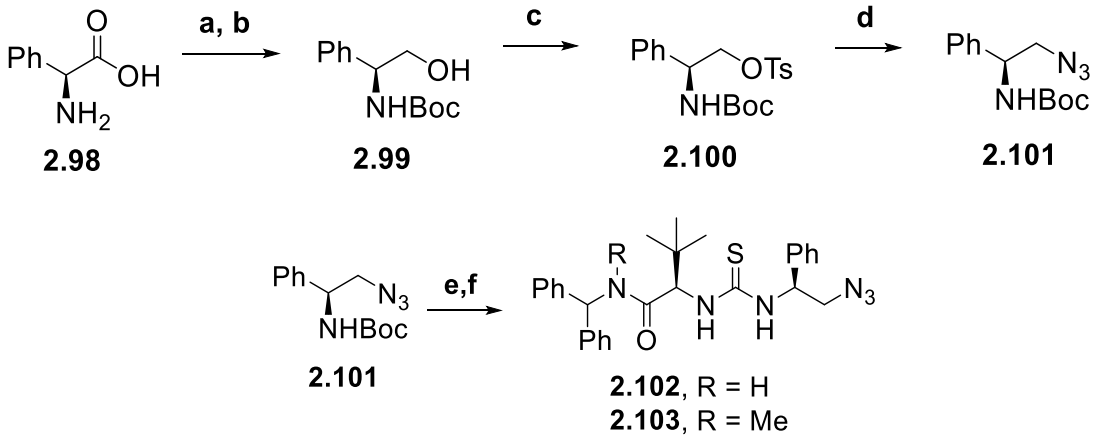
Table 2.2 Condition screening of SMA based on catalyst 2.96

Entry[a]	C (M)	T (°C)	Loading (%)	solvent	t (h)	yield (%)	ee (%)
1	0.5	rt	10	toluene	6	98	66
2	0.1	rt	10	toluene	24	96	75
3	0.05	rt	10	toluene	96	52	61
4	0.5	0	10	toluene	18	96	66
5	0.1	40	10	toluene	24	65	69
6	0.5	rt	5	toluene	24	88	64
7	0.1	rt	10	Et_2O	24	93	76

*a) All reactions were performed with tert-butyl crotonate **2.13d** (0.2 mmol), 1-propanethiol **2.73** (0.6 mmol) and 10 mol% catalyst **2.96** (0.02 mmol).*

In the meantime, we introduced *L*-phenyl glycine derived amino azide **2.101** to the

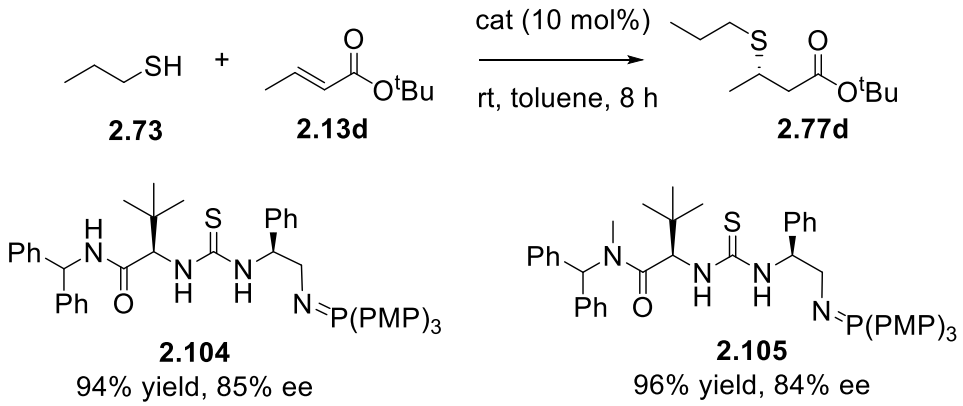
chiral amido-thiourea backbone as we have observed a better performance of this amino azide in the previously cooperative H-bond donor scaffold catalysts (see Chapter 2.4.3).



Scheme 2.24. Synthesis of *L*-phenyl glycine derived amido-thiourea BIMP catalyst. *a) $NaBH_4$ (2.4 eq), I_2 (1.0 eq), THF, 0 °C to reflux; b) Boc_2O (1.18 eq), NEt_3 (1.18 eq), CH_2Cl_2, overnight, 54% over two steps; c) TsCl (1.1 eq), Et_3N (2.0 eq), CH_2Cl_2, overnight, 71% yield; d) NaN_3 (1.1 eq), DMF, 45 °C, overnight, 70% yield; e) TFA, 0 °C to rt; f)* ***2.83*** *or* ***2.84****, Et_2O, 0 °C to rt, 60 - 68% yield.*

Amino azide **2.101** was synthesised from *L*-phenyl glycine **2.98** in four steps according to the previous method outlined in Scheme 2.16. Initial reduction of carboxylic acid group on the amino acid **2.98**, followed by N-Boc protection afforded Boc amino alcohol **2.99** in 54% yield over two steps. The hydroxyl group of the amino alcohol was subsequently tosylated (71% yield) and substituted with azide (70% yield) to afford the amino azide **2.101**. The amino azide was then reacted with isothiocyanate **2.83** and **2.84** to afford catalyst precursor **2.102** and **2.103** in 60% and 68% yield, respectively. These two catalyst precursors subsequently underwent Staudinger reaction with $P(PMP)_3$ to give BIMP catalysts **2.104** and **2.105** that was used for the SMA reaction (Scheme 2.25). To our delight, BIMP catalyst **2.104** provided the SMA adduct of 1-propanethiol and *tert*-butyl

crotonate in 94% yield and 85% ee in 8 h; while BIMP catalyst **2.105** afforded the same product in 96% yield and 84% ee in 8 h.



Scheme 2.25 SMA of 1-propanethiol and *tert*-butyl crotonate catalysed by *L*-phenyl glycine derived amido-thiourea BIMP catalyst 2.104 and 2.105.

With these promising results in hand, we started conditions optimisation on the best catalyst **2.104**.[v] The results are shown below in Tables 2.3, 2.4 and 2.5.

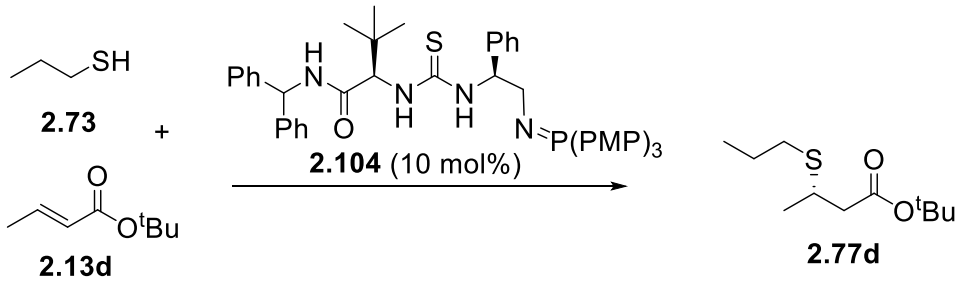


Table 2.3 conditions screening

Entry[a]	T (°C)	C (M)	t (h)	yield (%)	ee (%)
1	rt	0.5	8	94	85
2	rt	0.2	30	88	87
3	rt	0.1	48	45	86
4	0	0.5	24	92	87

[v] Although BIMP catalyst **2.105** also gave promising results, its corresponding isothiocyanate **2.85** could only be synthesised in low yield compared to **2.84**. Therefore, we decided to optimise reaction conditions based on catalyst **2.104**.

5	-20	0.5	30	88	89
6	-40	0.5	48	42	86

*a) All reactions were performed with tert-butyl crotonate **2.13d** (0.2 mmol), 1-propanethiol **2.73** (0.6 mmol) and 10 mol% catalyst **2.104** (0.02 mmol).*

Reaction conditions were first optimised using toluene as the solvent and the results are shown above (Table 2.3). The concentration of the reaction was first decreased to 0.2 M in toluene and gave excellent yield and 87% ee in 30 h (Table 2.3, entry 2). A further decrease in concentration to 0.1 M resulted in incomplete reaction, giving 45% yield and 86% ee after 48 h (Table 2.3, entry 3). In entry 4 and 5, SMA was performed at lower temperature and gradually increased enantiocontrol was obtained (87% ee at 0 °C and 89% ee at –20 °C). However, further lowering the temperature to –40 °C resulted again in an incomplete reaction and gave 42% yield and 86% ee after 48 h (Table 2.3, entry 6).

A full solvent screen was then performed to investigate the best solvent for this reaction (Table 2.4). The reaction was well tolerated in TBME, xylene, THF and EtOAc (Table 2.4, entries 1 to 5), giving 83 - 85% ee's and good yields after 8 h. However, the catalytic reactions conducted in $CHCl_3$ (Table 2.4, entry 6) only gave 23% yield and an eroded ee of 67%, and the reaction conducted in CH_2Cl_2 (Table 2.3, entry 7) gave trace amount of product. We postulated that these results are caused by trace amount of HCl in the chlorinated solvents. The catalytic reaction was next screened in hexane, and took longer time to reach completion, due to solubility issues of the catalyst (Table 2.4, entry 8). The use of DMF as solvent

only afforded the product in 3% ee (Table 2.4, entry 9). As DMF is a polar solvent, it might disturb the existing H-bonds formed between the catalyst and substrate that lead to high enantiocontrol during the reaction; therefore, resulted in poor enantiocontrol. Finally, when Et_2O was used as a solvent, the product was obtained in an increased 87% ee (Table 2.4, entry 10).

Table 2.4 Solvent Screening

Entry[a]	solvent	yield (%)	ee (%)	Entry	solvent	yield (%)	ee (%)
1	toluene	95	85	6	$CHCl_3$	23	67
2	TBME	92	83	7	CH_2Cl_2	trace	-
3	*p*-Xylene	91	84	8	Hexane[b]	92	75
4	THF	89	85	9	DMF	96	3
5	EtOAc	94	85	10	Et_2O	95	87

*a) All reactions were performed with tert-butyl crotonate **2.13d** (0.2 mmol), 1-propanethiol **2.73** (0.6 mmol) and 10 mol% catalyst **2.104** (0.02 mmol) in 0.4 mL solvent at rt and quenched after 8 h unless otherwise noted; b) The reaction time is 24 h.*

The relation of enantiocontrol and temperature was then studied. Lowering the reaction temperature to 0 °C gave a significant boost to the enantioselectivity (91% ee, Table 2.5, entry 2). Lowering the temperature further to –15 °C afforded **2.77d** in 94% yield and 94% ee in 72 h (Table 2.5, entry 3).

Table 2.5 Temperature Screening based on Et_2O

Entry[a]	T (°C)	t (h)	Yield (%)	ee (%)
1	rt	8	95	87
2	0	24	94	91

3	-15	72	94	94

a) *All reactions were performed with tert-butyl crotonate* ***2.13d*** *(0.2 mmol), 1-propanethiol* ***2.73*** *(0.6 mmol) and 10 mol% catalyst* ***2.104*** *(0.02 mmol) in 0.4 mL Et_2O.*

With the best conditions established, we decided to explore the ester group on the electrophile. A range of crotonates bearing different ester groups were synthesised by standard ester coupling of crotonic acid and their corresponding alcohols. The SMAs of 1-propanethiol to these esters were performed and the results are shown below (Table 2.6).

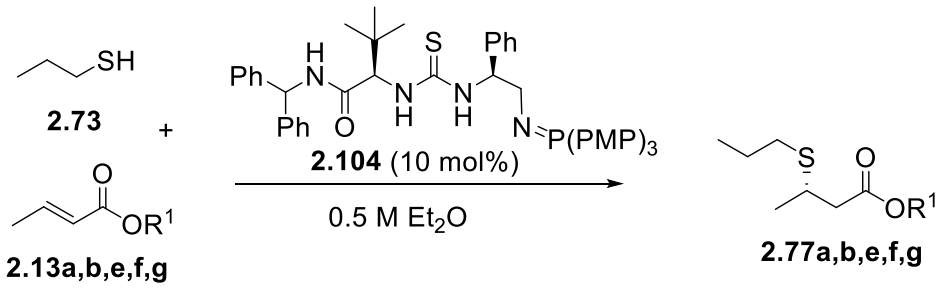


Table 2.6 Ester Screening

Entry[a]	R^1	Product	t (h)	Yield (%)	ee (%)
1	Me, **2.13a**	**2.77a**	3	>99	59[b]
2	Et, **2.13b**	**2.77b**	5	>99	66
3	$CH(CH_3)_2$, **2.13e**	**2.77e**	5	95	70
4	Bn, **2.13f**	**2.77f**	5	96	61
5	$CHPh_2$, **2.13g**	**2.77g**	1.5	>99	67

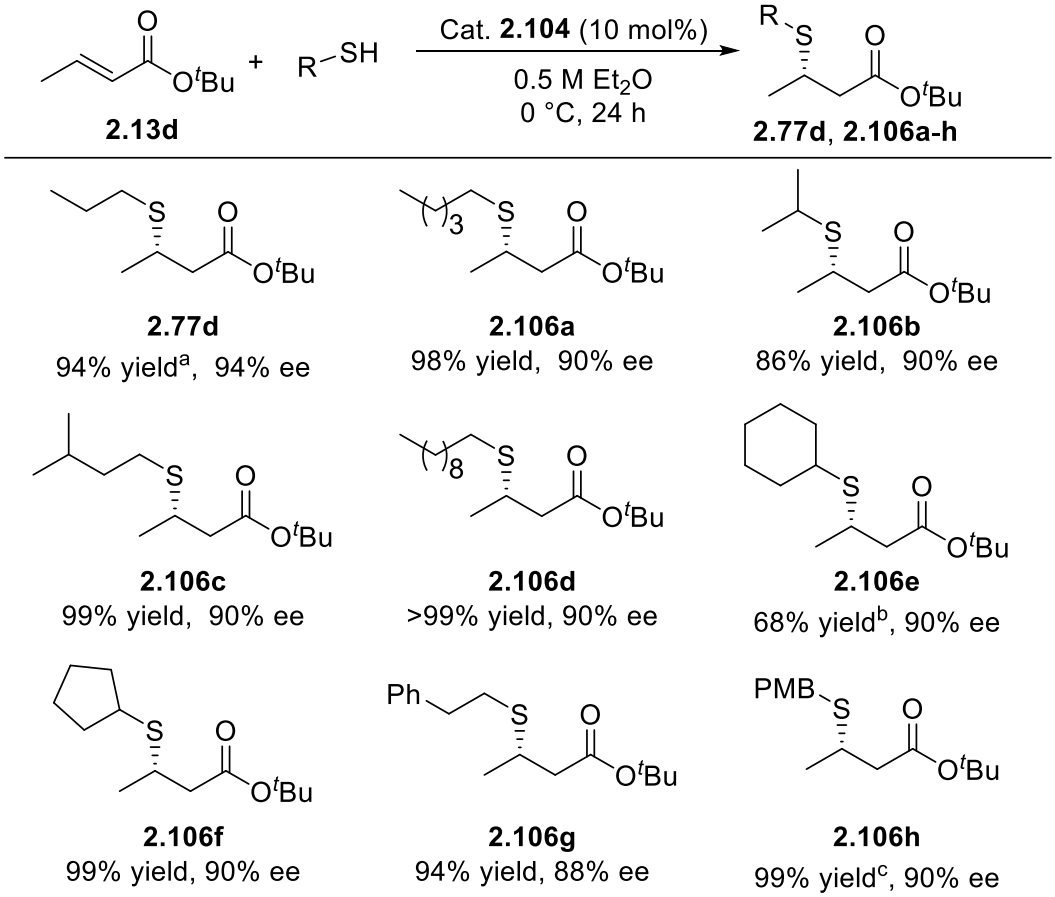
a) *All reactions were performed with tert-butyl crotonate* ***2.13*** *(0.2 mmol), 1-propanethiol* ***2.73*** *(0.6 mmol) and 10 mol% catalyst* ***2.104*** *(0.02 mmol) in 0.4 mL Et_2O at 0 °C; b) reaction was performed at rt.*

Interestingly, all of these esters were more reactive than *tert*-butyl crotonate, but all gave lower ee's. With increasing size of the alkoxy groups on the ester, an increase in ee was obtained (Table 2.6, entry 1, 2 and 3). In entry 4 and 5, when

using benzyl and benzhydryl crotonates, the ee's dropped a few percent compared to ethyl and isopropyl crotonates. This series of substrate scope further supports the higher ee with *tert*-butyl crotonate, as it is much more sterically hindered than other esters, which is beneficial for the transition state (*vide infra*).

2.5 Substrate Scope

Next, we began to investigate the scope of thiols and β-substituted α,β-unsaturated esters in the SMA reaction.

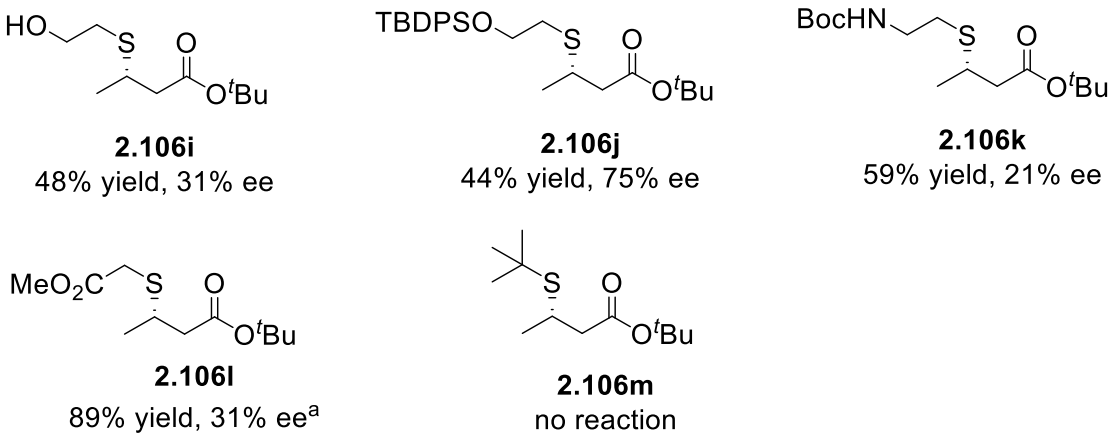


Scheme 2.26. Successful examples of thiol scope. *All reactions were performed with 0.2 mmol **2.13d**, 0.6 mmol thiol and 0.02 mmol catalyst **2.104** in 0.4 mL Et_2O at 0 °C for 24 h unless otherwise noted; a) Reaction was conducted –15°C and quenched after 72 h; b) Reaction was quenched after 96 h; c) Reaction was conducted at –15°C.*

The substrate scope[vi] with respect to the alkyl thiols was first investigated (Scheme 2.26). A long aliphatic chain on the thiol did not adversely affect the ee of the reaction as shown by the example of 1-pentanethiol (**2.106a**) and 1-decanethiol (**2.106d**). Thiols possessing branched aliphatic chain, such as 2-propanethiol (**2.106b**) and 3-methylbutane-1-thiol (**2.106c**) also afforded products in high yields and ee's. Cyclohexanethiol (**2.106e**) and cyclopentanethiol (**2.106f**) were also tolerated and gave excellent enantiomeric excess; however the reaction between cyclohexanethiol and *tert*-butyl crotonate was much slower, and required 96 h to go to completion. Although thiophenol was not well tolerated in this reaction, aliphatic thiol bearing an aryl group (**2.106g**) gave excellent yield and ee. (4-Methoxyphenyl)methanethiol (**2.106h**) was also investigated and gave higher reactivity and the reaction was finished within 24 hours at –15 ˚C.

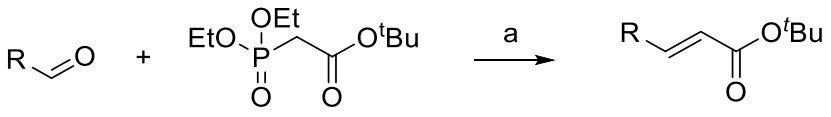
A range of thiols bearing functional groups, such as silyl protected hydroxyl and Boc protected amine were also tested in the reaction (Scheme 2.27).

[vi] We decided to carry out the SMA substrate scope at 0 °C instead of –15 °C. As some of the substrates required 72 - 96 h to go to completion at 0 °C, it would be not practical to conduct these reactions at –15 °C.



Scheme 2.27. Other examples of thiol scope. *All reactions were performed with 0.2 mmol **2.13d**, 0.6 mmol thiol and 0.02 mmol catalyst **2.104** in 0.4 mL Et_2O at 0 °C for 24 h unless otherwise noted. a) reaction was quenched after 2 h.*

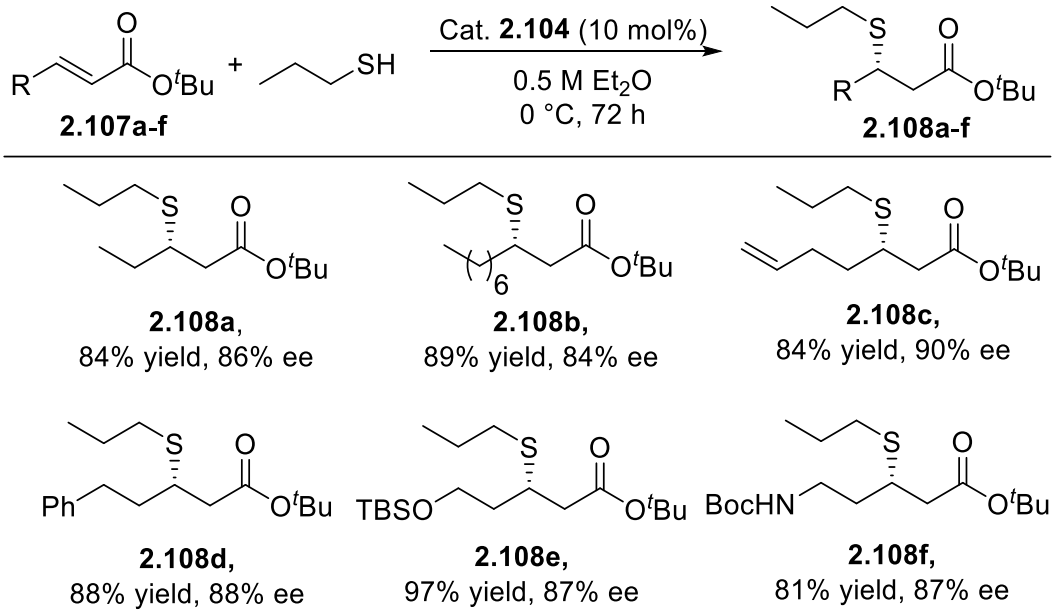
The use of 2-mercaptoethanol as the pronucleophile resulted in a 48% yield and only 29% ee (**2.106i**). We postulated that the possible H-bond interactions between the hydroxyl group of the thiol and the catalyst or the electrophile have disrupted the optimal H-bond interactions between the catalyst and substrate in the transition state, leading to a decreased reactivity and enantiocontrol. Accordingly, the hydroxyl group was protected with TBDPS group and the ee was boosted to 75% (**2.106j**). The use of 2-aminoethane thiol only gave the product in 21% ee (**2.106k**). Methyl 2-mercaptoacetate gave excellent reactivity and yield but low ee was obtained (**2.106l**). Finally, no product was observed when *tert*-butyl thiol was used as pronucleophile, which is probably due to a combination of steric hindrance of the *tert* butyl group and the higher p*Ka* of the thiol compared with other thiols.[41]



2.107a-i, l and **m**

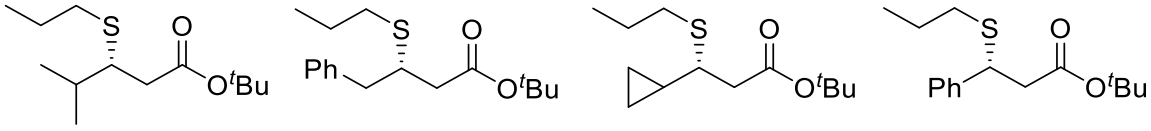
Scheme 2.28. Synthesis of α,β-unsaturated ester. *a) MeMgCl (1.0 eq), THF.*

We then turned our investigation towards the substrate scope of β-substituted α,β-unsaturated esters. A range of β-substituted α,β-unsaturated esters were synthesised according to a literature procedure [42] using the corresponding aldehydes and *tert*-butyl diethyl-phosphonoacetate (Scheme 2.28). These substrates were subjected to our conditions for the SMA and all gave excellent yields and ee's (Scheme 2.29).



Scheme 2.29. Successful examples of β-substituted-α,β-unsaturated esters substrate scope. *All reactions were performed with 0.2 mmol ester, 0.6 mmol thiol and 0.02 mmol catalyst **2.104** in 0.4 mL Et_2O at 0 °C for 72 h.*

As the chain size increased, the ee decreased slightly. 86% and 84% ee's were obtained for ethyl and heptyl substituted ester **2.108a** and **2.108b** respectively. Alkene (**2.108c**) and phenyl (**2.108d**) derivatives were also obtained in very good enantioselectivities. Substrates bearing TBS protected hydroxyl group **2.108e** and Boc-protected amine group **2.108f** were tolerated in the reaction as well.



2.108g
92% yield, 74% ee

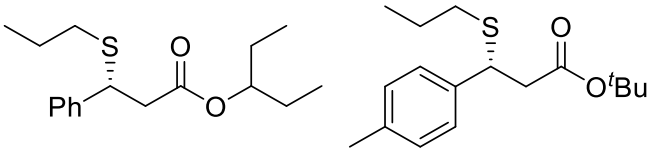
2.108h
89% yield, 75% ee

2.108i
N.R.

2.108j
98% yield,68% ee

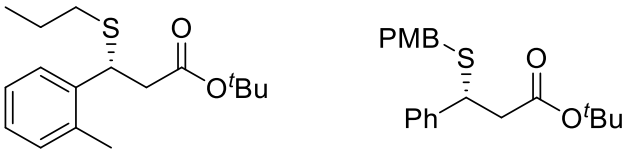
Scheme 2.30. Other examples of β-substituted α,β-unsaturated esters scope. *All reactions were performed with 0.2 mmol ester, 0.6 mmol thiol and 0.02 mmol catalyst **2.104** in 0.4 mL Et_2O at 0 °C for 72 h.*

We also examined α,β-unsaturated esters bearing other β-substituents [vii] (Scheme 2.30). The product with isopropyl β-substituent (**2.108g**) was obtained in 92% yield and 74% ee. The product with benzyl β-substituent (**2.108h**) was obtained in 89% yield and 75% ee. The cyclopropane substituted substrate (**2.107i**) gave no reaction after 7 d. Finally, *tert*-Butyl cinnamate (**2.107j**) was investigated and 68% ee was obtained using 1-propanethiol as pronucleophile.



2.108k
89% yield, 51% ee

2.108l
97% yield, 65% ee



2.108m[a]
80% yield, 13% ee

2.109
98% yield, 76% ee

Scheme 2.31. Investigation of cinnamate substrates. *All reactions were performed with 0.2 mmol α,β-unsaturated esters, 0.6 mmol thiol and 0.02 mmol catalyst **2.104** in 0.4 mL Et_2O at 0 °C for 72 h unless otherwise noted. a) The reaction was quenched after 96 h.*

Cinnamates and their β-substituted-derivatives are a large group of interesting substrates. The initial result of the SMA of 1-propanethiol to *tert*-butyl cinnamate

[vii] *tert*-Butyl cinnamate **2.107j** was prepared *via* ester coupling and used for the SMA to generate conjugate adduct **2.108j**.

was encouraging, therefore, we decided to further explore different cinnamate substrates[viii] (Scheme 2.31). We first tried the SMA of 1-propanethiol to isopentyl cinnamate (**2.107k**) in the hope that the isopentyl group might induce high enantioselectivity due to its steric effect. However, the product was obtained in only 51% ee, lower than that of *tert*-butyl cinnamate (Scheme 2.30, **2.108j**). We then changed the phenyl group to *o*- and *p*-tolyl substituents as the methyl substituent on the aromatic ring could increase the ee of the product as shown in literature.[43] The reaction with *p*-tolyl substituted substrate (**2.107l**) gave good yield and slightly lower ee compared with *tert*-butyl cinnamate. The reaction with *o*-tolyl substituted substrate (**2.107m**) was slower and gave very lower ee.

As the optimisation on the structure of cinnamate was not successful, we decided to try other pronucleophile for this reaction. (4-Methoxyphenyl)methanethiol was used and the ee was boosted to 76% (**2.109**).

tert-Butyl *(E)*-3-(4-nitrophenyl) acrylate **2.107n** was also tested for the SMA reaction. To our surprise, regioisomers **2.110a** and **2.110b** were obtained, arising from the attack of the thiol at both the α and ß positions of the ester (Table 2.7).

[viii] Isopentyl cinnamate **2.107k** was synthesised *via* ester coupling, while substrates **2.107l** and **m** were prepared according to method in Scheme 2.27. These substrates were used for the SMA to generate conjugate adduct **2.108k**, **l** and **m**.

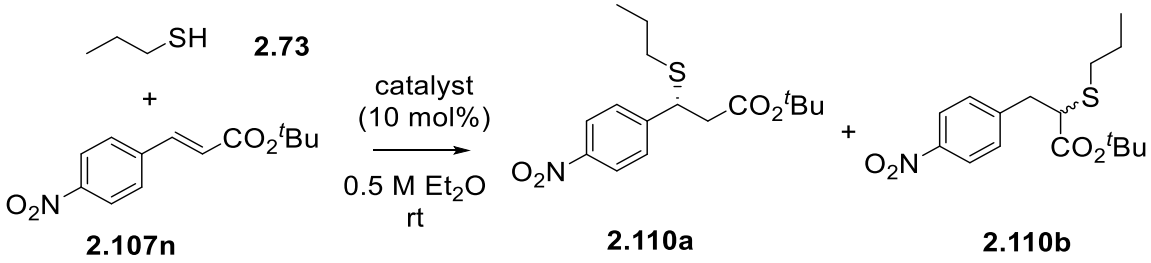
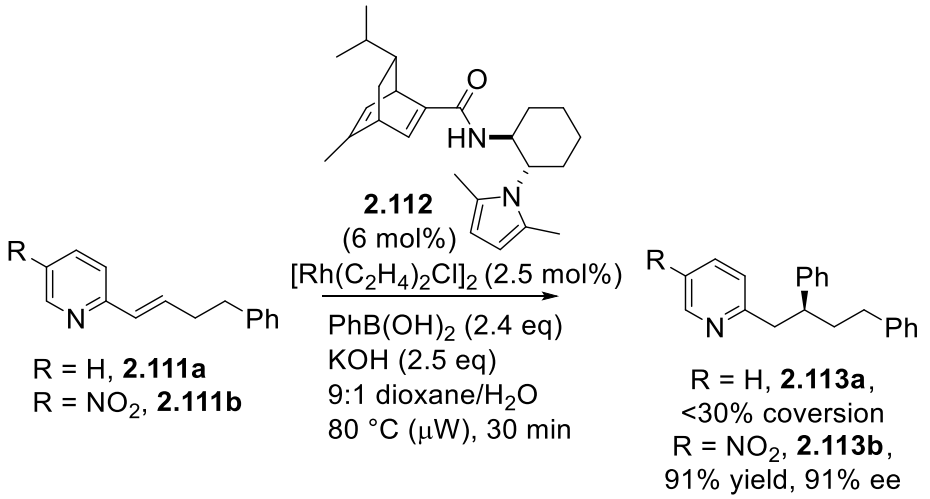


Table 2.7 SMA of *tert*-butyl *(E)*-3-(4-nitrophenyl) acrylate and 1-propanethiol

Entry[a]	Catalyst	t (h)	Ratio (a:b)	yield[b] (%)	ee (%)
1	BEMP	16	1:5	94%	NA
2	**2.104**	16	5:4	>99%	71%, 29%

a) Reactions were performed using 0.1 mmol ester, 0.3 mmol 1-PrSH in 0.2 mL Et_2O; b) combined yield of regioisomers.

The SMA with substrate **2.107n** catalysed by BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine) and **2.104** both gave excellent yields after very short time compared with that of *tert*-butyl cinnamate, probably due to the higher electrophilicity of the substrate arising from the electron withdrawing nitro group. The nitro group also affected the position of the nucleophilic attack in making both α and ß positions of the conjugated ester electrophilic. The nitro group effect has also been reported by Lam[44,45], where the author used nitro-substituted 2-alkenylpyridine **2.111b** for 1,4-arylation catalyzed by rhodium. Interestingly, this reaction gave very low conversion when simple 2-alkenylpyridine **2.111a** was used as electrophile (Scheme 2.32).

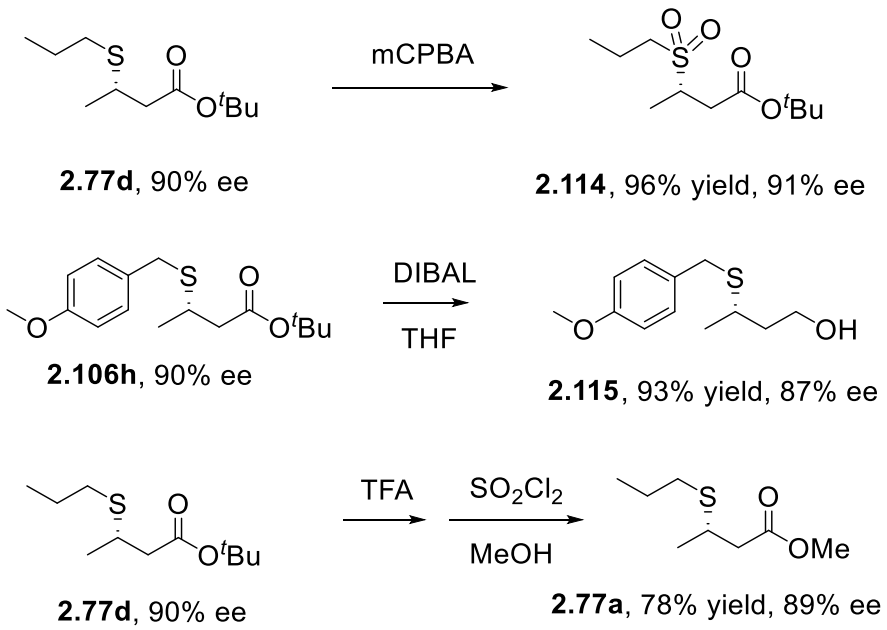


Scheme 2.32. Nitro group electron withdrawing effect in the 1,4 arylation of alkenylpyridine.

The SMA catalysed by BEMP gave a 1:5 ratio in preference to nucleophilic attack at the α-position of the ester (Table 2.7, entry 1). The SMA catalysed by **2.104** gave a 5:4 ratio in preference to nucleophilic attack at the β-position of the ester (Table 2.7, entry 2). This switch in ratios of the regioisomers suggested the catalyst formed H-bond with carbonyl group of the electrophile in the transition state, as a result, blocked the α-position for nucleophilic attack as well as increased the electrophilicity of the β-position of the carbonyl group. The ee of **2.110a** is 71%, comparable to that of *tert*-butyl cinnamate, whereas the ee of **2.110b** is only 29%. Conjugated adduct **2.110b** might be generated through a different transition state, and thus its absolute stereochemical configuration was not deduced from that of **2.110a**.

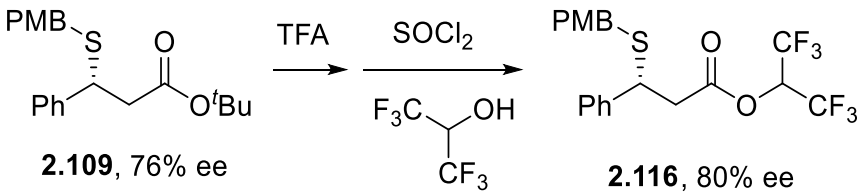
At this stage, we have synthesised a range of β-sulfide esters and decided to derivatise these products to demonstrate the application of this methodology. The oxidation of sulfide to sulfone **2.114** gave the product in very good yield and the ee was maintained after the reaction. The reduction of carboxylic ester to primary

alcohol **2.115** also afforded the product in good yield with slightly eroded ee. The transesterification of *tert*-butyl ester to methyl ester **2.77a** was carried out in two steps and ee was maintained as well (Scheme 2.33).



Scheme 2.33. Derivatisation of the product.

The absolute stereochemical configuration of the conjugate adduct was determined by converting the phenyl substituted conjugate adduct **2.109** to its corresponding hexafluoroisopropyl ester **2.116** and its specific rotation and HPLC retention times were compared to the literature values[22] (Scheme 2.34).



$[\alpha]_D^{23}$ = +102.2 (c 0.9, $CHCl_3$), (R)-**2.116**
lit. $[\alpha]_D^{23}$ = -69.5 (c 0.41, $CHCl_3$), (S)-**2.116**

Scheme 2.34. Absolute stereochemical configuration determination.

2.6 Catalyst Studies

2.6.1 Catalyst Loading Study

With the substrate scope of the SMA investigated, we decided to carry out catalyst loading studies in the hope that the strong basicity of BIMP catalysts could lead to low catalyst loading for the SMA reaction. Using 1-propanethiol and *tert*-butyl crotonate as substrates, the reaction was conducted in Et_2O (0.5 M) at 0 °C and took 24 h to reach completion (Table 2.8, entry 1). At 2 M concentration and 10% catalyst loading, the reaction rate was significantly increased and the reaction was complete in 4 h, and only a slightly lower ee of 90% was obtained (Table 2.8, entry 2). When the catalyst loading was dropped to 1%, at 2 M concentration, the reaction was slow and gave only 38% yield after 24 hours (Table 2.8, entry 3). The concentration was then increased to 5 M, and pleasingly, the reaction was complete in 20 hours and gave 99% yield, and 90% ee (Table 2.8, entry 4). In entry 5, no solvent was used and the reaction was conducted in 0.4 mL of 1-propanethiol. The reaction rate was similar but the ee was slightly lower than with 5 M Et_2O as solvent. In particular, the 1% loading reaction was conducted on 2 mmol scale of *tert*-butyl crotonate (Table 2.8, entry 4).

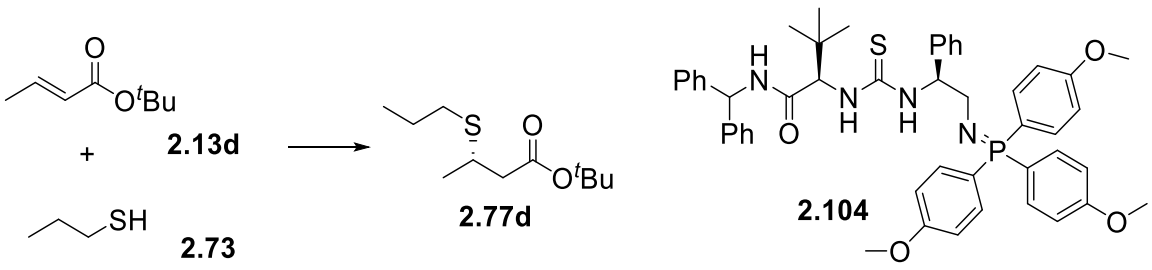


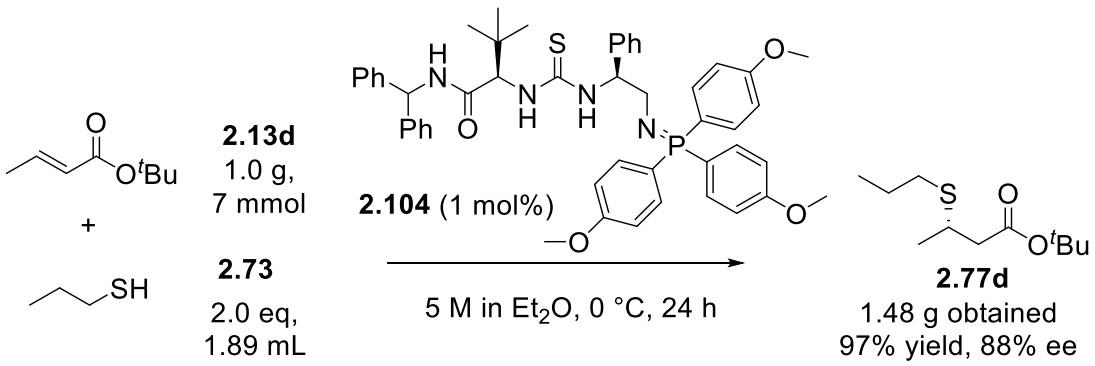
Table 2.8 Catalyst loading study

Entry[a]	C (M)	catalyst loading (%)	t (h)	yield (%)	ee (%)
1	0.5	10	24	94	91
2	2	10	4	92	90
3	2	1	24	38	90
4	5	1	20	99	90
5	Neat[b]	1	20	95	84

*a) The reactions were conducted using 0.02 mmol of catalyst **2.104**, 3.0 eq thiol and the amount of substrate and solvent used are calculated using corresponding catalyst loading and concentration. b) 0.4 mL 1-propanethiol was used in the reaction.*

2.6.2 Preparative Scale Reaction

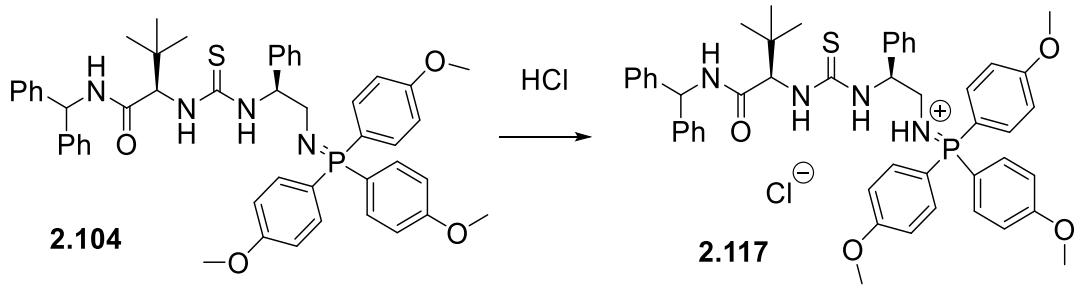
Encouraged by the low catalyst loading and reaction time we achieved for this SMA reaction, we postulated that a scale-up of this reaction is feasible. The reaction was then performed on a 1.0 g (7.0 mmol) scale of *tert*-butyl crotonate with 1 mol% catalyst loading. Under the previous optimised conditions, the reaction went to completion in 24 h and afforded the conjugate adduct **2.77d** in 97% yield and 88% ee (Scheme 2.35).



Scheme 2.35. Preparative scale of SMA reaction.

2.6.3 Catalyst Solution Structure Study

The reaction was normally conducted with iminophosphorane catalyst formed *in situ* from precursor azide and phosphine. This is because freshly prepared iminophosphorane shows signs of decomposition when it is left on the bench after a few days, and gives low reactivity and enantiocontrol if used for catalytic reaction. We then decided to make a more stable form of the catalyst. The *in situ* formed iminophosphorane was treated with 2 M HCl in Et_2O at 0 °C. White solid was formed instantly and filtered. The white solid collected was identified as the iminophosphorane HCl salt **2.117** (Scheme 2.36).



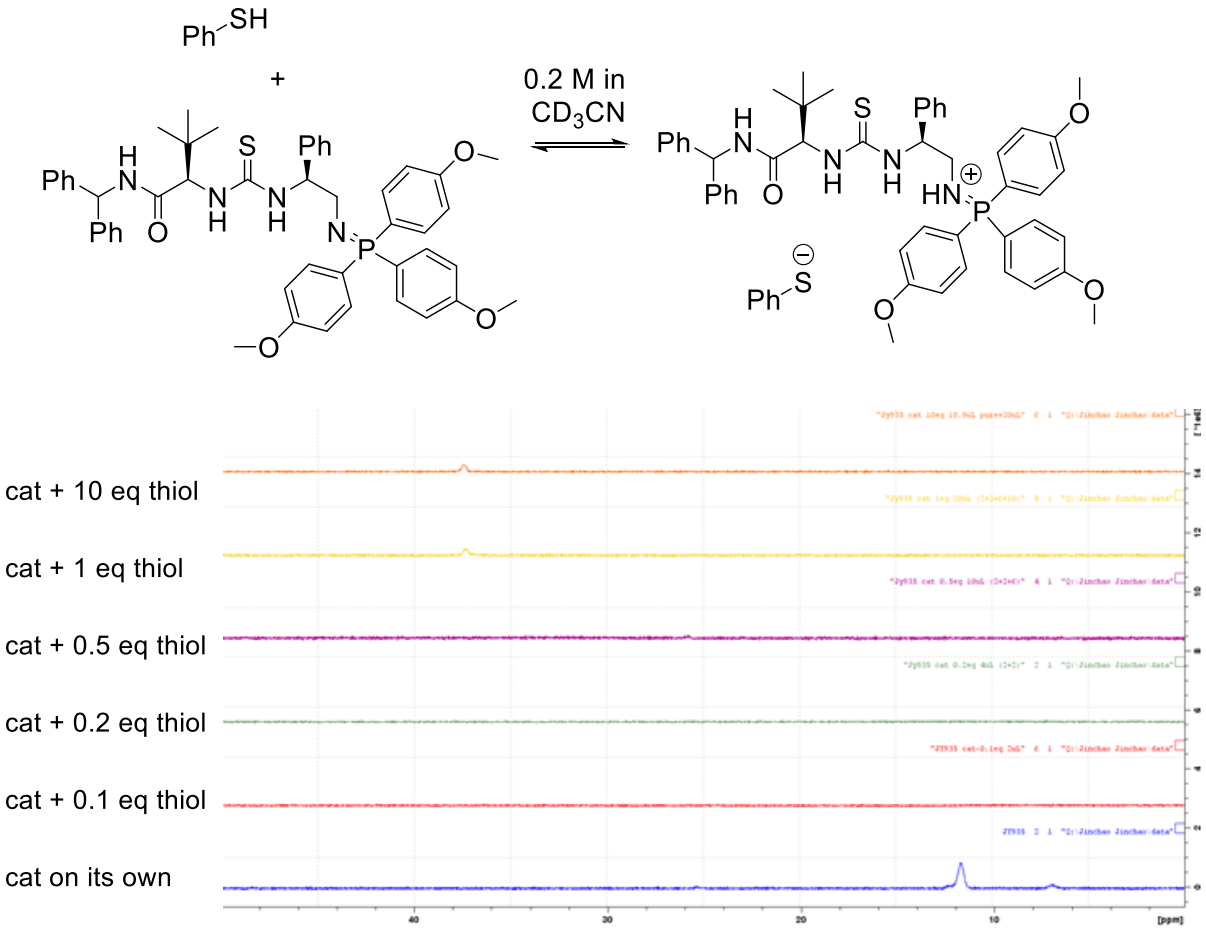
Scheme 2.36. Iminophosphorane salt formation.

The salt was dissolved in CH_2Cl_2 and was treated with 1.1 equivalent of PS-BEMP for 2 h according to a literature procedure[28], followed by filtration to remove excess of PS-BEMP and PS-BEMP HCl salt. The filtrate, which is the active iminophosphorane catalyst, was subsequently used for the catalytic SMA of 1-propanethiol to *tert*-butyl crotonate. However, no reaction was observed after 24 h under optimised conditions. The most likely reason for this is that the free base of the catalyst was not formed after the treatment of catalyst salt with PS-BEMP. Accordingly, the catalyst salt was treated with ground KOH in CH_2Cl_2 for 2 h. The

KOH was filtered and the filtrate was concentrated and used for the reaction of 1-propanethiol to *tert*-butyl crotonate. The reaction was performed under optimised condition, and 89% yield and 92% ee was obtained after 8 hours, which is comparable to the reaction catalysed by iminophosphorane catalyst formed *in situ*. This experiment demonstrated that our catalyst could be stored as a salt and used after a simple base wash.

2.7 Mechanism Studies

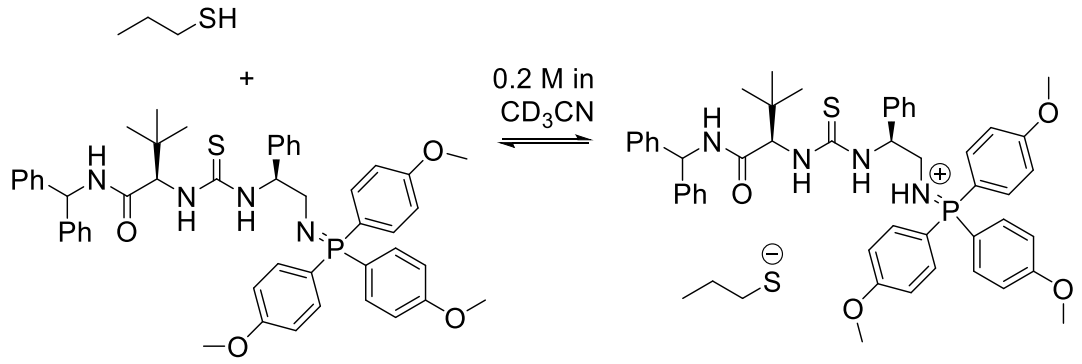
2.7.1 NMR Studies

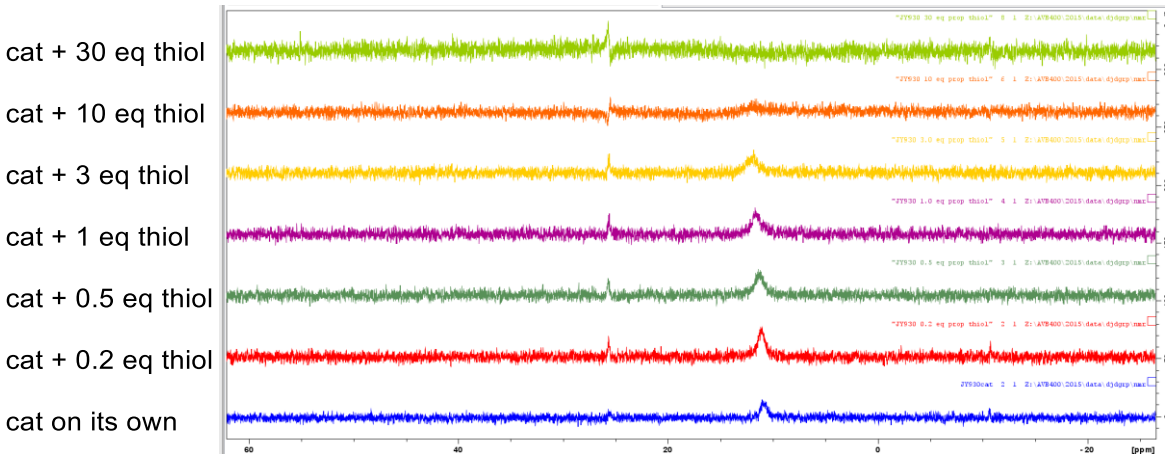


Scheme 2.37. Reaction of PhSH and catalyst 2.104 monitored by ^{31}P NMR. The equivalent of thiols are based on catalyst.

A solution study of thiophenol and catalyst **2.104** was conducted in an NMR tube

with 0.1 mmol catalyst and 0.5 mL CD_3CN as the solvent. The ^{31}P NMR of the catalyst was first measured and was presented at the bottom of the traces shown in Scheme 2.37. The indicated amount of thiol was then added into the NMR tube and the ^{31}P NMR of the mixture was taken each time (Scheme 2.37). A single peak at 12 ppm was observed and identified as the free iminophosphorane signal when catalyst was measured on its own. After adding 0.1 equivalent of thiophenol, the phosphine peak of the catalyst disappeared, and after adding 0.5 equivalent of thiol, a new peak around 25 ppm was formed. When 1.0 equivalent of thiophenol was added, a new peak was observed around 37 ppm, which is close to the phosphine peak of the catalyst HCl salt. This indicates a near full protonation of the catalyst. We could also conclude that the p*Ka* of iminophosphorane salt is higher than thiophenol (p*Ka* of PhSH = 10.3 DMSO[46]).





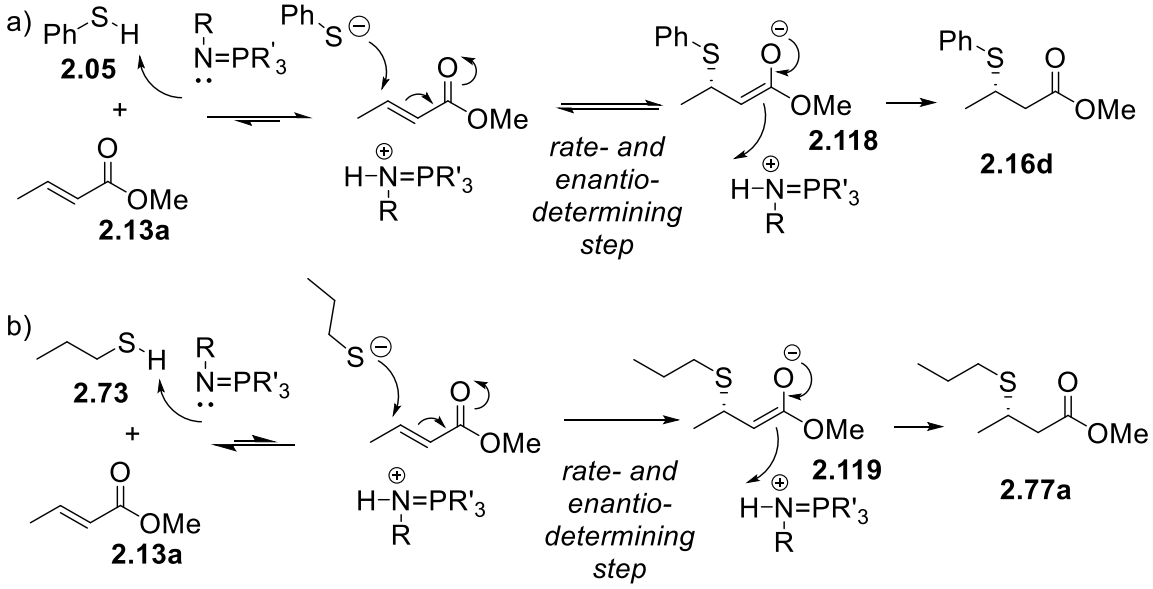
Scheme 2.38. Reaction of 1-PrSH and catalyst 2.104 monitored by ^{31}P-NMR. The equivalent of thiols are based on catalyst.

The same NMR experiments were also performed with 1-propanethiol as the proton source (Scheme 2.38). When 0.2 equivalent of thiol was added, the peak became broader, and there was a new peak formed around 25 ppm. This indicates that iminophosphorane was partially protonated. As more thiol was added, the original peak became broader and eventually disappeared when 30 equivalent of thiol was added. One possible explanation for the broadness and disappearance of the phosphine peak is the fast exchange between iminophosphorane free base and iminophosphorane salt.[47] The iminophosphorane salt peak was not observed and this implies that 30 eq thiol was not enough to fully protonate iminophosphorane. This also indicates that the p*Ka* of iminophosphorane salt is lower than that of 1-propanethiol (p*Ka* of 1-BuSH = 17.0 in in DMSO[46]).

2.7.2 Proposed Reaction Mechanism

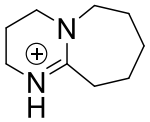
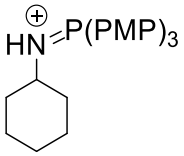
Taking all the experimental data together, we proposed a reaction mechanism to explain the differences in reactivity and stereoselectivity we observed for the reactions between thiophenol and 1-propanethiol.

We propose that this reaction proceeds *via* an initial deprotonation of the thiol pronucleophile by BIMP catalyst. Subsequent rate- and enantio-determining nucleophilic attack by the thiolate to methyl crotonate gives the conjugate adduct in the enolate form. A final proton transfer from the BIMP salt to the enolate yields the final conjugate adduct (Scheme 2.39).



Scheme 2.39. Proposed reaction mechanism of the SMA of thiols to methyl crotonate.

We propose the initial deprotonation of the thiol pronucleophile is a fast and reversible equilibrium; and the equilibrium constant is associated with the p*Ka* values difference between the thiol and the base. A p*Ka* value scheme is shown below for reference (Scheme 2.40).

	PhSH	1-BuSH		
	2.05	**2.120**	**1.29**	**1.60**
DMSO	10.3	17.0	13.9	-
MeCN	-	-	24.3	25.0

Scheme 2.40. p*Ka* value of PhSH and ^{n}BuSH in DMSO and pK_{BH+} values of DBU and triaryliminophosphorane 1.60 in DMSO and MeCN (Chapter 1).

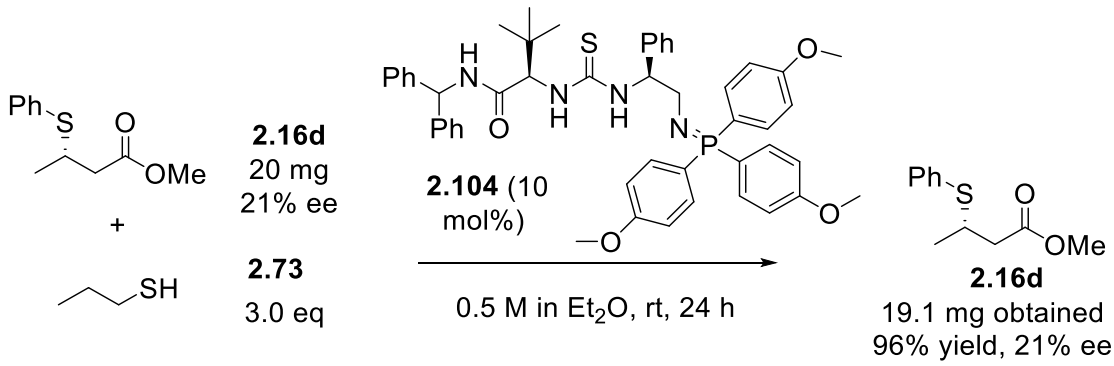
The NMR experimental results are in line with the p*Ka* value difference between thiophenol and 1-propanethiol. The p*Ka* values of PhSH and 1-BuSH are 10.3 and 17.0 in DMSO, respectively. In addition, the pK_{BH+} of achiral iminophosphorane **1.60** is 25.0 in MeCN (Chapter 1.3). The pK_{BH+} of DBU is 13.9 in DMSO and 24.33 in MeCN. These data suggested iminophosphorane possesses a similar basicity to that of DBU.[ix] Therefore, in the deprotonation of thiophenol by BIMP catalyst, the equilibrium lies much further towards the thiolate than the thiol starting material; while in the deprotonation of 1-propanethiol by BIMP catalyst, the equilibrium lies much further towards the thiol starting material than the thiolate.

We then propose that the subsequent nucleophilic attack by the thiolate to methyl crotonate is the rate- and enantiodetermining step of the reaction. This step is a bimolecular process and the rate of reaction will therefore be dependent on the concentration of the nucleophile. However, the reaction with 1-propanethiol is faster than the reaction with thiophenol, although there is more deprotonated form

[ix] Caution must be taken when comparing p*Ka* values across different solvents. In addition, the pK_{BH+} value of BIMP catalysts containing a H-bond donor group is likely to be slightly different from the achiral iminophosphorane.

of thiophenol than 1-propanethiol in those reactions. One possible explanation for this observation is that the nucleophilic attack by the PhS^- thiolate anion to methyl crotonate is reversible. The reversible sulfa-Michael addition has also been reported in the sulfa-Michael/Mannich cascade reaction [48] and sulfa-Michael/Michael cascade reaction[49]. The proposition that the nucleophilic attack is reversible could also explain the low ee we obtained with thiophenol pronucleophile.

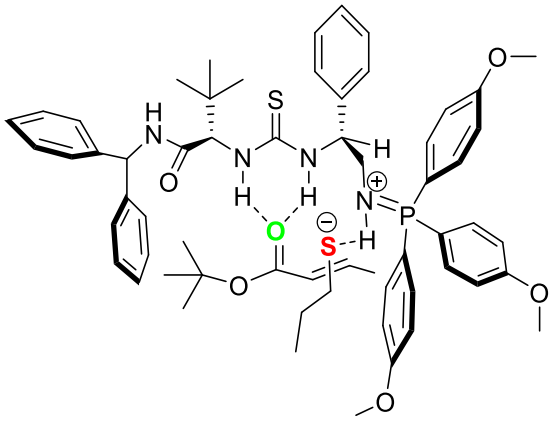
Although we have proposed that the nucleophilic attack by the PhS^- thiolate to methyl crotonate is reversible, we are not certain if the subsequent protonation of **2.118** is reversible. To probe this, we performed a SMA reaction with conjugate adduct **2.16d** (21% ee), 1-propanethiol and catalyst **2.104** to study the reversibility of the final protonation step (Scheme 2.41). After the reaction, conjugate adduct **2.16d** was recovered in 96% yield and the same ee (21%) and no sign of conjugate adduct of 1-propanethiol to crotonate was observed. This experiment indicates that the final protonation step of **2.118** is not reversible.



Scheme 2.41. Test for the reversibility of conjugate adduct 2.16d.

2.7.3 Proposed Transition State Model

Furthermore, we propose a transition structure that could explain the absolute stereochemical configuration of the product and the fact that reaction with *tert*-butyl crotonate gave the best enantiocontrol, albeit with the slowest reaction rate. As postulated in the reaction mechanism, this reaction proceeds *via* the deprotonation of the pronucleophile, after which the two substrates (thiolate and unsaturated ester) are activated by means of H-bonding with the catalyst and the bond-forming step takes place. The proposed transition state for this bond-forming step is depicted in Scheme 2.42.



Scheme 2.42. Proposed transition state model for the SMA of 1-propanethiol to *tert*-butyl crotonate.

In our model, the carbonyl group of the *tert*-butyl crotonate forms a dual H-bond with the two thiourea protons of the catalyst. We postulate that the hydrogen on the amide of the catalyst was not involved in the H-bonding in the transition state, because the reaction catalysed by BIMP catalyst **2.104** bearing a secondary amide and BIMP catalyst **2.105** bearing a tertiary amide gave very similar ee's.

The crotonate bearing *tert*-butyl ester is locked by the benzhydryl group and the

p-methoxyphenyl group on the catalyst. On the other hand, the use of other ester groups makes the size of crotonate smaller and would allow the crotonate to move from its optimal position for the enantioselective attack by the thiolate, therefore lead to lower ee. In addition, the thiolate forms a H-bond with the protonated iminophsophorane and attacks the *si*-face of the β-carbon on the crotonate to form the conjugate adduct in the enolate form with high enantiomeric excess. Final proton transfer from the protonated iminophosphorane salt to the enolate affords the conjugate adduct and releases the freebase BIMP catalyst for next catalytic cycle.

2.8 Conclusion

This chapter described the BIMP catalyst development for the first highly enantioselective sulfa-Michael addition (SMA) of alkyl thiol pronucleophiles to unactivated β-substituted α,β-unsaturated esters. A range of BIMP catalysts bearing different H-bond donors was synthesised and the chiral amido-thiourea BIMP catalysts proved to be the best catalyst in promoting the SMA reaction. A range of alkyl thiols and unactivated β-substituted α,β-unsaturated esters were well-tolerated in the reaction. The reaction was successfully carried out on a preparative scale using 1 mol% catalyst with maintained reactivity and stereocontrol. Reactions mechanism and transition state were also proposed to understand the reaction.

2.9 Reference

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Chapter 3 Enantioselective Desymmetrisation of Prochiral Cyclohexadienones

3.1 Chapter Overview

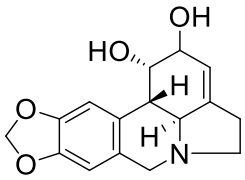
This chapter describes the BIMP catalysed asymmetric desymmetrisation of prochiral cyclohexadienones *via* a stepwise dearomatisation/enantioselective intramolecular Michael addition of cyclohexadienones to afford 5,6-membered bicyclic compounds. A range of high pKa pronucleophiles were tested, such as malonates, malonamates and amides, and promising results were obtained after extensive BIMP catalyst screening. Modifications of the substrate have also been conducted and new substrates have been screened for the best catalyst conditions.

3.2 Introduction

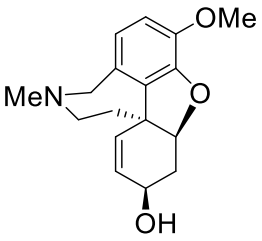
3.2.1 Natural Product Containing Bicyclic Ring

Ring systems based on 5,6- and 6,6-bicycles are common building blocks contained within many biologically interesting natural products and pharmaceutical compounds (Scheme 3.1). For example, (-)-lycorine **3.1**, belonging to the family of *Amaryllidaceae* alkaloids, displays antiviral activity and apoptosis induction ability.[1,2,3] (-)-Galanthamine **3.2** has been used in the early treatment of Alzheimer's disease due to its properties as a selective, reversible

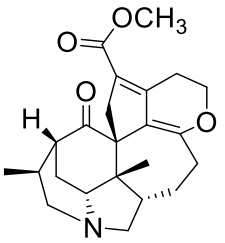
and competitive acetylcholinesterase inhibitor.[4] *Daphniphyllum* alkaloids are a large family of natural products, and over 200 of them have been discovered.[5] Some of them have shown interesting biological activities against a variety of diseases.[6,7,8]



3.1, (-)-lycorine



3.2, (-)-galanthamine



3.3, daphnilongeranin A

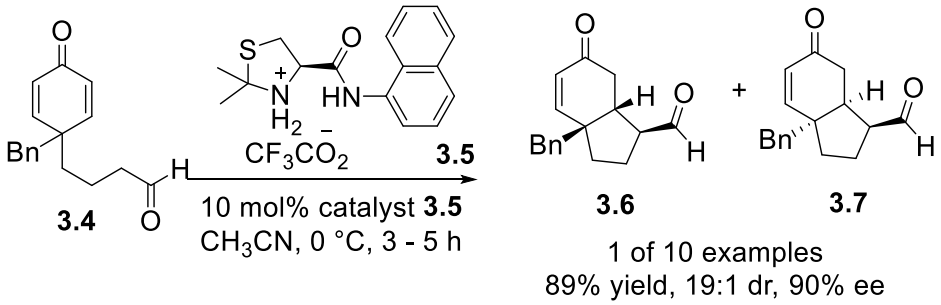
Scheme 3.1. Representative natural products containing bicyclic ring systems.

3.2.2 Asymmetric Desymmetrisation *via* Enantioselective Michael Reactions with Carbon Pronucleophiles

Asymmetric desymmetrisation reactions are useful methods for transforming prochiral or meso-molecules into functionalised enriched compounds, which can be useful intermediates for the synthesis of natural products.[9,10,11] A commonly used substrate is cyclohexadienone, which is prepared from oxidative dearomatisation of simple phenol derivatives, can be easily transformed into bicyclic systems *via* a Michael addition of an intramolecular pendant carbon pronucleophile. There has been a growing interest in these reactions, and representative examples are shown below.

In 2005, Hayashi[12] reported an intramolecular Michael addition of aldehyde to cyclohexadienone catalysed by a cysteine-derived organocatalyst **3.5**, to give 5,6-

bicyclic products in excellent diastereo- and enantioselectivities (Scheme 3.2).

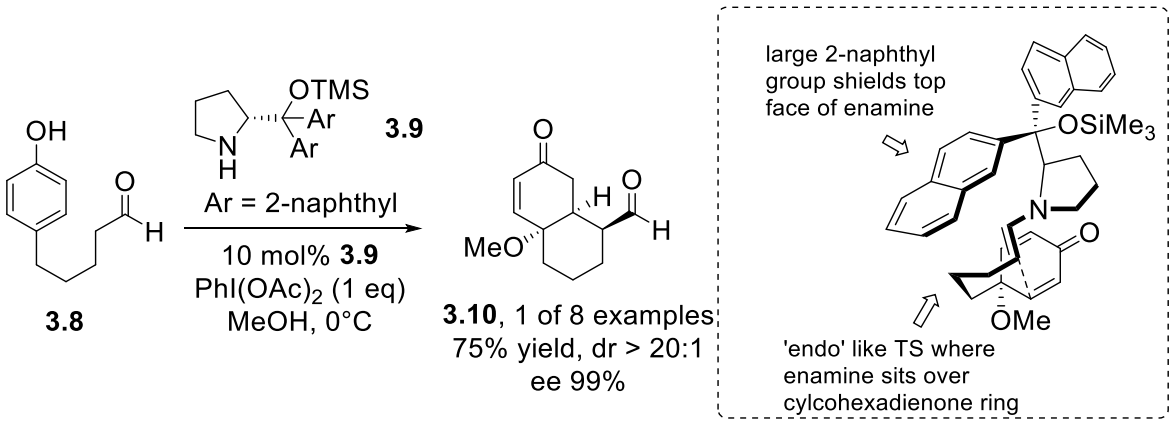


Scheme 3.2. Intramolecular 5,6-bicyclic ring formation.

5,6-Bicyclic compounds bearing three continuous stereogenic centres were formed after the Michael addition with the cis-isomer being the major diastereomer. A few examples with variation to the γ-substituent were presented, such as benzyl, methyl, n-butyl and allyl substituents, with high yields, dr's and ee's.

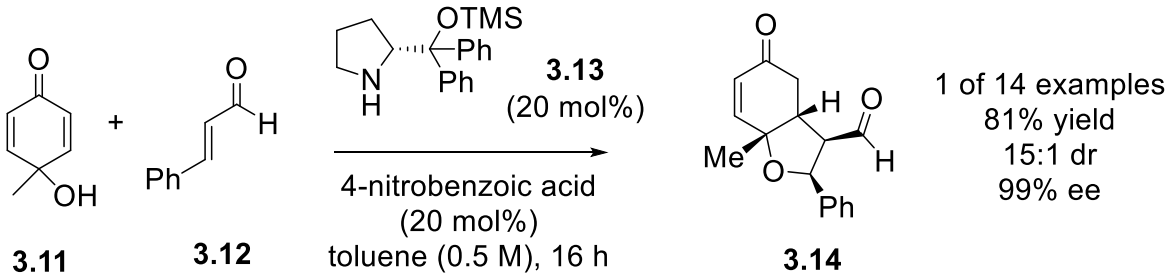
Gaunt[13] presented a diarylprolinol catalysed cascade desymmetrisation reaction, where *p*-substituted phenol **3.8** underwent oxidative dearomatisation followed by enantioselective intramolecular Michael addition under the catalysis of diarylprolinol silyl ether **3.9** to give highly functionalised 6,6-bicyclic compounds **3.10** in high dr's and ee's, albeit with moderate yields (Scheme 3.3). Interestingly, this low yield could be improved – whilst maintaining the high dr and ee previously observed – by carrying out the two transformations in a single step.

Heteroatoms, such as, nitrogen and oxygen could be incorporated into the tethering unit and also produce the product with high ee and dr. However, shortening the aliphatic chain of the pendant aldehyde pronucleophile only afforded the 5,6-bicyclic products in low stereoselectivities.



Scheme 3.3. Direct asymmetric dearomatisation and its transition state model.

A transition state model was also postulated by the author in order to explain the observed enantioselectivity (Scheme 3.3). The large 2-naphthyl group on the catalyst shields the top face of the enamine; therefore, the cyclohexadienone could only approach the enamine from the bottom face. The enamine then attacks the *si*-face of the cyclohexadienone to form the bicyclic product in high dr and ee. Building on Hayashi's and Gaunt's earlier reports, Johnston described an oxy-Michael/Michael cascade reaction of *p*-quinols and α,β-unsaturated aldehydes catalysed by diarylprolinol silyl ether **3.13** to afford tetrahydrobenzofurans in high yields, good to excellent dr's and high enantioselectivities (Scheme 3.4).

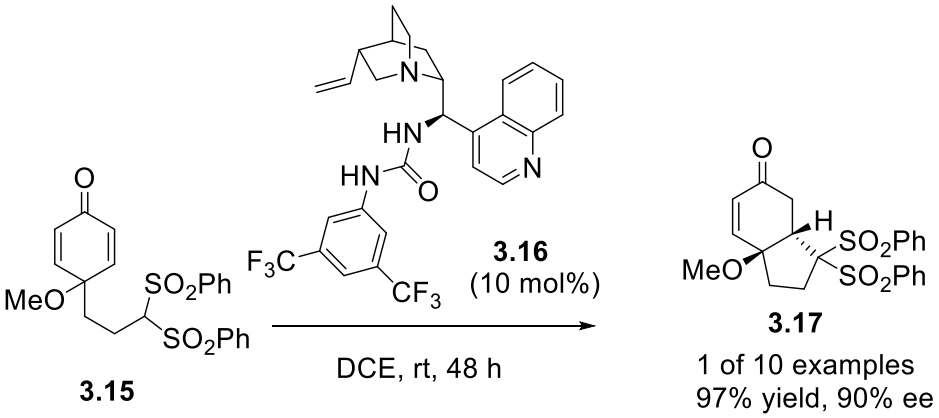


Scheme 3.4. Asymmetric dearomatisation *via* oxy-Michael/Michael cascade.

This strategy was also applied to the aza-Michael/Michael cascade reaction of *p*-quinamines and α,β-unsaturated aldehydes to afford hydroindoles in good yields,

dr' and ee's.[14]

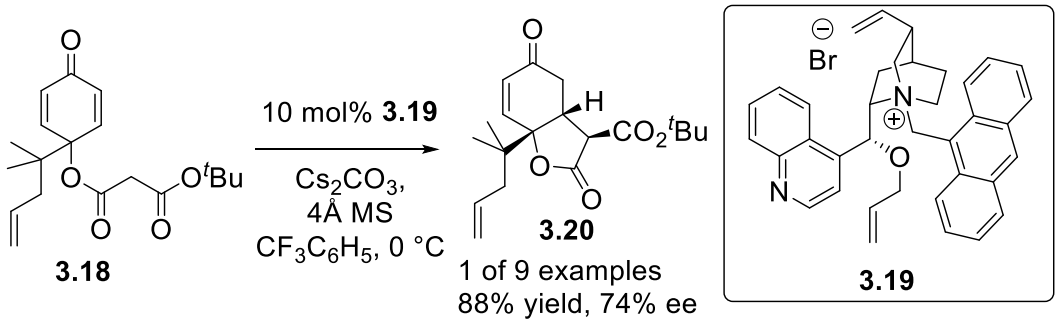
Whilst examples described above all involve using an aldehyde as the pendant pronucleophile in the intramolecular Michael reaction, there are also a few literature examples involving the use of other carbon pronucleophiles. For instance, You [15] presented a desymmetrisation of cyclohexadienones using bisphenylsulfonyl methylene as a pronucleophile in the enantioselective intramolecular Michael reaction catalysed by cinchona alkaloid derivative **3.16** (Scheme 3.5). Despite the good yields and ee's, the reactions typically required 48 to 96 h to reach completion with 10 to 20 mol% catalyst loading. The one-pot dearomatisation/Michael reaction process was also investigated, but slightly lower ee's and poor yields were obtained.



Scheme 3.5. Asymmetric dearomatisation *via* Michael reaction with bisphenylsulfonyl methylene pronucleophile.

Harned [16] was the first to introduce malonate as the pronucleophile in the intramolecular Michael reaction step of the asymmetric dearomatisation/desymmetrisation strategy (Scheme 3.6). The racemic cis-product was obtained as a single diastereomer when using cesium carbonate as

catalyst. The enantioselective reactions were catalysed by phase transfer catalyst **3.19** and afforded the products in moderate to good yields and poor to moderate ee's (up to 74% ee).



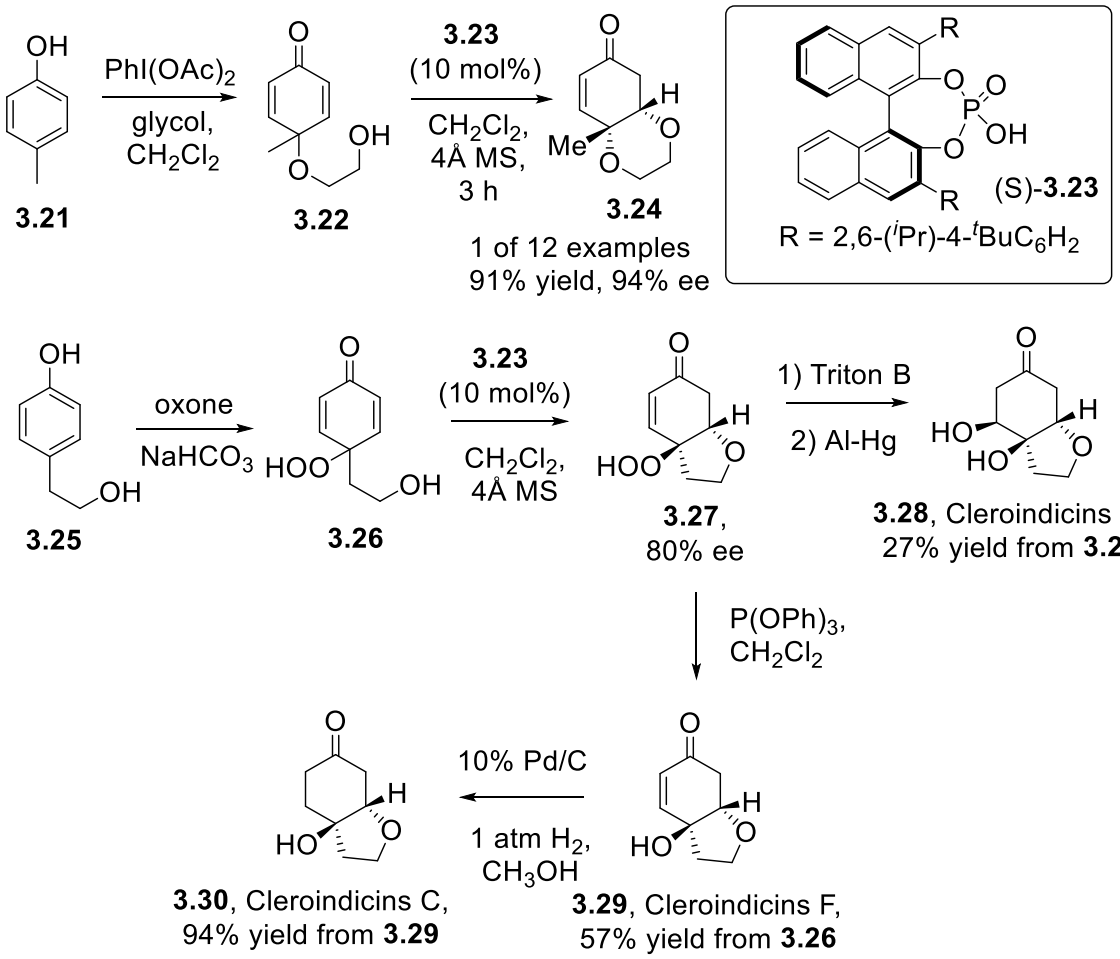
Scheme 3.6. Desymmetrisation *via* Michael reaction with malonate.

A range of aliphatic *p*-substituted cyclohexadienones was tested and increased enantioselectivities were observed on substrates bearing more sterically hindered γ-substituents. Substrate bearing small γ-substituent, such as methyl group, could only be obtained in 50% ee. Cyclohexadienones containing *o*- and *m*- substituents were also tested in this reaction. Excellent regioselectivity was obtained as the nucleophile attacked the enone possessing fewer substituents. However, reactivity was lowered and the levels of enantiocontrol with these substrates were poorer compared to those of substrates with only *p*-substituents.

3.2.3 Asymmetric Desymmetrisation *via* Enantioselective Oxy-Michael and Aza-Michael Reactions

The enantioselective desymmetrisation strategy involving Michael reaction has also been performed with heteroatom pronucleophiles, for example, oxygen pro-nucleophiles and nitrogen pronucleophiles. Some of the representative examples are shown below.

You[17] reported a Brønsted acid catalysed intramolecular oxy-Michael reaction, affording chiral 1, 4-dioxane derivatives in high yields and ee's (Scheme 3.7).

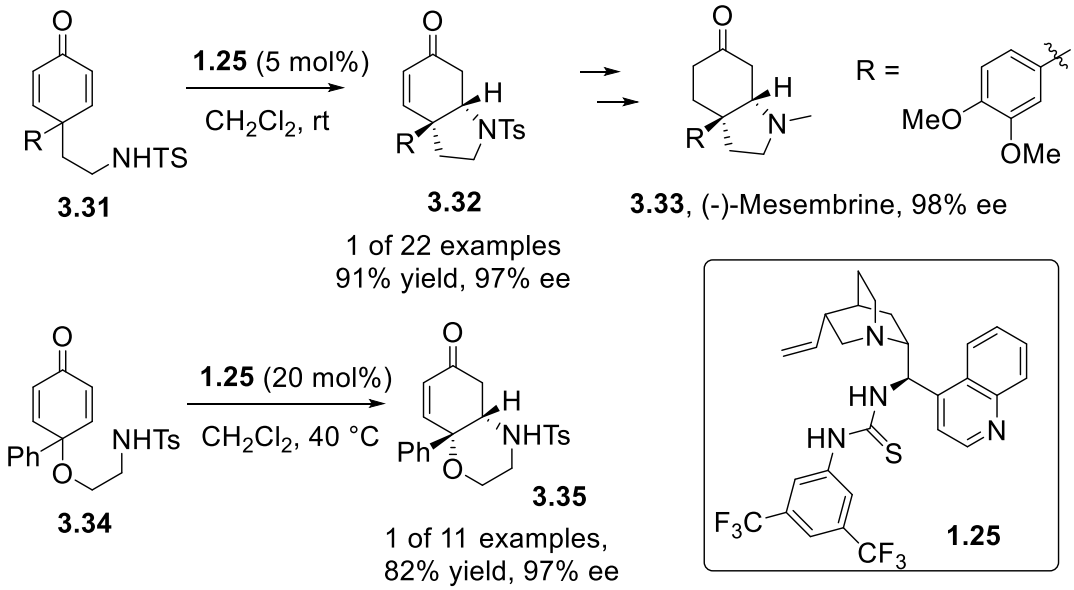


Scheme 3.7. Enantioselective desymmetrisation *via* oxo-Michael reaction and its application in total synthesis.

Chiral phosphoric acid derivative **3.23** proved to be the best catalyst for this reaction and could afford the product in 91% yield and 94% ee. This methodology was applied in the synthesis of Cleroindicins C, D and F, which are used to treat malaria and rheumatism.[18, 19] The synthesis started with 4-(2-hydroxylethyl) phenol **3.25**, which underwent oxidative dearomatisation mediated by oxone to give the cyclohexadienone substrate **3.26**. Subsequent intramolecular oxy-Michael reaction of **3.26** afforded the cyclised product **3.27** in 80% ee. This

cyclised product was subsequently transformed into Cleroindicins C, D and F in one or two steps with maintained enantioselective purity (Scheme 3.7).

The same group also reported desymmetrisation of cyclohexadienones *via* an enantioselective intramolecular aza-Michael reaction (Scheme 3.8).[20] The reaction was first tested with previous best phosphoric acid catalyst **3.23** used in the oxy-Michael reaction; giving 99% yield and 71% ee. Instead, cinchona alkaloids derived catalyst **1.25** proved to be suitable in making this family of 5,6-bicyclic compounds and gave high yields and ee's.



Scheme 3.8. Desymmetrisation *via* an aza-Michael reaction.

Several nitrogen-protecting groups were tested in the reaction and all gave good ee's, with the exception of N-Boc carbamate, where no reaction was observed. In addition, tosyl protected substrate displayed the highest ee (97%). This reaction also worked well in making 6,6-bicyclic compounds with various γ–substituents when the reaction was conducted at 40 °C with 20 mol% catalyst loading.

This methodology was later applied to the total synthesis of (-)-Mesembrine.[21,22] Cyclohexadienone **3.31** was used for this synthesis. Subjection of **3.31** to the optimised catalytic conditions described above afforded cyclised product **3.32** in 91% yield and 97% ee. This product was subsequently transformed into the (-)-Mesembrine **3.33** in 35% yield and 98% ee over four steps.

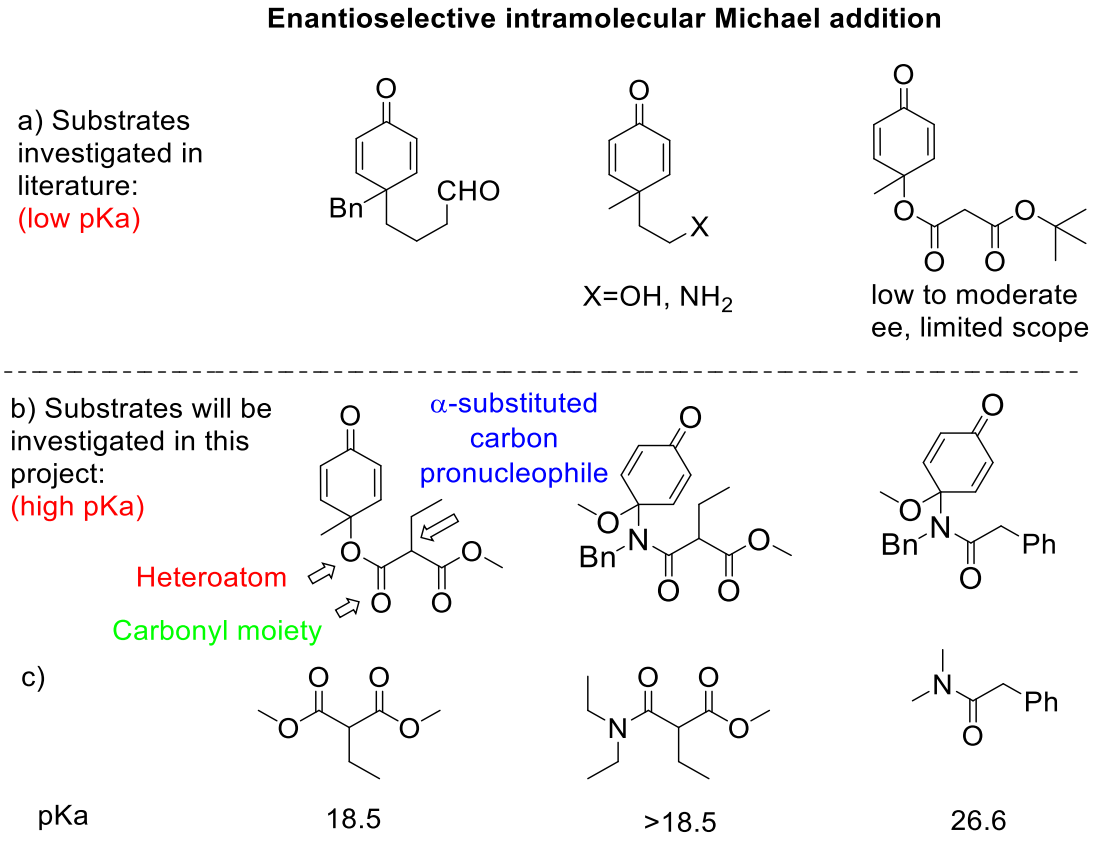
3.3 Aims

The existing methods of asymmetric desymmetrisation reactions mostly involve the use of either aldehyde or heteroatoms as the pendant pronucleophile tethered to cyclohexadienone in the enantioselective intramolecular Michael addition (cyclisation) step, whereas the use of less reactive carbon nucleophiles, such as malonates and malonamates, have been less exploited (Scheme 3.9a and b). This is presumably due to the low catalytic reactivity associated with known chiral catalysts. Given the excellent reactivity and stereoselectivity BIMP catalysts have demonstrated in SMA reaction (Chapter 2), we decided to test their catalytic ability with high p*Ka* pronucleophiles, such as malonates, malonamates and amides. The exact p*Ka* values of these substrates are not available, but the p*Ka* values of their analogies are shown in Scheme 3.9c. If these reactions are successful, they could largely expand the reaction scope of asymmetric desymmetrisation (Scheme 3.9). In addition, the bicyclic products generated *via* these new methodologies are potentially useful for three reasons discussed below:

1. The incorporation of heteroatoms, for example, nitrogen and oxygen to the tether unit are useful as many biological interesting compounds contain heteroatoms in the ring (Scheme 3.1).

2. The carbonyl functionalities on the malonates/malonamates would allow versatile functional group transformations for the cyclised product.

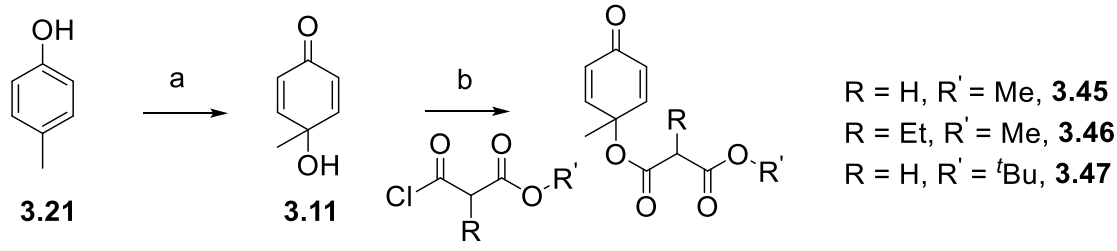
3. The α-substituted carbon pronucleophile would allow the construction of all-carbon quaternary stereogenic centres.



Scheme 3.9. a) Existing substrate scope in the asymmetric desymmetrisation *via* enantioselective intramolecular cyclisation; b) Substrates planned to be investigated for the asymmetric desymmetrisation *via* enantioselective intramolecular cyclisation; c) p*Ka* in DMSO for the analogies of substrates to be investigated.[23,24]

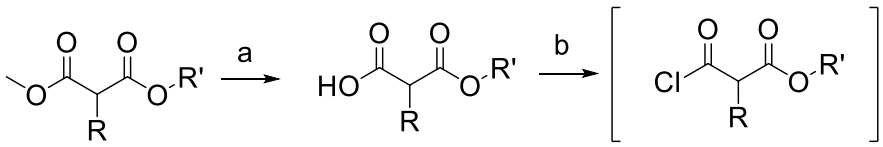
3.4 Intramolecular Cyclisation of Malonates Tethered Cyclohexadienones

The intramolecular Michael reaction of malonates tethered cyclohexadienones has been described in Scheme 3.6. The use of phase transfer catalyst could only afford the cyclised product in low to moderate ee. The substrate scope is also limited. We, therefore, began our investigation with malonates tethered cyclohexadienone substrates **3.45**-**3.47** in the hope the ee's could be improved using BIMP catalysts and the substrate scope could also be expanded. The synthesis of these cyclohexadienone substrates followed a two-step procedure. Initial treatment of *p*-cresol with hypervalent iodine reagent $PhI(OAc)_2$[25] yielded cyclohexadienone **3.11** in 92% yield. In parallel, malonic acid half esters **3.39**-**3.41** were prepared from their corresponding malonates **3.36**-**3.38** in 64-98% yield. Subsequent treatment of malonic acid half esters **3.39**-**3.41** with oxalyl chloride and catalytic amount of DMF yielded the corresponding acid chlorides **3.42**-**3.44** (Scheme 3.11), which were used *in situ* for the esterification of **3.11** to give the pre-cyclised substrates **3.45**-**3.47** in 60 - 81% yields (Scheme 3.10).



3.21 **3.11**

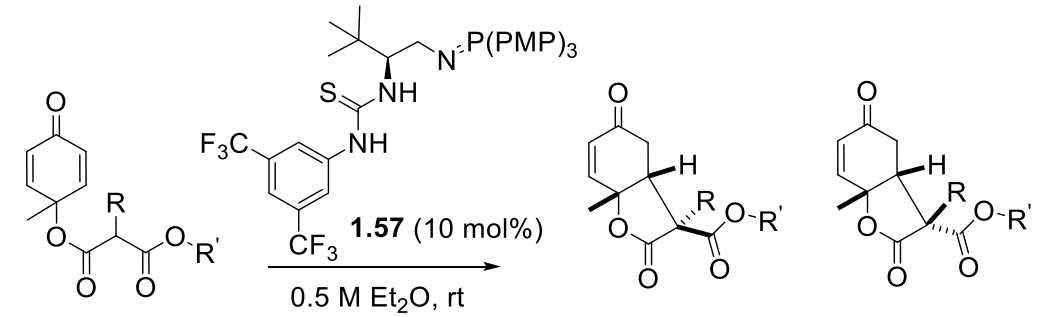
Scheme 3.10. Cyclohexadienones tethered to malonates substrates 3.45-3.47 synthesis. *a) $PhI(OAc)_2$ (1.2 eq) and MeOH (0.5 M), 92%; b) DCC (3.0 eq), DMAP (0.1 eq), malonic acid (2.0 eq) in MeCN (0.2 M), 60 - 81%;*



R = H, R' = Me:	**3.36**	**3.39**	**3.42**
R = Et, R' = Me:	**3.37**	**3.40**	**3.43**
R = H, R' = ^{t}Bu:	**3.38**	**3.41**	**3.44**

Scheme 3.11. Synthesis of acid chloride from corresponding malonates. *a) KOH, 2 h, then HCl, 64 - 98%; b) $(COCl)_2$, DMF, 30 min.*

With the cyclohexadienone substrates **3.45**-**3.47** in hand, we first studied the intramolecular Michael addition of substrate **3.45** with BIMP catalyst **1.57**. Pleasingly, using 10 mol% catalyst, the cyclised product was obtained in quantitative yield after 24 h as a 2:3 (**3.48a**:**3.48b**) mixture of two inseparable diastereomers (Scheme 3.12). Unfortunately, the ee's could not be measured as the enantiomers could not be separated on the HPLC or GC columns available in our lab.



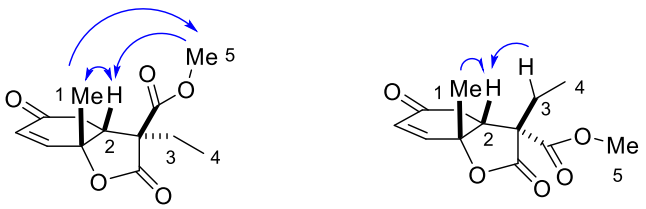
R = H, R' = Me, **3.45**
R = Et, R' = Me, **3.46**
R = H, R' = ^{t}Bu, **3.47**

3.48a **3.48b**
3.49a **3.49b**
N.A.

Scheme 3.12. Asymmetric desymmetrisation *via* enantioselective Michael addition of malonates tethered cyclohexadienones. *The reaction was performed with 0.1 mmol substrate, 0.01 mmol catalyst in 0.2 mL Et_2O.*

Substrate **3.46** bearing an α-substituted malonate was also tested for comparison in this reaction. Initially, treatment of **3.46** with 10 mol% BEMP gave racemic cyclised products (±)-**3.49a** and (±)-**3.49b** as a 4:1 mixture of diastereomers in

quantitative yield after 48 h. The relative stereochemistry of the diastereomers was determined by Nuclear Overhauser Effect (NOE) NMR experiments (Scheme 3.13). The major diastereomer, (±)-**3.49a**, showed a clear NOE interaction between the hydrogen on C (1) and the hydrogen on C (2) in a 1D NOE experiment. In another NOE experiment, irradiating hydrogen on C (1) showed a signal of the hydrogen on C (5). On the basis of this, the major diastereomer was assigned with the structure shown in Scheme 3.13. In addition, irradiating hydrogen on C (5) showed a signal of the hydrogen on C (2), thus supporting the assignment. For the minor diastereomer (±)-**3.49b**, 1D NOE experiment irradiating the C (1) hydrogen showed an NOE to C (2) hydrogen. Irradiating the C (3) hydrogen also showed an NOE to C (2) hydrogen. Thus the structure was assigned as shown in Scheme 3.13.



3.49a **3.49b**

Scheme 3.13. Assignment of relative stereochemical configuration of diastereomers 3.49a and 3.49b.

The same reaction was subsequently performed with BIMP catalyst **1.57**, and product was obtained as a 2:3 (**3.49a**:**3.49b**) mixture of diastereomers in quantitative yield after 48 h. Unfortunately, the ee's could not be measured as the enantiomers could not be separated on the HPLC or GC columns.

The cyclisation reaction was also conducted using substrate **3.47** possessing a

tert-butyl ester group on the malonate. However, no product was observed in reactions using either BEMP, or BIMP catalyst **1.57** or **2.104** after 96 h. This is presumably due to the steric hindrance of *tert*-butyl ester that prohibits the formation of the cyclised product.

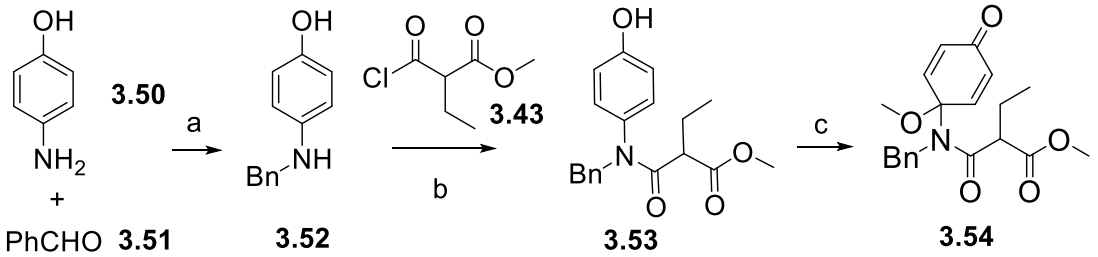
3.5 Intramolecular Cyclisation of Malonamates Tethered Cyclohexadienones

Due to the unsuccessful results with malonates tethered cyclohexadienones, we decided to study the cyclisation of malonamate tethered cyclohexadienone **3.54**. To the best of our knowledge, the cyclisation of this new substrate has not been reported in literature, presumably due to the high p*Ka* of malonamate. An analogy of the p*Ka* difference between an amide and an ester is described below. The p*Ka* of α-proton on the N,N-dimethyl acetoacetamide (p*Ka* = 18.2 in DMSO) is 4 unit higher than that of ethyl acetoacetate (p*Ka* = 14.2 in DMSO).[26,27] In addition, the α-substituent on the malonamate has made the α-proton on the malonamate even less acidic due to the $A_{1,3}$-strain between the N- and the α-substituent.[28,29] Therefore, we could speculate that the p*Ka* of α-substituted malonamate is higher than α-substituted malonate.

3.5.1 Substrate Synthesis

Because of the superior reactivity – linked directly to the enhanced Brønsted basicity – of our BIMP catalysts in the sulfa-Michael reaction (chapter 2) and other

reactions developed in our group[30,31], we envisaged that the relatively high p*Ka* of malonamate pronucleophile could be overcome and the intramolecular cyclisation of malonamate tethered cyclohexadienone would become feasible.



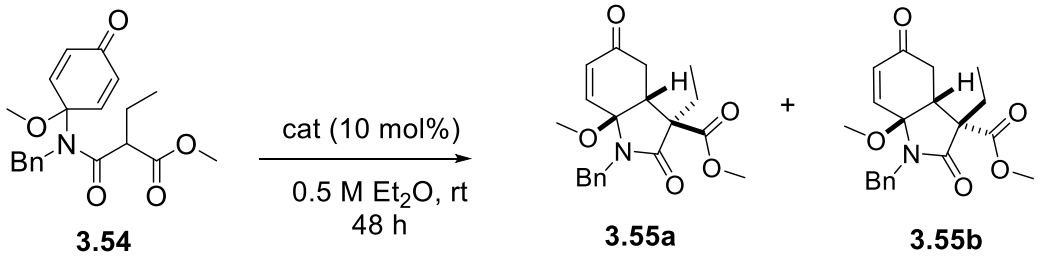
Scheme 3.14. Substrate Synthesis. *a) MeOH, reflux then $NaBH_4$, 30 min, >99%; b) pyridine, overnight, 83%; c) $PhI(OAc)_2$, MeOH, 1 h, 75%.*

The synthesis of the cyclohexadienone substrate **3.54** was carried out in three steps as shown above (Scheme 3.14). Initial condensation of 4-aminophenol and benzaldehyde followed by *in situ* reduction gave secondary amine **3.52** in quantitative yield. Subsequent treatment of amine **3.52** with acid chloride **3.43** gave amide **3.53** in 83% yield. Finally, amide **3.53** was treated with $PhI(OAc)_2$ to afford the cyclohexadienone substrate **3.54** in 75% yield.

3.5.2 Initial Trial of the Catalytic Intramolecular Cyclisation

With the substrate **3.54** in hand, we set out to investigate the catalytic intramolecular cyclisation reaction. BEMP (10 mol%) was first used to catalyse the synthesis of the racemic product. Interestingly, no reaction was observed after 96 h. According to a modified literature procedure[32], a stoichiometric amount of DBU was used to promote the reaction and a 6:1 (**3.55a**:**3.55b**) mixture of two diastereomers was obtained in 86% combined yield (Table 3.1, entry 1). An enantioselective reaction was first performed using a cinchona derived

bifunctional catalyst **1.25** (Scheme 3.8), but no reaction was observed after 96 h (Table 3.1, entry 2). When BIMP catalyst **1.57** was employed, the reaction gave a 1:1 (**3.55a**:**3.55b**) mixture of diastereomers[x] in 57% conversion after 48 h. The ee's for **3.55a** and **3.55b** are 74% and 39% respectively. Interestingly, the unreacted starting material had an enantiomeric excess of 66% (Table 3.1, entry 5).



3.54 **3.55a** **3.55b**

Table 3.1 Initial trial of the catalytic intramolecular cyclisation

Entry[a]	Time (h)	Cat	Conversion[b] to **3.55** (%)	dr[b]	ee **3.55a** (%)	ee **3.55b** (%)	ee **3.54** (%)
1	24	DBU[c]	86[d]	6:1	-	-	-
2	96	**1.25**	0	-	-	-	-
3	1	**1.57**	25	3:1	84	23	45
4	3	**1.57**	35	5:2	78	20	66
5	48	**1.57**	57	1:1	74	39	66

*a) Reaction was conducted using 0.1 mmol of **3.54**, 0.01 mmol of catalyst in 0.2 mL of Et_2O at rt; b) Determined by ^{1}H-NMR analysis of the crude reaction mixture; c) 100 mol% DBU was used; d)*

[x] Quantitative mass return was obtained and the ratio of diastereomers was determined by ^{1}H NMR analysis of the crude reaction mixture. The relative stereochemical configuration was determined by analogy to cyclised products **3.80a** and **3.80b**, which were determined by NOE and HOSEY NMR experiments.

Yield was measured based on isolated product.

To gain better understanding of the reactivity and stereoselectivity of this reaction, an aliquot of the reaction mixture was taken at 1 h and 3 h and analysed by ^{1}H NMR to monitor the progress of the reaction (Table 3.1, entry 3 and 4). The aliquots were also subjected to chiral HPLC analysis to obtain the ee's of each compound. From the table, we could see that the reaction rate was fast at the beginning (Table 3.1, entry 3 and 4). The final conversion at 48 h is low considering the relative high conversions at 1 h and 3 h. This suggested that the reaction rate decreased over time. A possible explanation is that the catalyst was decomposed during the reaction. The dr of the product and the ee of the diastereomer **3.55a** also eroded over time. At this stage, we concluded that the reaction might be reversible; however, more experiments is needed to confirm this (*vide infra*).

3.5.3 Optimisations of the Intramolecular Cyclisation

With the initial promising results in hand, we decided to perform a brief screen of temperatures and solvents on this intramolecular cyclisation in the hope that the reactivity and stereoselectivity of the reaction could be improved. The results are shown in Table 3.2 and 3.3, respectively.

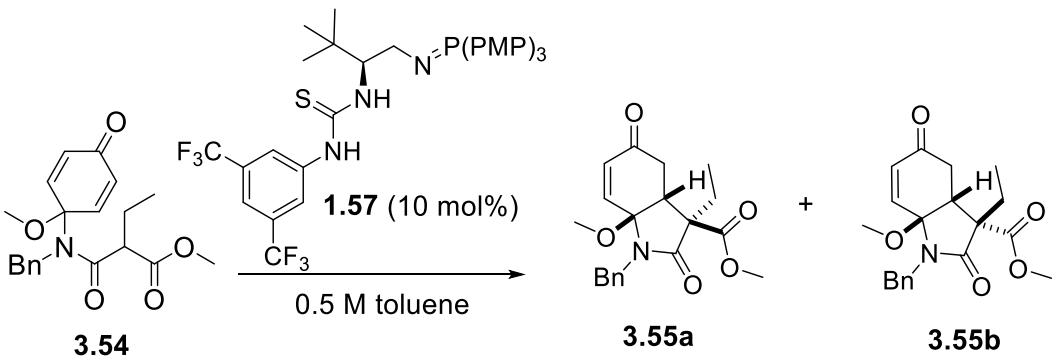


Table 3.2 Temperature Screen of intramolecular cyclisation

Entry[a]	T (°C)	t (h)	Conversion[b] to **3.55** (%)	dr[b]	ee **3.55a** (%)	ee **3.55b** (%)	ee **3.54** (%)
1	rt	48	36	1:1	75	37	40
2	55	24	97	2:3	45	17	N.A.
3	0	96	35	1:2	65	20	60

a) The reactions were conducted using 0.1 mmol substrate, 0.01 mmol catalyst in 0.2 mL toluene; b) Determined by ^{1}H-NMR analysis of the crude reaction mixture.

The reaction was first carried out in toluene at room temperature, and a 1:1 (**3.55a**:**3.55b**) mixture of two diastereomers were obtained in 36% conversion. The ee's of **3.55a** and **3.55b** were 75% and 37% respectively. The reaction was then conducted at 55 °C in toluene. Most of the starting material was converted to the product and gave a 2:3 (**3.55a**:**3.55b**) mixture of diastereomers. The ee's of **3.55a** and **3.55b** were 45% and 17% ee, respectively, lower than those of room temperature example (Table 3.2, entry 1 vs 2). Finally, the reaction was performed at 0°C; lower reactivity was observed and the prolonged reaction time (96 h) led to an erosion of ee (Table 3.2, entry 3).

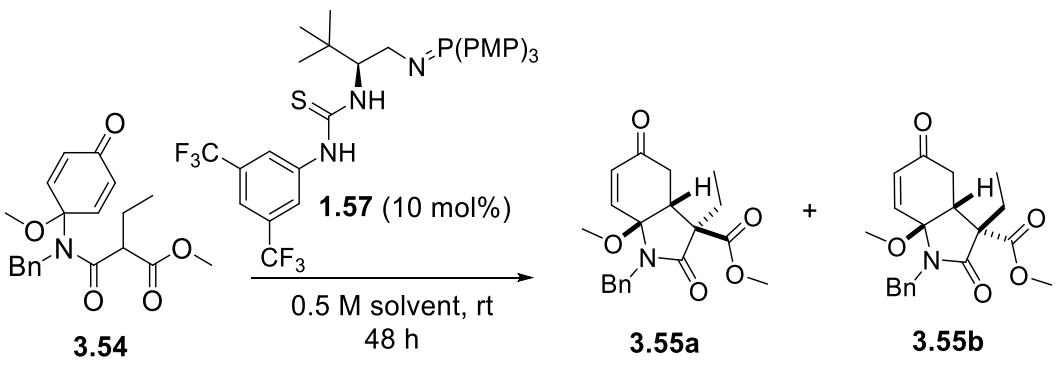
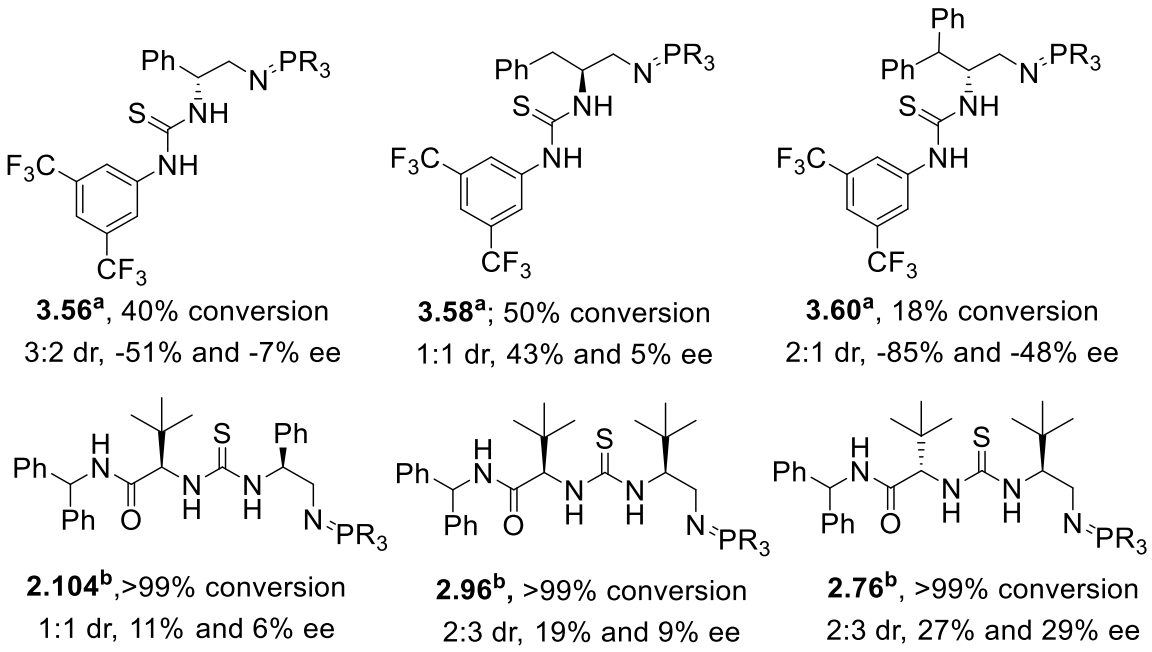


Table 3.3 Solvent Screen of intramolecular cyclisation

Entry[a]	solvent	Conversion[b] to **3.55** (%)	dr[b]	ee **3.55a** (%)	ee **3.55b** (%)	ee **3.54** (%)
1	CH_2Cl_2	27	1:5	40	29	3
2	TBME	57	1:1	76	35	50
3	EtOAc	30	2:3	68	25	47

a) The reactions were conducted using 0.1 mmol substrate, 0.01 mmol catalyst in 0.2 mL solvent; b) Determined by ^{1}H-NMR analysis of the crude reaction mixture.

A brief screen of solvent was subsequently conducted (Table 3.3). Interestingly, when CH_2Cl_2 was used, the reaction gave a 1:5 (**3.55a**:**3.55b**) mixture of two diastereomers. However, the conversion and ee's were poor (Table 3.3, entry 1). The use of TBME (tert-butyl methyl ether) as solvent afforded a 1:1 (**3.55a**:**3.55b**) mixture of diastereomers in 57% conversion. The ee's of **3.55a** and **3.55b** were 76% and 35%, respectively (Table 3.3, entry 2). Finally, using EtOAc as solvent gave lower conversion and slightly lower ee's compared to that of TBME (Table 3.3, entry 2 vs 3).

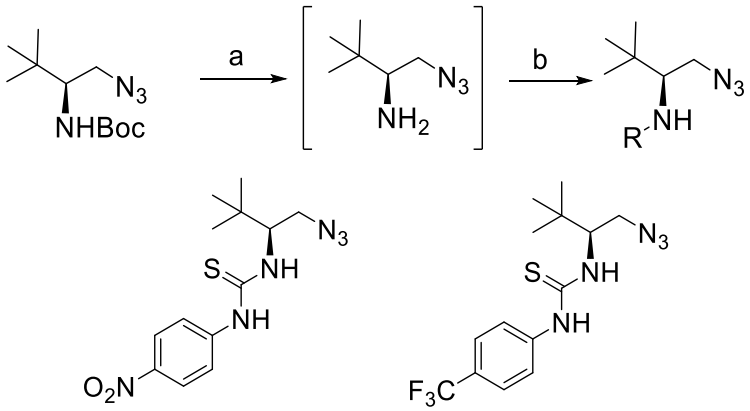


Scheme 3.15. Intramolecular cyclisation promoted by various BIMP catalysts (R =PMP).[xi] *Reactions were conducted with 0.1mmol substrate, 0.01 mmol catalyst in 0.2 mL TBME at rt. a) reaction quenched after 48 h; b) reaction quenched after 24 h.*

Having identified TBME as the best solvent for the enantioselective intramolecular cyclisation, we then screened representative BIMP catalyst family members for this reaction (Scheme 3.15). The derivatives of catalyst **1.57** were first investigated. Catalysts **3.56** and **3.58** gave similar conversions, but lower ee's compared with that of **1.57**. Catalyst **3.60** gave lower conversion but higher dr and the highest ee so far (85% ee for the major diastereomer). The lower reactivity probably arise from the electron withdrawing effect of the benzhydryl group that decreased the basicity of the iminophosphorane moiety.[33] The reactions catalysed by **3.56** and **3.60** gave the opposite enantiomer compared to those catalysed by **1.57** and **3.58**. This suggested that the stereochemical configuration of the product was

[xi] Catalyst **3.58** and **3.60** were prepared from their corresponding catalyst precursors **3.57** and **3.59** via Staudinger reaction. Ee's of the remaining cyclohexadienones are not shown here.

determined largely by the stereogenic centre nearest to the iminophosphorane. Next, the cyclisation reaction was carried out with three amido-thiourea BIMP catalysts **2.104**, **2.96** and **2.76**. The reaction catalysed by previously best catalyst **2.104** in the SMA reaction afforded the cyclisation product in >99% conversion after 24 h, but with very low ee's. The other two amido-thiourea BIMP catalysts gave similar results.



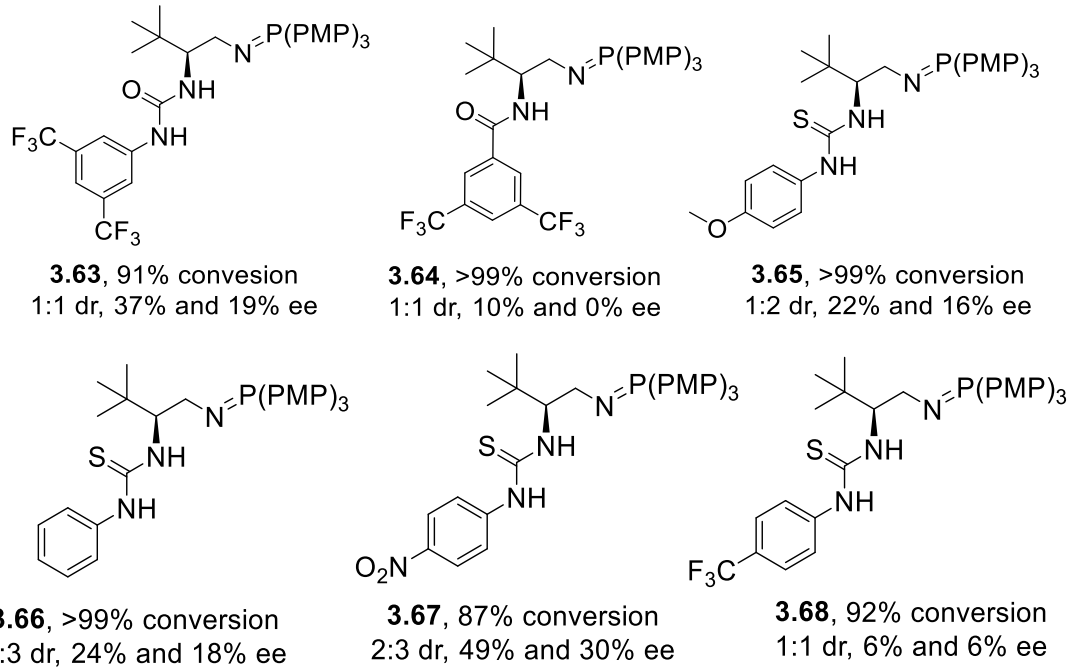
3.61, 79% yield **3.62**, 78% yield

Scheme 3.16. Synthesis of various H-bond donor BIMP catalysts. *a) TFA, then NaOH; b) isothiocyanate, isocyanate or acid chloride, Et_2O; c) $P(PMP)_3$, Et_2O;*

As the 1st generation BIMP catalysts **1.57** and **3.60** could afford the cyclised product in high ee's, we decided to optimise the H-bond donor group based on the *tert*-leucine derived 1st generation BIMP catalyst (Scheme 3.16). These catalyst precursors were prepared by coupling the *L-tert*-leucine derived amino azide to the corresponding isothiocyanate. Excellent yields were obtained in the synthesis of these catalyst precursors **3.61** and **3.62**. The catalysts[xii] were then formed *via* the Staudinger reaction with $P(PMP)_3$ and used *in situ* for the cyclisation reaction.

[xii] The catalyst precursors to **3.63**-**3.66** were synthesised by other members in the group.

The results are shown below (Scheme 3.17).



Scheme 3.17. Intramolecular cyclisation promoted by BIMP catalysts with different H-bond donor groups. *Catalytic reactions were conducted with 0.1mmol substrate, 0.01 mmol catalyst in 0.2 mL TBME at rt for 48 h.*

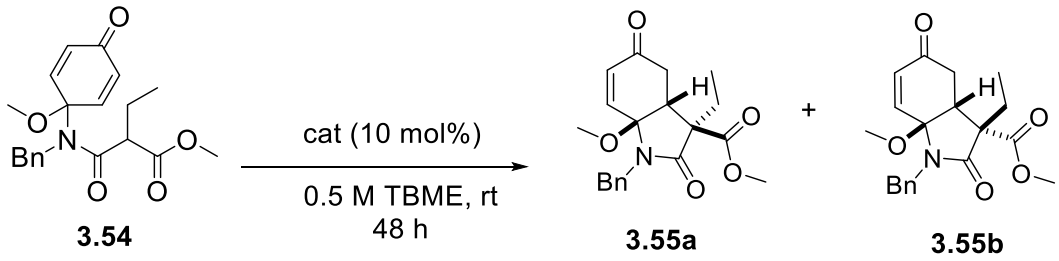
The reaction was first performed with catalysts bearing urea H-bond donor **3.63** and amide H-bond donor **3.64**. Higher reactivities were obtained and the reactions were almost complete after 48 h compared with that of catalyst **1.57**. However, the ee's of the products were lower. We then varied the aromatic substituent on the H-bond donor moiety of the catalyst, ranging from electron-donating methoxide group to electron withdrawing nitro and CF_3 group. All these catalysts were tested in the catalytic cyclisation reaction and generally gave good conversion after 48 h. Unfortunately, catalysts **3.65**, **3.66**, **3.67** and **3.68** all gave the cyclised products in moderate dr's and poor to moderate ee's. Overall, the best result was obtained when catalyst **1.57** was used, and we concluded that 3,5-$(CF_3)_2C_6H_3$ thiourea H-bond donor is superior to other H-bond donors in terms of enantioselectivity for

this intramolecular cyclisation reaction.

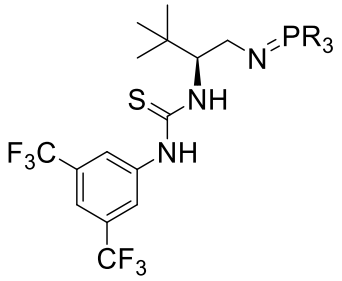
The BIMP catalysts possessing a less acidic H-bond donor group, such as, thiourea attached with aliphatic group (Scheme 3.15), amide or urea (Scheme 3.17), afforded the cyclised product in higher conversion than that of BIMP catalyst **1.57** bearing 3,5-$(CF_3)_2C_6H_3$ thiourea group. This suggested that the pK_{BH+} of the iminophosphorane on the former catalysts are lower than that of the later catalyst. The lower reactivity of catalyst **1.57** possessing the 3,5-$(CF_3)_2C_6H_3$ thiourea relative to BIMP catalysts bearing less acidic thiourea protons may be due to competing catalyst aggregation in the former case. Solution state NMR of catalyst **1.56** revealed that it existed in exchange with its dimeric form. Preliminary computational calculations revealed that the monomeric form may preferentially exist as the zwitterion with the acidic thiourea proton residing on the iminophosphorane. We also hypothesised that the structure of the dimeric form in solution is similar to that observed in the solid state and it is catalytically inactive due to the internal interaction between thiourea and iminophosphorane.[34] Therefore, we propose that catalyst possessing less acidic H-bond donor group could shift the catalyst monomer/dimer equilibrium to the active monomer. In addition, a less acidic H-bond donor group weakens the intramolecular proton transfer from hydrogen on the thiourea to iminophosphorane; thus increases the reactivity of the catalyst. The reactions promoted by the catalysts possessing less acidic H-bond donor group indeed are faster; however, they afforded the product

in lower ee as exemplified in the results shown in Scheme 3.15 and 3.17.

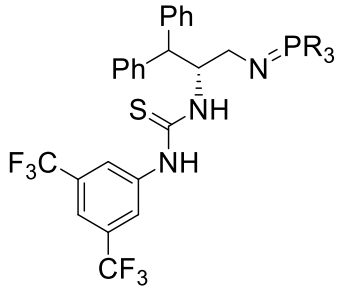
Finally, we decided to investigate the iminophosphorane moiety as it plays an important role in the catalyst through deprotonation of the pronucleophile and H-bonding with the substrate. This means changing the phosphines used in the Staudinger reaction could have an influence on the reactivity and enantiocontrol of the reaction.



3.54 **3.55a** **3.55b**

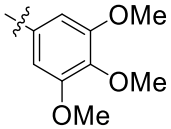
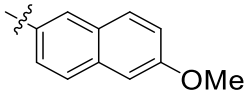


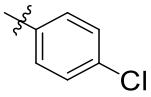
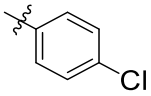
3.69-3.72



3.73

Table 3.4 Screen of catalyst with variations to the phosphine group on the intramolecular cyclisation

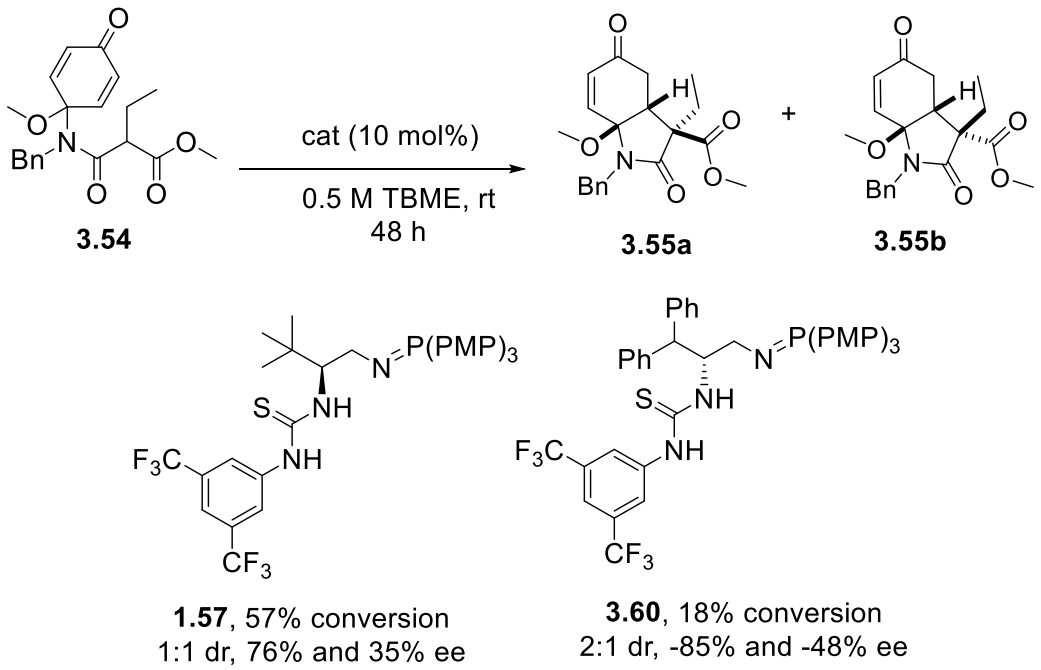
Entry[a]	Cat	R	Conversion[b] to **3.55** (%)	dr[b]	ee **3.55a** (%)	ee **3.55b** (%)
1	**3.69**		40	1:1	69	23
2	**3.70**		30	1:1	69	23
3	**3.71**	Ph	33	1:2	65	20

4	**3.72**		27	1:13	37	49
5	**3.73**		N.R.	N.A.	N.A.	N.A.

a) All reactions were conducted with 0.1mmol substrate, 0.01 mmol catalyst in 0.2 mL TBME at rt for 48 h; b) Determined by ^{1}H-NMR analysis of the crude reaction mixture.

The phosphine used previously to generate BIMP catalyst was $P(PMP)_3$. We decided to vary the aromatic substituents on the phosphine in order to tune the basicity of the iminophosphorane (Table 3.4). Catalyst **3.69**, **3.70** and **3.71** possessing different phosphine groups all gave the products in similar dr's, lower conversions and ee's compared with catalyst **1.57** (Table 3.4 entry 1, 2 and 3 vs Table 3.3, entry 2). We then introduced the tris(4-chlorophenylphosphine), which bears the electron withdrawing Cl atom at the 4-position on the phenyl ring to the catalyst. Interestingly, under the catalysis of **3.72**, the reaction gave an excellent dr of 1:13 with **3.55b** as the major diastereomer with 49% ee. However, lower conversion was obtained, which is likely due to the decreased basicity of the iminophosphorane. As the catalyst possessing tris(4-chlorophenylphosphine) gave a high dr for the reaction, it was also reacted with 3,3-diphenyl-*L*-alanine derived amino azide to form catalyst **3.73** in the hope that this catalyst would give product with better stereoselectivity. Catalyst **3.73** was then tested in the cyclisation reaction, to our disappointment, no reaction was observed at all after 48 h. This is probably due to the weak Brønsted basicity of the catalyst, arising from a combination of the electron withdrawing effect of benzhydryl group and

tris(4-chlorophenylphosphine) group.



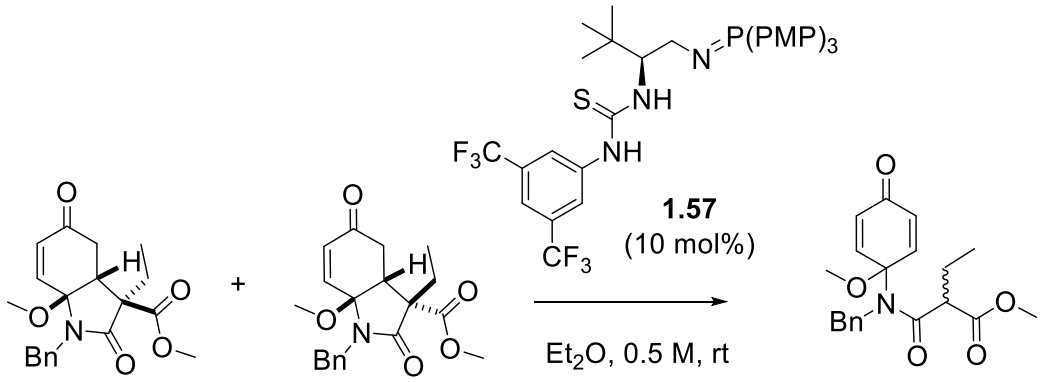
Scheme 3.18. Optimal conditions for the enantioselective intramolecular cyclisation of malonamate tethered cyclohexadienone. *Both reactions were conducted with 0.1 mmol substrate, 0.01 mmol catalyst in 0.2 mL TBME at rt for 48 h.*

After extensive catalyst and conditions optimisation for the intramolecular cyclisation reaction, we obtained two promising results (Scheme 3.18). The reaction catalysed by 3,3-diphenyl-*L*-alanine derived BIMP catalyst **3.60** afforded the product in 18% conversion, 2:1 dr, 85% and 48% ee. The reaction with *L-tert*-leucine derived BIMP catalyst **1.57** gave the product in 57% conversion, 1:1 dr, 76% and 35% ee.

3.5.4 Reversibility of the reaction

Based on our previous observations that the dr and ee's of the product changed over time (Table 3.1), we suggested that the reaction is reversible. To verify this, we subjected the 5,6-bicyclic product as a 1:1 (**3.55a**:**3.55b**) mixture of diastereomers with 11% and 6% ee, respectively (Table 3.5, entry 1), to the

reaction conditions of the previous cyclisation, and the results are given in table 3.5, entry 2.



3.55a **3.55b** **3.54**

Table 3.5 Reversibility of the reaction using cyclised product 3.55 catalysed by 1.57

Entry[a]	t (h)	Conversion[b] to **3.54** (%)	dr[b] of **3.55a**:**3.55b**	ee **3.55a** (%)	ee **3.55b** (%)	ee **3.54** (%)
1	0	0	1:1	11	6	0
2	48	34	3:2	71	20	91

*a) Reaction was conducted using 0.1 mmol of **3.55**, 0.01 mmol of catalyst **1.57** in 0.2 mL of toluene at rt; b) Determined by ^{1}H-NMR analysis of the crude reaction mixture, quantitative mass return was recovered after the reaction.*

After 48 h, cyclohexadienone **3.54** was obtained in 34% conversion. HPLC analysis showed product **3.54** was enantioenriched with an ee of 91%. This indeed demonstrates that the reverse reaction (retro-Michael) is energetically possible, and that the regeneration of cyclohexadienone **3.54** is enantioselective. Furthermore, the ee's of the cyclised compounds (**3.55a** and **3.55b**) had also increased to 71% and 20%. One explanation for the observed retro-Michael reaction is that the cyclised products (**3.55a** and **3.55b**) possess two quaternary

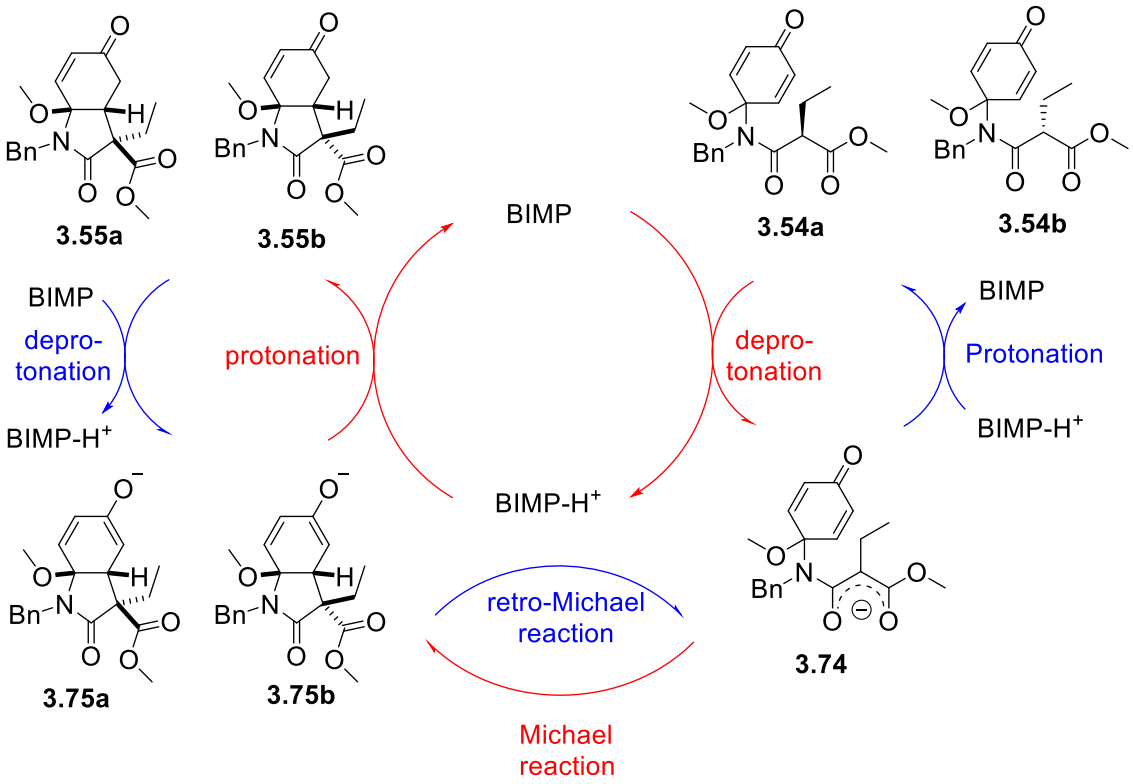
and one tertiary stereogenic centres in close proximity; therefore the products are prone to undergo ring-opening reaction to relieve the steric congestion. A more detailed reaction mechanism is proposed below in section 3.5.5.

3.5.5 Proposed Reaction Mechanism

A mechanistic profile presenting forward Michael reaction and retro-Michael reaction is shown in Scheme 3.19.

The reaction pathway for the forward Michael reaction follows a three-step sequence, namely initial deprotonation of **3.54**, subsequent Michael reaction and final protonation of diastereomeric enolate **3.75a** and **3.75b** (Scheme 3.19).

The remaining starting material **3.54** is enantioenriched after the forward Michael addition. One possible explanation is that the rates of deprotonation of cyclohexadienone **3.54a** and **3.54b** by the catalyst are different, thus resulting in a kinetic resolution (Scheme 3.19). The chiral BIMP catalyst probably forms H-bonds with the carbonyl group on the malonamate, and selectively deprotonates one enantiomer over the other. The subsequent Michael reaction takes place to form a pair of diastereomeric cyclised intermediates **3.75a** and **3.75b**. Protonation of the enolate affords the final cyclised products **3.55a** and **3.55b**. As cyclised products **3.55a** and **3.55b** are enantioenriched after the reaction, this indicates that the bond formation in the Michael reaction is also controlled by the chiral BIMP catalyst.



Scheme 3.19. Proposed reaction pathway for the Michael reaction (drawn in red) and retro-Michael reaction (drawn in blue).

The reaction pathway for the retro-Michael reaction follows a similar three-step sequence, namely initial deprotonation of **3.55a** and **3.55b**, subsequent retro-Michael reaction and final protonation of enolate **3.74** (Scheme 3.19).

Although ketones have relatively high pKa (for example, acetone, pKa 26.5 in DMSO)[26], BIMP catalyst is still able to deprotonate its α-proton (*vide infra* Section 3.6) in the initial deprotonation of cyclised product **3.55a** and **3.55b**. In addition, the ee's of the diastereomers **3.55a** and **3.55b** were both found to have increased after the reaction (Table 3.5, entry 1 vs 2). One possible explanation is that the rates of deprotonation of **3.55a** and **3.55b** by the catalyst are different, thus resulting in a kinetic resolution.

The subsequent retro-Michael reaction occurs presumably to relieve the steric

congestion of multiple quaternary and tertiary carbons in close proximity in the molecule. Although the retro-Michael addition more likely occurs in the presence of heteroatom pronucleophiles,[35,36] it is known to occur in molecules where sterically congested all-carbon quaternary stereogenic centres are present. For example, Cordova reported a reversible Michael addition of dimethyl propargylmalonate to α,β-unsaturated aldehydes catalysed by pyrrolidine and a palladium complex.[37] Also, Hayashi presented another reversible Michael addition of nitroalkanes to β,β-disubstituted α,β-unsaturated aldehydes catalysed by diphenylprolinol catalyst.[38] Therefore, the retro-Michael reaction of cyclised product **3.55a** and **3.55b** is not unexpected.

Finally, the enolate **3.74** undergoes enantioselective protonation to afford enantioenriched cyclohexadienone **3.54** (Table 3.5, entry 2). The origin of the enantioselectivity probably arises from H-bonding interactions between the protonated form of the chiral BIMP catalyst (BIMP-H^+) and the enolate **3.74**, allowing the preferential protonation of prochiral enolate.

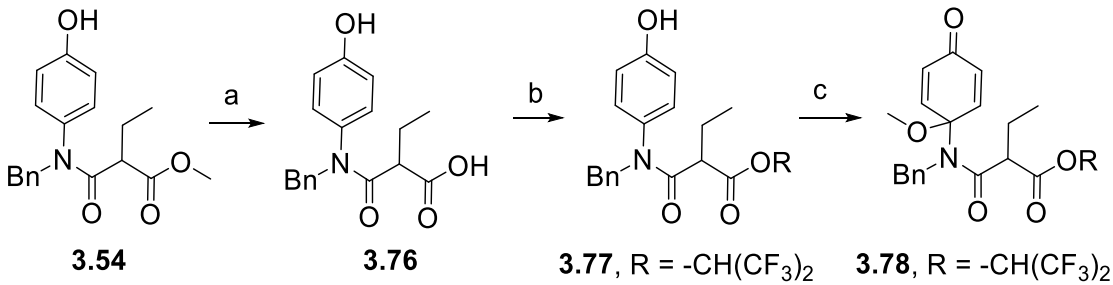
Overall, in both forward and retro-Michael reaction, the BIMP catalyst is able to catalyse the kinetic resolution of the starting material and the enantioselective formation of the product.

Further investigations into this Michael reaction are required to fully understand the reaction pathway and origin of stereocontrol.

3.5.6 Substrate Optimisation for the Cyclisation Reaction

Following the reaction mechanism, we continued our investigation in the enantioselective desymmetrisation. The aims of this project, as mentioned in Section 3.3, were to test the catalytic ability of BIMP catalysts on challenging pronucleophiles and to expand the reaction scope of enantioselective desymmetrisation. We, therefore, decided to modify the existing substrates with the expectation that the new substrates may not suffer from the same reactivity issues. We envisaged that there are two possible solutions to solve the reactivity problem, one is to slightly increase the acidity of the pronucleophile; the other is to decrease the steric congestion in the product.

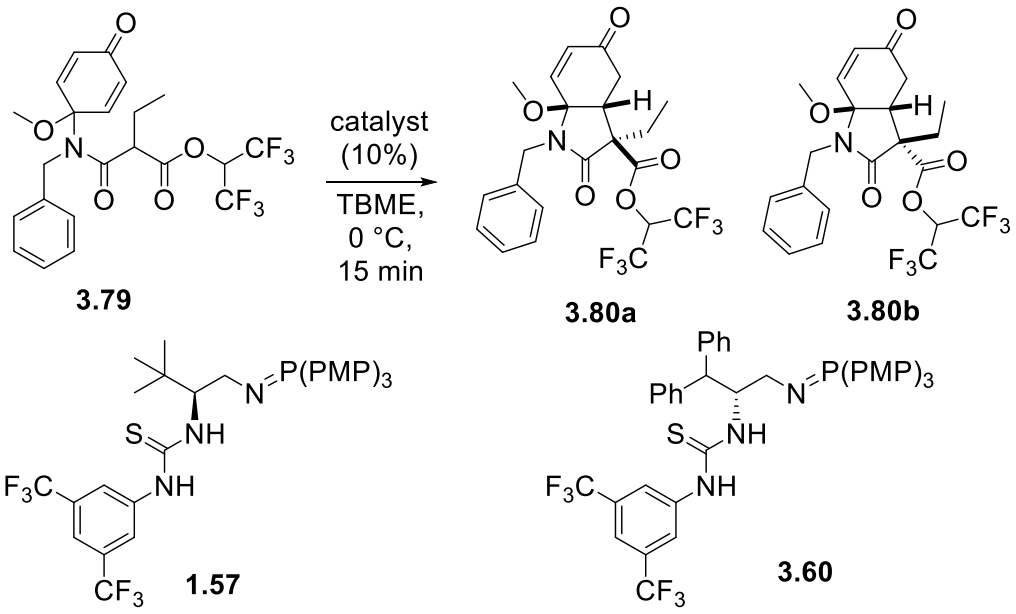
We set out to investigate the first solution, i.e. slightly increasing the acidity of the malonamate pronucleophile. To this end, we prepared the hexafluoroisopropyl ester derivative **3.78**, because hexafluoroisopropyl ester is a strong electron withdrawing group and is able to activate the malonamate pronucleophile.[39] Substrate **3.78** was synthesised *via* transesterification from methyl ester derivative **3.54** followed by an oxidative dearomatisation to afford cyclohexadienone substrate **3.78** (Scheme 3.20).



Scheme 3.20. Synthesis of hexafluoroisopropyl ester derivative of the precyclised substrate. *a) LiOH, THF/MeOH/H_2O, 83% yield; b) DCC, DMAP, $(CF_3)_2CHOH$, 81%; c) $PhI(OAc)_2$, MeOH,*

43%.

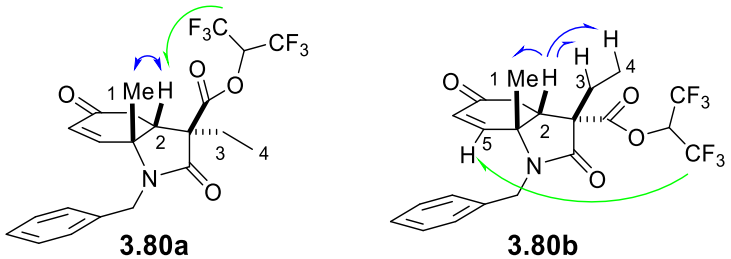
We then tested the enantioselective cyclisation reaction with this substrate. To our delight, the reaction went to completion in 15 min at 0 °C with catalyst **1.57** and gave a 2:1 (**3.80a**:**3.80b**) mixture of diastereomers in quantitative yield. Disappointingly, the ee's were only 4% and 3% (Scheme 3.21). When **3.60** was used as catalyst, the reaction also went to completion in 15 min at 0 °C and gave 1:1 (**3.80a**:**3.80b**) mixture of diastereomers in 96% yield. The ee's of **3.80a**:**3.80b** were 58% and 23% ee, respectively. The reactivities were significantly increased in both cases, but to our disappointment, the ee's were decreased compared to methyl ester malonamate substrate **3.54**.



Scheme 3.21. Michael reaction with hexafluoroisopropyl ester derivative 3.79. *Reactions were conducted with 0.1mmol substrate, 0.01 mmol catalyst in 0.2 mL TBME.*

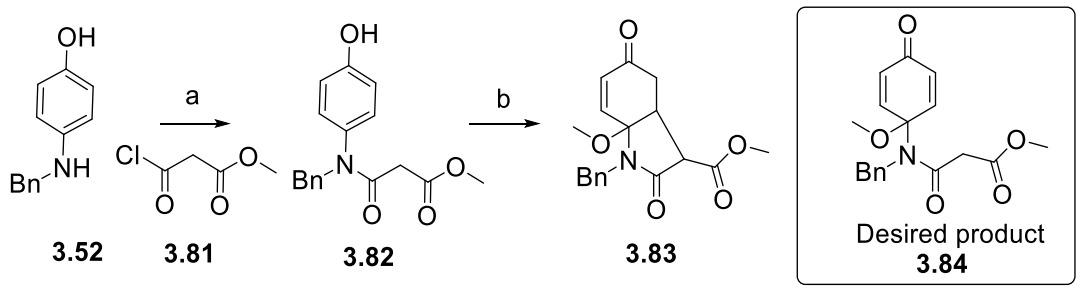
The relative stereochemical configuration of the two diastereomers was determined by NOE experiments. Diastereomer **3.80a** showed a clear NOE interaction between the hydrogen on C (1) and the hydrogen on C (2) in a 1D NOE

experiment. A further ^{1}H-^{19}F heteronuclear Overhauser spectroscopy (HOSEY) was conducted. Irradiating the fluorine atom showed a signal on C (2) hydrogen. Thus diastereomer **3.80a** was assigned with the structure shown in Scheme 3.22. For diastereomer **3.80b**, 1D NOE experiment irradiating the C (2) hydrogen showed signals on C (1), C (3) and C (4) hydrogens. Thus the structure was assigned as shown in Scheme 3.22. Irradiating the fluorine atom also showed a signal on C (5) hydrogen. This supported the structure assigned for (±)-**3.80b**.



Scheme 3.22. Relative stereochemical configuration of 3.80 determined by NOE and HOSEY.

The use of more acidic pronucleophile increased the reactivity, but decreased the selectivity of the reaction. Next, we decided to modify the cyclohexadienone substrate by reducing the steric congestion in the cyclised product formed. Accordingly, cyclohexadienone substrate **3.84** was targeted as it possesses fewer substituents on the nucleophilic carbon centre. The hope was that this substrate would be more reactive in the cyclisation reaction and give rise to more stable cyclised product.

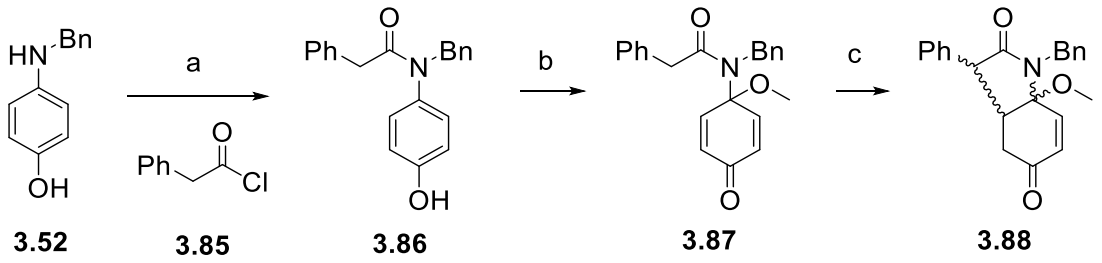


Scheme 3.23. Synthesis of malonamate substrate 3.84. *a) pyridine, 88%; b) PhI(OAc)$_2$, MeOH, 80%.*

The synthesis of substrate **3.84** was carried out in two steps. Initial amide coupling of secondary amine **3.52** and acid chloride **3.81** using our standard conditions afforded amide **3.82** in excellent yield (88%). However, attempted dearomatisation of this amide gave exclusively cyclised product **3.83** at room temperature (Scheme 3.23). Lowering the reaction temperature to –20 °C also resulted in the exclusive formation of cyclised product **3.83**. Further lowering of the temperature to –50 °C gave no reaction. Despite our attempts, cyclohexadienone substrate **3.84** could not be obtained and the synthesis was not pursued any further.

3.6 Intramolecular Cyclisation of Amide Tethered Cyclohexadienone

We postulated that the exclusive formation of cyclised product **3.83** is due to the relatively high acidity of the malonamate, therefore, we decided to reduce the acidity of the malonamate by replacing the ester group on the malonamate with a phenyl group.



Scheme 3.24. Synthesis and enantioselective desymmetrisation of 3.87. *a) Et_3N, 59%; b) $PhI(OAc)_2$, MeOH, 53%; c) catalyst **1.57** (10 mol%), Et_2O (0.5 M), rt*, 84%.

To this end, cyclohexadienone substrate **3.87** was prepared in two steps. Initial treatment of secondary amine **3.52** with acid chloride **3.85** afforded amide **3.86** in 54% yield. Subsequent treatment of amide **3.86** with $PhI(OAc)_2$ afforded the cyclohexadienone **3.87** in 91% yield (Scheme 3.24).

With the substrate **3.87** in hand, the enantioselective cyclisation reaction was carried out with catalyst **1.57** and pleasingly, excellent conversion to product **3.88** was observed after 48 h. Overall, mixture of four diastereomers was obtained in 84% combined yield. The dr was 8:2:1:0.25 and ee's of the two major diastereomers were 45% and 30%, respectively. The p*Ka* of diethyl phenylacetamide is 26.6 in DMSO,[24] comparable to that of acetone (p*Ka* in DMSO, 26.5)[26]. This is much higher than some of the more commonly studied pronucleophiles, for example, dimethyl malonate (p*Ka* in DMSO, 15.9)[23], nitromethane (p*Ka* in DMSO, 17.2)[40]. In addition, iminophosphorane possesses a similar basicity to that of DBU (p*Ka* in DMSO, 13.9, Chapter 2.7.2). This indicated that the initial deprotonation of the α-proton of the amide on the substrate **3.87** lied predominantly on the amide and there was only a very small amount of enolate present. We postulated that the initial deprotonation of amide is slow, and the

enolate generated would rapidly react with the pendant Michael acceptor within the molecule. This would shift the initial deprotonation equilibrium to the enolate and lead to complete consumption of the starting material.

Overall, this experiment offered a good proof of principle for an unprecedented enantioselective intramolecular Michael addition of an amide pronucleophile to tethered cyclohexadienone.

3.7 Conclusion and Future Directions

In conclusion, we have achieved an enantioselective desymmetrisation of cyclohexadienone *via* a stepwise dearomatisation/enantioselective Michael addition in moderate yield, dr and ee's with previously developed BIMP catalysts. Higher ee's could be achieved, only at the expense of yield in those cases. Further catalyst structure optimisation could be conducted in the future to achieve better results in these reactions. The proof of principle was obtained for the first enantioselective intramolecular Michael addition of amide to tethered cyclohexadienone was performed with good yield, dr and moderate ee's. A full BIMP catalyst screen could be carried out in the future. We hope that through this screening and further catalyst structure optimisation, we could achieve high enantioselectivities for this unprecedented reaction.

3.8 Reference

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Chapter 4 Michael Additions of Malonates to Crotonates and Acrylate Derivatives

4.1 Chapter Overview

This chapter describes the applications of BIMP family catalyst members in the Michael additions of malonate to crotonate, cinnamate and methacrylate derivatives. The existing BIMP catalysts were screened for these challenging reactions. New classes of BIMP catalysts were also designed and tested for these Michael additions.

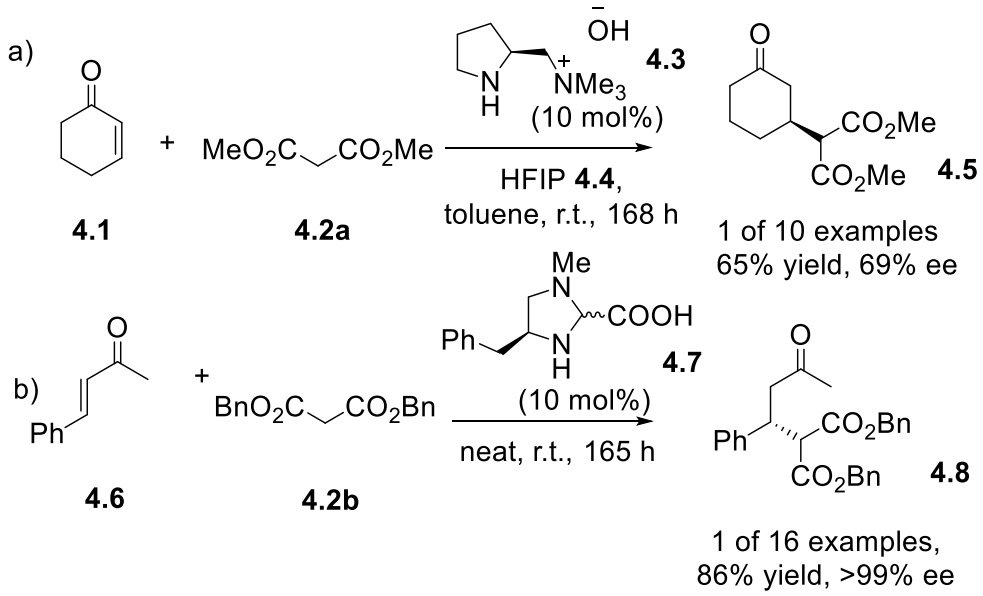
4.2 Introduction

4.2.1 Michael Addition of Malonate to β-Substituted α,β-Unsaturated Carbonyl Compounds

The use of carbon pronucleophiles in the enantioselective Michael addition is one of the most powerful and reliable tools for the stereocontrolled formation of carbon-carbon bonds.[1,2,3] The use of malonate as pronucleophiles has been of great interest, not only because malonate is readily available, but also because the conjugate product derived from malonate could easily undergo simple functional group transformations to afford useful compounds, for example, decarboxylation to give optically active δ ketoesters[4] and hydrolysis to give carboxylic acid[5].

In 1994, Kawara[6] reported an asymmetric Michael addition of malonates to cyclic

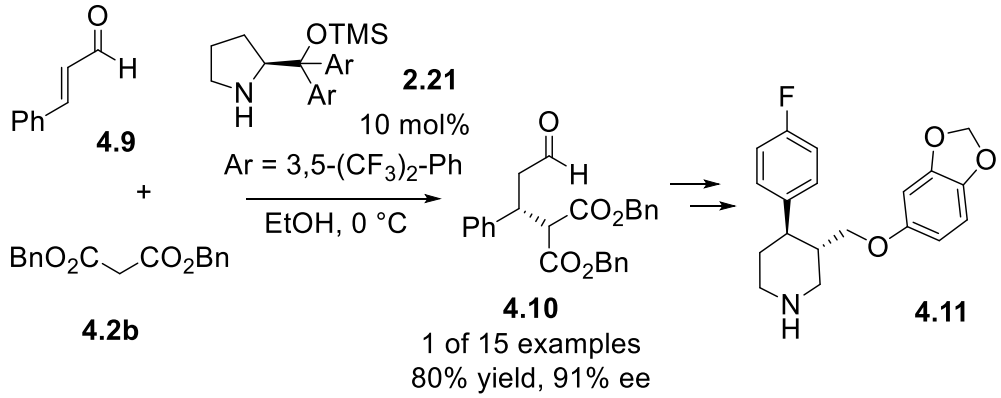
and acyclic enones catalysed by (2-pyrrolidinylmethyl) ammonium hydroxide **4.3** in moderate yields and enantioselectivities (Scheme 4.1a). Only 3% ee was obtained without the presence of any additives, presumably due to the background reaction caused by the strong basicity of the hydroxide form of the catalyst. Therefore, HFIP (1,1.1,3,3.3-hexafluoro-2-propanol) **4.4** was used as an acidic additive and the ee was significantly increased. The author proposed that HFIP reduced the basicity of the catalyst, thus controlling formation of the iminium intermediate.



Scheme 4.1. Michael additions of malonate to α, β-unsaturated ketones.

It was not until a decade later that a further advancement in the field was achieved when Jørgensen[4] reported the first highly enantioselective Michael addition of malonates into acyclic enones promoted by imidazolidine bifunctional catalyst **4.7** (Scheme 4.1b). The substituent on the ester groups of the malonate played an important role in achieving high yield and enantioselectivity. Initially, the model reaction between dimethyl malonate and benzylideneacetone **4.6** only gave 66%

yield and 73% ee. Optimisation on the ester group of the malonate revealed that dibenzyl malonate was the best pronucleophile; afforded the product in 93% yield and 99% ee in the model reaction. One limitation of this methodology is that the reaction times were generally long, ranging from 150 h to 288 h (12 d).



Scheme 4.2. Michael additions of malonate to α, β-unsaturated aldehydes catalysed by *L*-proline derivative 2.21.

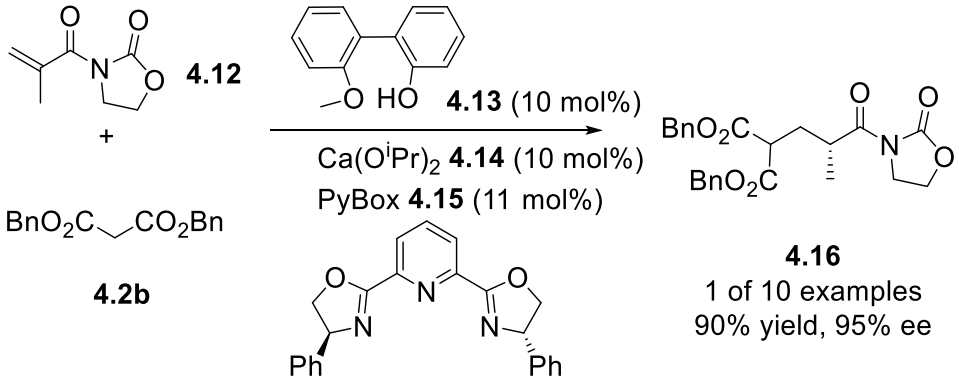
The same group[7] has also reported the Michael addition of malonates to α,β-unsaturated aldehydes **4.9** catalysed by *L*-proline derivative **2.21** (Scheme 4.2). Different malonate derivatives and various aromatic β-substituents on the α,β-unsaturated aldehyde were well-tolerated in this reaction. The conjugate adduct was later transformed into the antidepressant (-)- paroxetine **4.11**[8] in a few steps.

4.2.2 Michael Addition of Malonate to α-Substituted α,β-Unsaturated Carbonyl Compounds

The enantioselective Michael reaction between malonate and α-substituted α,β-unsaturated carbonyl compounds proceeds *via* a non-enantioselective Michael addition of malonate to the β-position of the conjugated carbonyl compound followed by a subsequent enantioselective protonation at the α-position of the

intermediate.

Kobayashi [9] described a Michael addition of malonate to α-substituted α,β-unsaturated imides **4.12**, which is an active form of an ester. Calcium complex $Ca(O^iPr)_2$ **4.14** was used as catalyst, combined with phenol **4.13** and pyridinebisoxazoline (PyBox) **4.15** as ligands (Scheme 4.3). The reaction proceeded well with aliphatic α-substituents. However, Michael acceptors possessing α-aryl substituents only gave the product in moderate ee.



Scheme 4.3. Michael addition of malonate to α-substituted α, β-unsaturated imide.

4.3 Aims

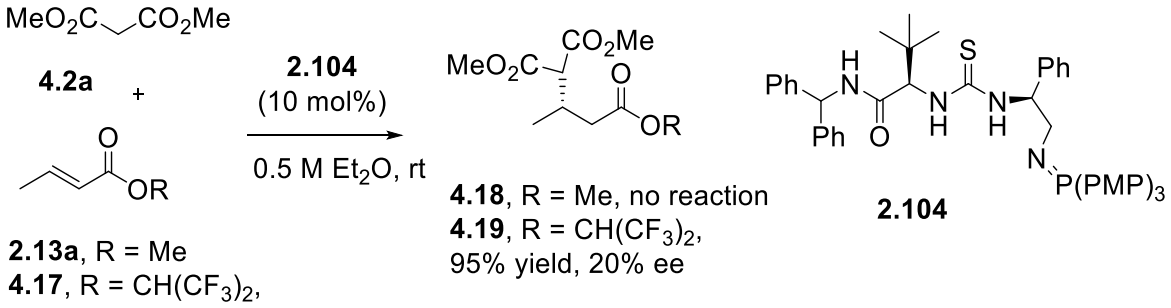
To the best of our knowledge, there is no literature presence of Michael addition between malonate and crotonate or methacrylate; this is due to a combination of moderate nucleophilicity and p*Ka* of malonate and the poor electrophilicity of α, β-unsaturated esters.

Given the good reactivity and the high enantiocontrol demonstrated by BIMP catalysts on the challenging SMA reaction (chapter 2), we envisaged that these catalysts could promote the Michael addition between malonates and α,β-unsaturated esters.

4.3 Michael Addition of Malonate to Crotonate and Cinnamate Derivatives

4.3.1 Catalyst Library Screening

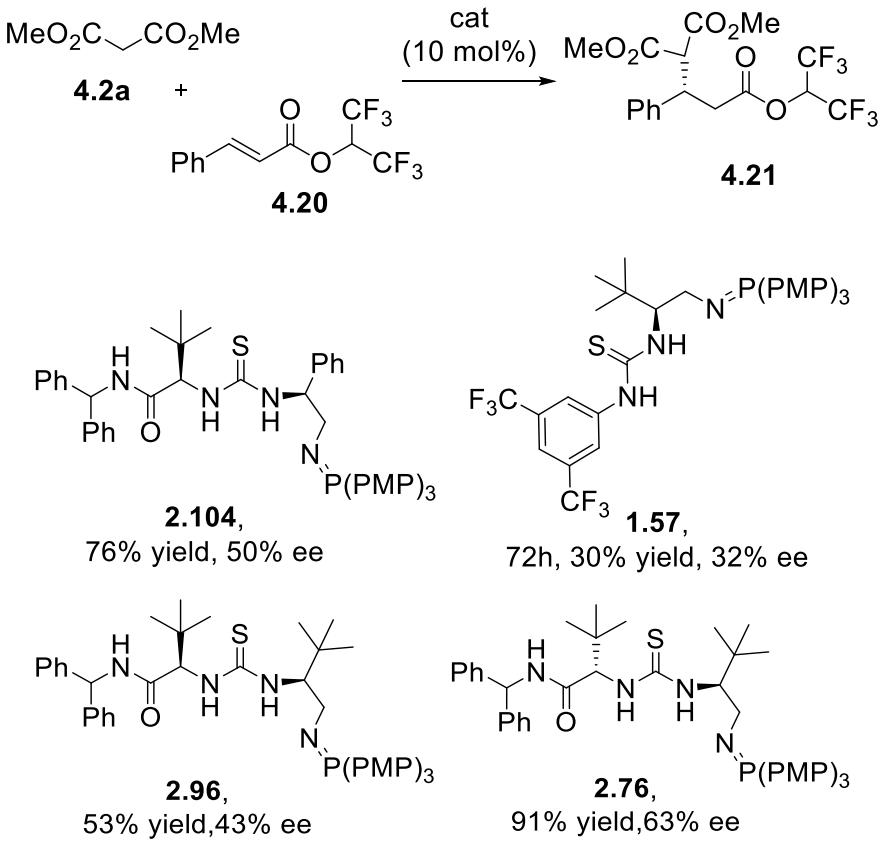
We first used our previously best catalyst **2.104** in the enantioselective SMA reaction (chapter 2) to test the Michael reaction between dimethyl malonate **4.2a** and methyl crotonate **2.13a**. Unfortunately, no product was observed after 72 h (Scheme 4.4). We then prepared hexafluoroisopropyl crotonate **4.17** according to standard procedures for ester coupling[10] (chapter 2). To our delight, the reaction between this substrate and dimethyl malonate gave the desired product in 95% yield and 20% ee after 24 h.



Scheme 4.4. Initial trial between crotonate and dimethyl malonate. *The reactions were conducted using 0.1 mmol crotonate, 0.12 mmol malonate, and 0.01 mmol catalyst in 0.2 mL Et_2O.*

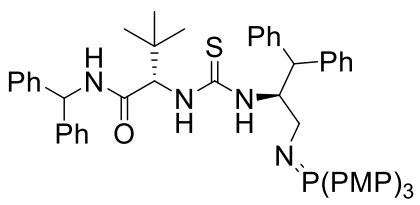
We then tried this catalyst in the Michael addition between hexafluoroisopropyl cinnamate **4.20** and dimethyl malonate **4.2a**. The reaction rate was slower, but the enantioselectivity of the reaction was boosted to 50%. The reaction was initially carried out with cinnamate as the limiting substrate and 1.2 equivalents of malonate. However, the addition product was co-spotting with malonate on the TLC plate, making it difficult to follow the reaction. Therefore, the Michael addition

was performed using malonates as limiting reagent and 1.2 equivalent of cinnamate. The reaction rates remained relatively similar when different ratios of starting materials were used. A range of chiral amido-thiourea BIMP catalysts was next screened for this reaction and the results are shown below (Scheme 4.5).

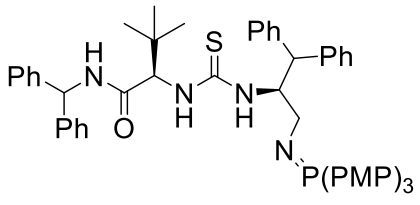


Scheme 4.5. Screening of Michael addition of malonate and hexafluoroisopropyl cinnamate using existing BIMP catalysts. *The reactions were performed using 0.1mmol malonate, 0.12 mmol cinnamate and 0.01 mmol catalyst in 0.2 mL Et_2O for 48 h unless otherwise noted.*

The reaction catalysed by the *L-tert*-leucine derived BIMP catalyst **1.57** was much slower than that of amido-thiourea catalyst **2.104** and only gave the product in 30% yield after 72 h and 32% ee (Scheme 4.5). In the presence of catalyst **2.96**, the reaction gave the product in 53% yield and 43% ee, lower than that of **2.104**. Using catalyst **2.76**, which is the diastereomer of **2.96**, the reaction afforded the product in an increased yield of 91% and an increase ee of 63%.



4.24, 88% yield, 37% ee



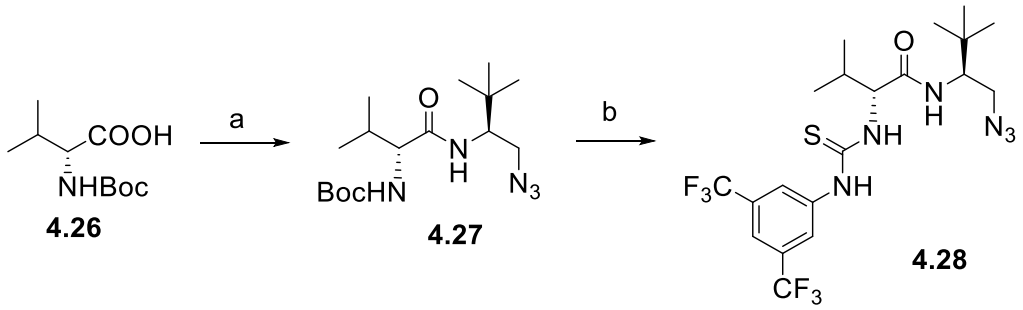
4.25, 92% yield, 33% ee

Scheme 4.6. Screening of Michael addition of dimethyl malonate and hexafluoroisopropyl cinnamate. *The reactions were performed using 0.1mmol malonate, 0.12 mmol cinnamate and 0.01 mmol catalyst in 0.2 mL Et_2O for 72 h.*

As the 3,3-diphenyl-*L*-alanine derived catalyst **3.60** showed better enantiocontrol than the *L-tert*-leucine derived catalyst **1.57** (Chapter 3), we decided to incorporate the 3,3-diphenyl-*L*-alanine derived amino azide with the chiral amido-thiourea backbone (see chapter 2, Scheme 2.20). A pair of diastereomeric catalyst precursors **4.22** and **4.23** were synthesised according to the standard procedures for the synthesis of chiral amido-thiourea catalysts (chapter 2). Catalysts **4.24** and **4.25** were prepared *via* Staudinger reaction with $P(PMP)_3$ and tested in this reaction. The Michael addition of dimethyl malonate **4.2a** to hexafluoroisopropyl cinnamate **4.20** catalysed by **4.24** afforded conjugate adduct **4.21** in 88% yield and 37% ee, while the reaction catalysed by **4.25** afforded **4.21** in 92% yield and 33% ee (Scheme 4.6). Both catalysts gave lower enantiocontrol over the reaction compared with previous catalysts.

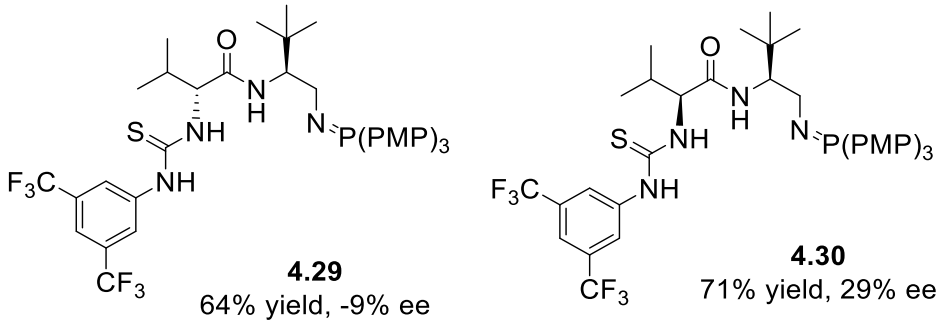
4.3.2 New Catalyst Development

A new generation of catalysts was also synthesised and used in this reaction, utilising an amino acid to link chiral amino azide and thiourea groups.



Scheme 4.7. Synthesis of new generation of catalysts. *a) ethyl chloroformate, **2.52**, 88%; b) TFA then 3,5-bis(trifluoromethyl)phenyl isothiocyanate, 85%.*

The synthesis of these catalysts started with N-Boc-protected *D*-valine[xiii] (Scheme 4.7). Treatment of the amino acid **4.26** with chloroformate afforded the activated ester, which then underwent amide coupling with *L-tert*-leucine derived amino azide **2.52** to afford amide **4.27** in 88% yield. The Boc group of **4.27** was then removed to give a free amine that was subsequently treated with isothiocyanate to form the catalyst precursor **4.28** in 85% yield. Both enantiomers of valine were used in the synthesis and gave a pair of diastereomeric catalyst precursors, which were subsequently reacted with $P(PMP)_3$ to form the catalysts *in situ* and tested in the Michael addition of dimethyl malonate **4.2a** to hexafluoroisopropyl cinnamate **4.20**. The results are shown in Scheme 4.8.



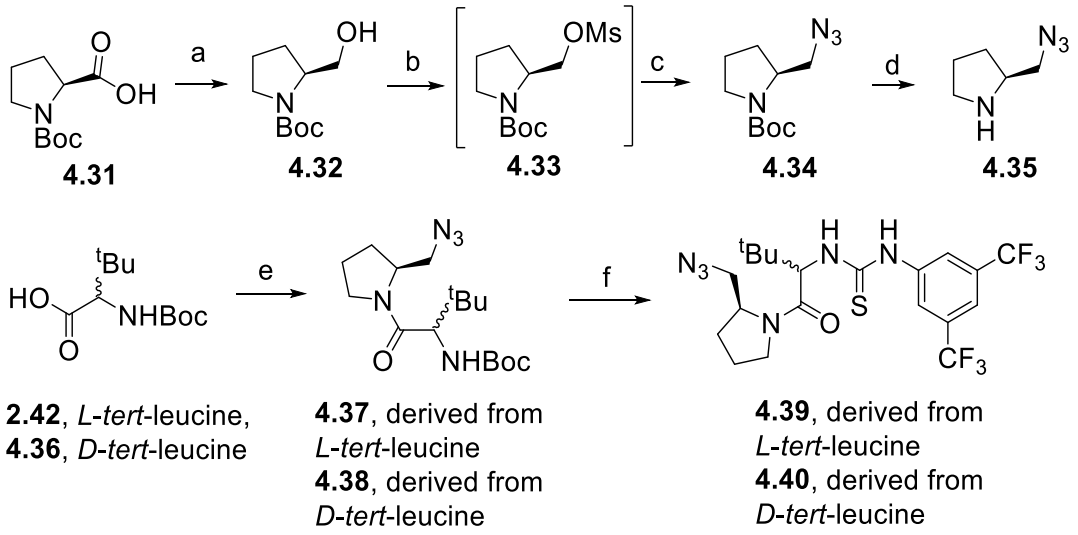
Scheme 4.8. Screening of Michael addition of malonate and hexafluoroisopropyl cinnamate using newly made catalysts. *The reactions were conducted using 0.1 mmol malonate, 0.12 mmol*

[xiii] *L*-Valine derived catalyst was synthesised by other people in the group.

cinnamate and 0.01 mmol catalyst in 0.2 mL Et_2O for 40 h.

Under the catalysis of **4.29**, the reaction gave 64% yield and -9% ee. The reaction catalysed by **4.30** gave 71% yield and 29% ee. It is noteworthy that the major enantiomers were opposite when catalysts bearing opposite stereocentre on the valine linker were used.

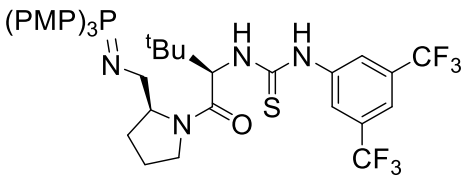
We then switched our attention to the chiral pyrrolidine backbone, which has been used extensively as chiral building block in organocatalysts.[11,12] The chiral pyrrolidine backbone was used as a replacement for amino acid backbone (*tert*-leucine etc.) in building our BIMP catalysts.



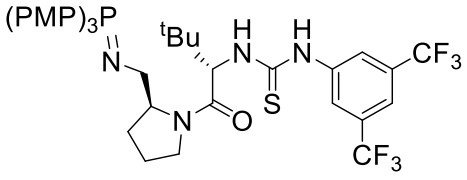
Scheme 4.9. Synthesis of pyrrolidine backbone BIMP catalysts. *a) $NaBH_4$ (1.6 eq), $BF_3{\cdot}OEt_2$ (2.0 eq), THF, 4 h, 95%; b) $MeSO_2Cl$ (1.5 eq), Et_3N (1.5 eq), CH_2Cl_2, 0 °C, 2 h; c) NaN_3 (2.5 eq), DMF, 60 °C, 24 h, 81% over 2 steps. d) TFA, CH_2Cl_2, 0 °C; e) EDC hydrochloride (1.1 eq), 1-hydroxybenzotriazole hydrate (1.1 eq),* ***4.35*** *(1.0 eq), rt, overnight, 96->99%; f) TFA, then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.2 eq), 2 h, 49-51%;*

The synthesis of amino azide **4.34** followed the standard procedures for the synthesis of the amino azide mentioned in Chapter 2 (see Scheme 2.20). Initial reduction of the carboxylic acid on the N-Boc protected proline **4.31** afforded the amino alcohol **4.32** in 95% yield. Subsequent mesylation and azide substitution

afforded the N-Boc protected amino azide **4.34** in 81% yield over two steps. The Boc group was then removed to give the free amino azide **4.35**, which was subsequently coupled with *L-tert*-leucine **2.42** and *D-tert*-leucine **4.36** to form amides **4.37** and **4.38**. The Boc group on these amides were then removed to give the free amines, which were treated with 3,5-bis(trifluoromethyl)phenyl isothiocyanate to give the final catalyst precursors **4.39** and **4.40** (Scheme 4.9).



4.41,
15% yield, 13% ee



4.42,
21% yield, 5% ee

Scheme 4.10. Pyrrolidine derived BIMP catalyst in Michael addition of malonate to cinnamate. *The reactions were performed using 0.1mmol malonate, 0.12 mmol cinnamate and 0.01 mmol catalyst in 0.2 mL Et_2O for 96 h.*

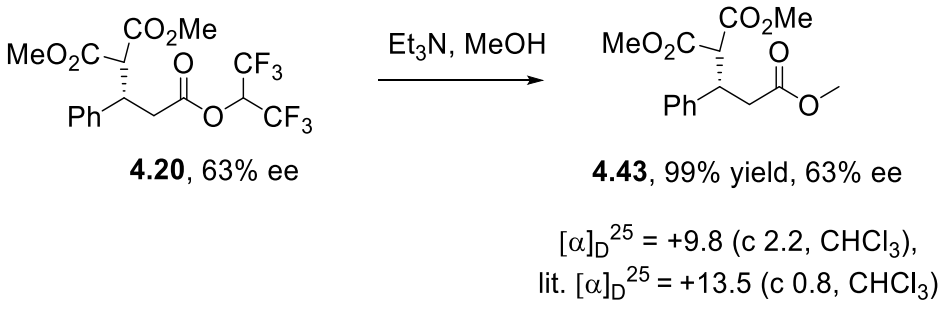
These catalyst precursors were then reacted with $P(PMP)_3$ to form the BIMP catalysts and tested in the Michael addition of dimethyl malonate **4.2a** to hexafluoroisopropyl cinnamate **4.20** (Scheme 4.10). Surprisingly, the iminophosphorane formation was very difficult, requiring harsh conditions and a long reaction time (reflux in Et_2O for 48 h). The Michael additions then proceeded very slowly and were left for 96 h. Poor yields were obtained and ee's were also low. One possible explanation is that the rigid proline ring prohibited the catalyst from coordinating with the substrate during the reaction, thus lowered the reactivity and enantioselectivity of the reaction. The steric hindrance effect could also explain the low reactivity of the Staudinger reactions because the rate of

Staudinger reaction is associated with the steric properties of the azide and phosphine.[13]

Overall, through multiple catalyst screens and reaction optimisation, the Michael addition of malonate to hexafluoroisopropyl cinnamate was achieved in 91% yield and 63% ee in 48 h with catalyst **2.76**.

4.3.3 Determination of Absolute Stereochemistry

The conjugate product (63% ee) was then transformed to its corresponding methyl ester derivative **4.43** in 99% yield and the ee was maintained. The absolute stereochemical configuration was determined by comparing its specific rotation and HPLC retention times with literature (Scheme 4.11).[14,15]



4.20, 63% ee

4.43, 99% yield, 63% ee

$[\alpha]_D^{25}$ = +9.8 (c 2.2, $CHCl_3$),
lit. $[\alpha]_D^{25}$ = +13.5 (c 0.8, $CHCl_3$)

Scheme 4.11. Determination of absolute stereochemical configuration.

4.4 Michael Addition of Malonate to Methacrylate Derivatives

4.4.1 Catalyst Library Screening

The catalyst library was next screened for the Michael addition of malonate to methacrylate derivatives. The Michael addition of dimethyl malonate and methyl methacrylate was first performed using previously best catalyst **2.104** and no

product was observed after 72 h. We then switched to the more electrophilic substrate phenyl methacrylate.[16]

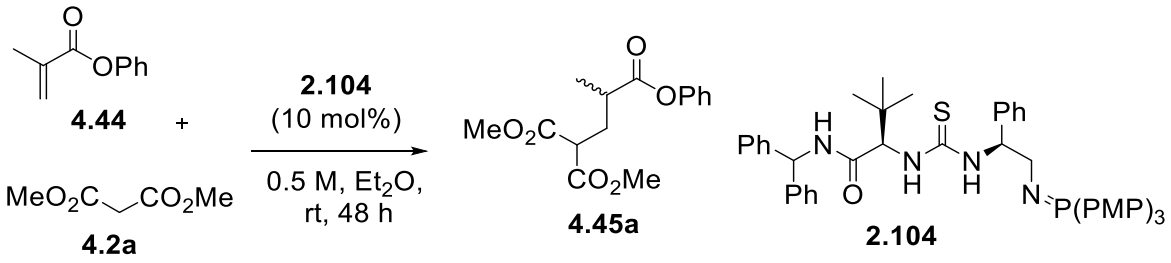
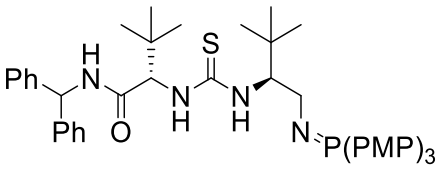


Table 4.1 Screening of Michael addition of malonate and phenyl methacrylate

Entry[a]	**4.44** (mmol)	**4.2a** (mmol)	Yield (%)	ee (%)
1	0.1	0.2	75	25
2	0.2	0.1	62	25

The reaction was carried out using catalyst **2.104** and different ratios of reagents were first studied. The reaction using two equivalents of malonate **4.2a** afforded the product **4.45a** in 75% yield after 48 h and 25% ee (Table 4.1, entry 1). The reaction with two equivalents of methacrylate **4.44** gave the product in a lower yield (62%) after 48 h and the same ee (25%) (Table 4.1, entry 2). Therefore, we decided to use two equivalents of dimethyl malonate **4.2a** in the investigation of this reaction.

Next, the reaction was performed using previously best catalyst **2.76** for the hexafluoroisopropyl cinnamate substrate, and thus gave rise to conjugate adduct **4.45a** over 99% yield and 57% ee (Scheme 4.12).

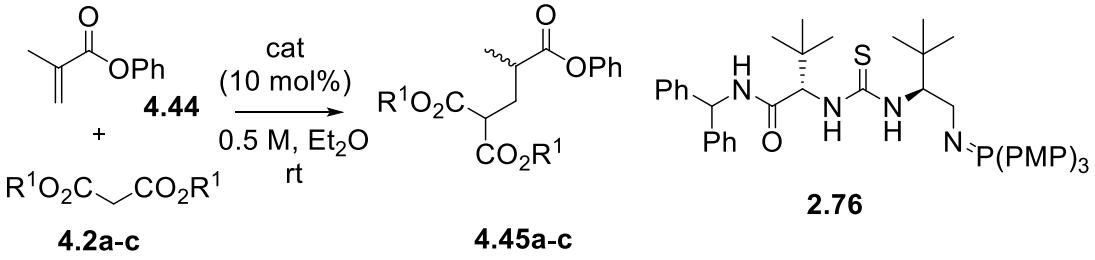


2.76, >99% yield, 57% ee

Scheme 4.12. Catalyst screening of Michael addition of malonate and phenyl methacrylate.

4.4.2 Substrate Modification and Screening

We also decided to try a few malonate derivatives as in the literature, malonates bearing different ester groups gave different enantioselectivities.[9]



4.2a-c **4.45a-c** **2.76**

Table 4.2 Ester group screening

Entry[a]	Malonate	R^1	Time	Yield (%)	ee[b] (%)
1	**4.2a**	Me	48	>99	57
2	**4.2b**	Bn	48	>99	62
3	**4.2c**	Et	72	86	64

*a) The reactions were conducted using 0.1 mmol of **4.44**, 0.2 mmol of malonate and 0.01 mmol catalyst in 0.2 mL Et_2O; b) determined by HPLC analysis on a chiral stationary phase.*

In entry 2, the reaction with dibenzyl malonate gave the product in excellent yield and 62% ee. In entry 3, the reaction using diethylmalonate afforded the product in 86% yield after longer reaction time and an increased ee to 64%.

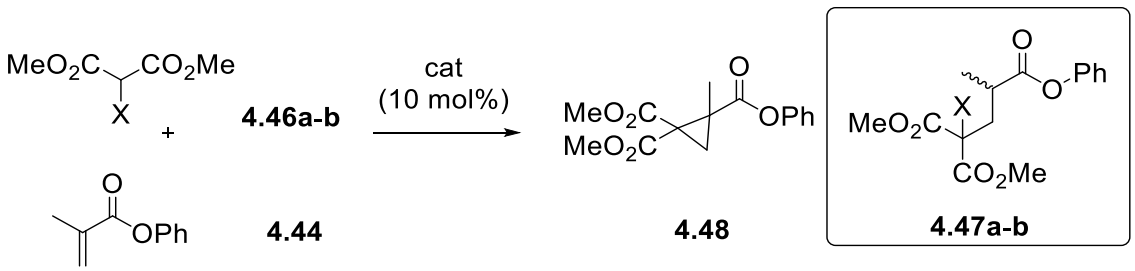


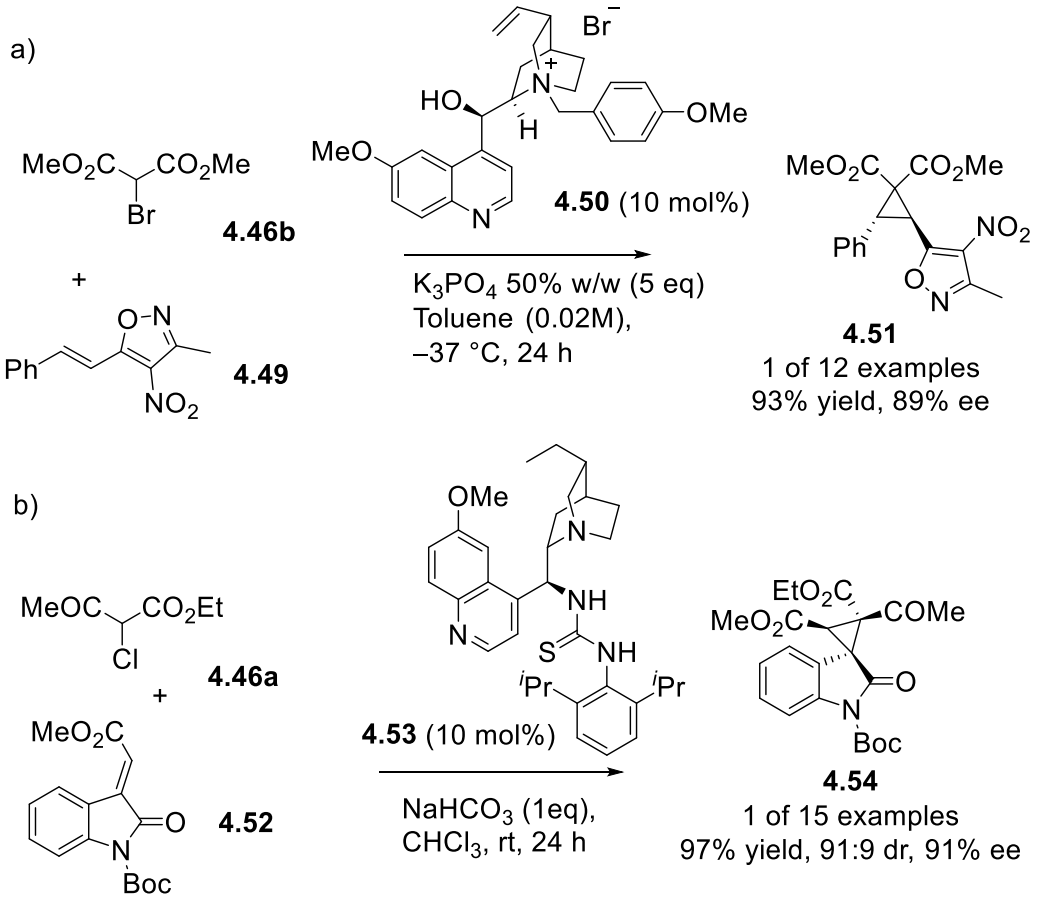
Table 4.3 Michael reaction of halogen substituted malonate and phenyl methacrylate

Entry[a]	Malonate	X	catalyst	yield	ee
1	**4.46a**	Cl	BEMP	8%	NA
2	**4.46b**	Br	BEMP	6%	NA
3	**4.46a**	Cl	**2.76**	0%	NA
4	**4.46b**	Br	**2.76**	0%	NA

*a) The reactions were conducted using 0.1 mmol of **4.44**, 0.2 mmol of malonate and 0.01 mmol catalyst in 0.2 mL Et_2O at rt.*

Halogen substituted dimethyl malonates were also investigated in the Michael addition. Instead of forming Michael adduct **4.47a** and **4.47b**, the BEMP promoted reaction gave 8% and 6% yields of cyclopropane **4.48**, respectively for malonate **4.46a** and **4.46b** after 72 h (Table 4.3, entry 1 and 2). The reactions were very slow and the majority of the starting materials were recovered after the reaction. This cyclopropane **4.48** was formed *via* the initial Michael addition followed by an intramolecular S_N2 reaction of the enolate to halogen substituted carbon centre. The same type of transformation has also been reported in literature, for example, Adamo[17] described a phase transfer catalyst **4.50** promoted Michael-initiated ring closure reaction of 4-nitro-5-styrylisoxazoles. Dimethyl 2-bromomalonate **4.46b** was used as the pronucleophile and good ee's were obtained for a range of

styrylisoxazoles bearing different β-substituents (Scheme 4.13a). In addition, Malkov [18] reported a cinchona thiourea catalysed spirocyclo-propanation of oxindole derivatives. Dimethyl 2-chloromalonate **4.46a**, 2-chloro-substituted ketoesters and diketones were well-tolerated in this reaction (Scheme 4.13b).



Scheme 4.13. Enantioselective formation of cyclopropane.

We then applied BIMP catalyst **2.76** to this reaction (Table 4.3, entry 3 & 4), however no product was observed after 96 h. This is presumably due to a combination of the steric hindrance of the pronucleophile and the low electrophilicity of the Michael acceptor.

4.5 Conclusion

In conclusion, we have reported the first Michael addition of malonate to cinnamate and methacrylate derivatives in excellent yield and moderate ee. More specifically, the Michael addition of dimethyl malonate to hexafluoroisopropyl cinnamate was achieved in 91% yield and 63% ee with the previously developed chiral amido-thiourea BIMP catalyst. In parallel, the Michael addition of diethyl malonate to phenyl methacrylate was obtained in 86% yield and 64% ee by using the same catalyst.

4.6 Reference

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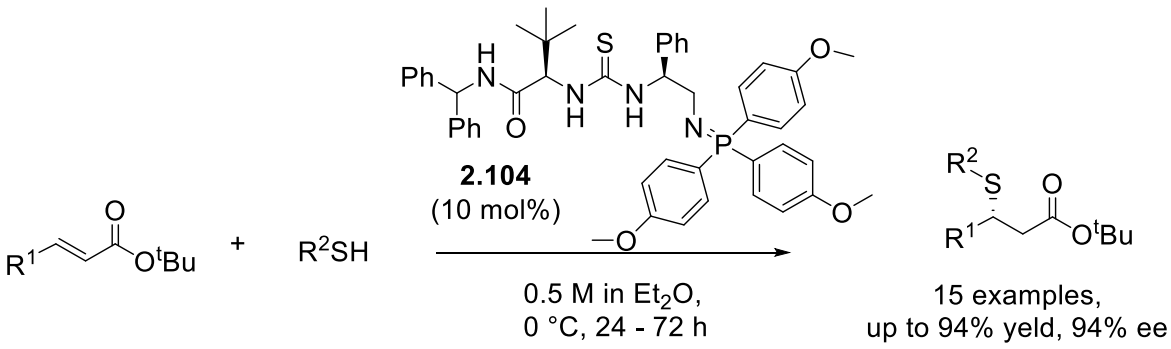
Chapter 5 Conclusions

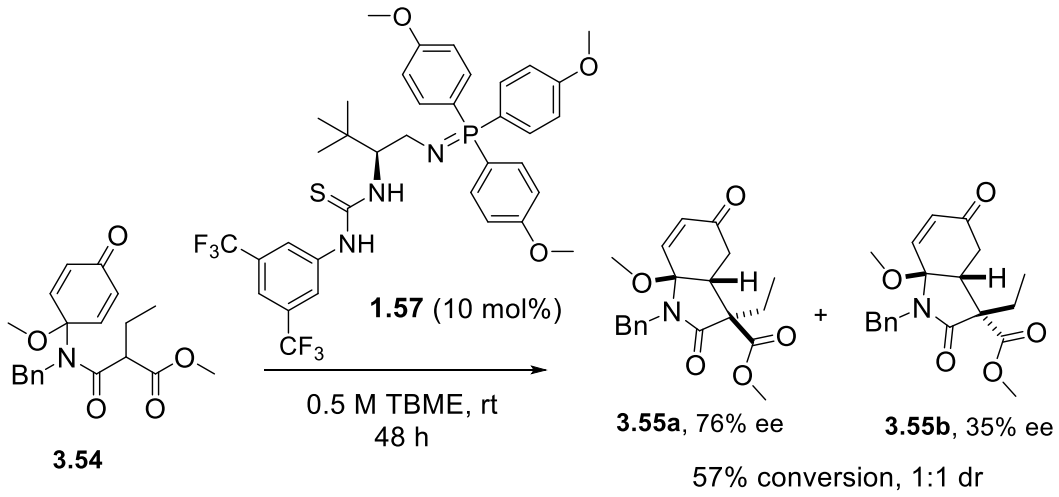
This thesis has demonstrated the ability of bifunctional iminophosphorane (BIMP) catalysts to provide access to new enantioselective organocatalytic methods. Overall, several new classes of BIMP catalysts were developed over the course of the DPhil. These catalysts have been incorporated into the BIMP catalyst library developed by our group and have been used for rapid catalyst screening for challenging reactions.

Chapter 2 described the development of a new class of BIMP catalyst possessing chiral amido-thiourea backbone and its successful application to the first highly enantioselective organocatalytic sulfa-Michael addition of thiols to *β*-substituted α,*β*-unsaturated ester. The high Brønsted basicity of this class of BIMP catalysts was also demonstrated in the preparative scale reaction with 1 mol% catalyst.

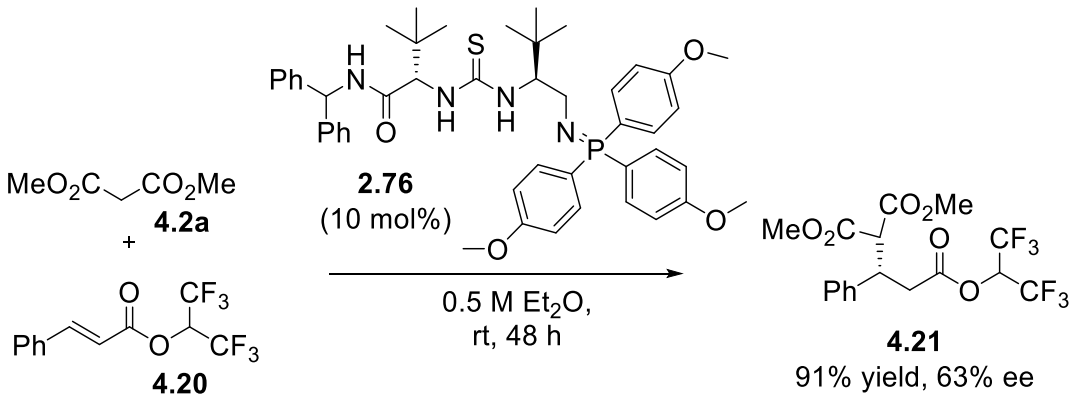


Chapter 3 described the catalyst library screening for the challenging enantioselective desymmetrisation of cyclohexadienone *via* Michael addition of high p*Ka* pronucleophiles, such as malonamate and amide. Moderate conversion, dr and moderate to high ee's were obtained using malonamate as the

pronucleophile. Better conversion was achieved when methyl ester on malonamate was replace with a hexafluoroisopropyl ester. In addition, an unprecedented Michael addition using amide as pronucleophile was achieved with high yield, dr and moderate ee's.



Chapter 4 presented the investigation on the Michael addition of malonates to crotonate, cinnamate and methacrylate derivatives as an extension to the SMA reaction of *β*-substituted α,*β*-unsaturated ester. Good reactivities and moderate ee's were achieved in the Michael addition of malonates to cinnamate and methacrylate derivatives. The development of two new classes of BIMP catalysts were also presented in this chapter.



Chapter 6 Experimental

6.1 General Experimental

6.1.1 Solvents and Reagents

Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were commercially supplied or dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns. Petroleum ether refers to the fraction collected between 30-40 °C. The following used reagents were obtained from commercial suppliers and used without further purification: Et_2O, Toluene, CH_2Cl_2, $CHCl_3$, THF, MeOH.

The following compounds were synthesised by members of the Dixon group: isothiocyanates **2.78, 2.79** and **2.82**, BIMP catalyst precursors **2.85**, **2.86**, **2.89**, **3.57**, **3.59**.

6.1.2 Chromatography

Column chromatography was carried out using VWR Kieselgel 60 silica gel (60-63 μm). All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F254 fluorescent treated silica which were visualised under UV light (λ_{max}= 254 or 365 nm) or by staining with aqueous basic potassium permanganate solutions. HPLC separation was performed on Agilent Technologies 1200 series machine.

6.1.3 Spectroscopy

^{1}H and ^{13}C NMR spectra were recorded using Bruker DPX-200, Bruker AVG-400, and Bruker AVF-400 spectrometers. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: ppm, (multiplicity, coupling constants, number of protons). **Low resolution mass spectra** were recorded on a Waters LCT premier XE Micromass spectrometer (EI) operating in positive and negative ionisation mode. **High resolution mass spectra** (HRMS, accurate mass) were recorded on a Bruker daltonios MicroTOF mass spectrometer. **IR spectra** (IR) were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film on a diamond ATR module. Only selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Optical rotations were recorded using a Perkin Elmer 341 polarimeter; $[\alpha]_D^T$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm); Temperatures (T) are given in degrees Celsius (°C). The enantiomeric excesses were determined by HPLC analysis in an Agilent 1200 Series instrument employing a chiral stationary phase column specified in the individual experiment, by comparing the samples with the appropriate racemic mixtures.

6.1.4 Melting points

Melting points (m.p.) were recorded in degrees Celsius (°C), using a Leica Galen

III hot-stage microscope apparatus and are reported uncorrected.

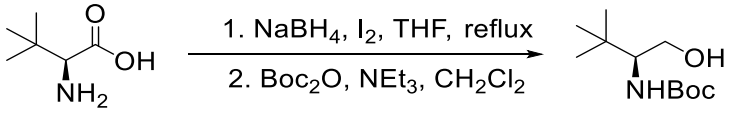
6.1.5 Names

Compound names are those generated by Reaxys following the IUPAC nomenclature.

6.2 Synthesis of BIMP Catalysts and Precursors

6.2.1 General Procedures

6.2.1.1 General Procedure A for the Carboxylic Acid Reduction and Boc Protection

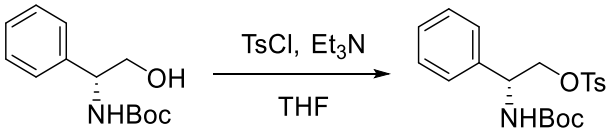


According to a literature procedure[1], to a solution of sodium borohydride (2.4 eq) in THF (0.35 M) was added *L-tert*-leucine (1.0 eq). The reaction mixture was cooled to 0 °C and a solution of iodine (1.00 eq) in THF (0.35 M) was added dropwise over 30 minutes and then the reaction mixture was warmed to room temperature for 15 minutes and then refluxed for 18 h. The reaction mixture was cooled to room temperature and MeOH was added until a clear solution was obtained and stirring maintained for 30 minutes before the volatiles were removed *in vacuo*. The white paste was dissolved in 20% aq KOH (1.5 mL/mmol) and stirring was maintained for 3 h and the reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL/mmol), washed with brine (0.5 mL/mmol), dried over $MgSO_4$ and the

volatiles removed *in vacuo* to afford the crude amino alcohol.

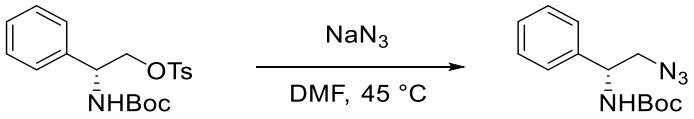
According to a modified literature procedure,[2] the crude material was dissolved in CH_2Cl_2 (0.4 M) and triethylamine (1.18 eq) was added and the reaction mixture was cooled to 0 °C using an ice bath. Boc anhydride (1.18 eq) was added and stirring was maintained at 0 °C for 1 h and then 8 h at room temperature. The reaction mixture was washed with water (1 mL/mmol), brine (1 mL/mmol), dried over $MgSO_4$ and volatiles removed *in vacuo*. The crude mixture was concentrated *in vacuo*, and was purified by FCC to afford the pure product.

6.2.1.2 General Procedure B for the Tosylation of Alcohol



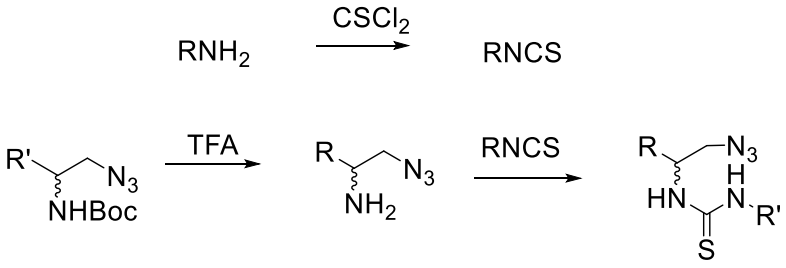
According to a literature procedure[3], *p*-toluenesulfonyl chloride (1.1 eq) and triethylamine (1.8 eq) were added to a stirred solution of amino alcohol (1.0 eq) in CH_2Cl_2 (0.2 M) at room temperature. The resulting mixture was stirred overnight and then quenched with H_2O (1 mL/mmol) and extracted with CH_2Cl_2 (3 x 5 mL/mmol). The combined organic layers were washed with citric acid (20%, 1 mL/mmol) and dried over $MgSO_4$. The resulting mixture was purified by FCC to afford the pure product.

6.2.1.3 General Procedure C for the S_N2 Azide Substitution of Tosylate



According to a modified procedure[4], To a stirred solution of tosylate (1.0 eq) in DMF (0.2 M) was added sodium azide (1.1 eq) at room temperature. The reaction mixture was warmed to 45 °C and stirring was maintained for 14 h. The reaction mixture was cooled to room temperature then diluted with water (1 mL/mmol) and Et_2O (5 mL/mmol). The aqueous phase was extracted with Et_2O (2 x 5 mL/mmol) and the combined organics were washed with brine (2 mL/mmol) and dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by FCC to afford the pure product.

6.2.1.4 General Procedure D for the Synthesis of Catalyst Precursors

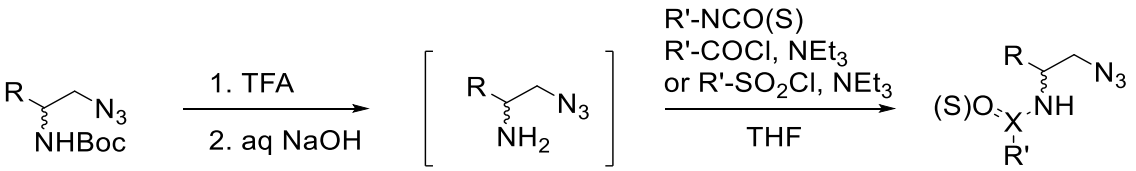


According to a modified procedure[5], The primary amine (1.0 eq) was dissolved in CH_2Cl_2:THF:$NaHCO_3$ (sat. aq.) (10:1:10 by volume, 1 M for CH_2Cl_2) and the resulting solution stirred at 0 °C. After 5 min, stirring was stopped and $CSCl_2$ (1.2 eq) was added to the organic layer. The resulting reaction mixture was stirred at 0 °C for 2 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 1 mL/mmol) and the combined organic layers dried over Na_2SO_4, filtered and concentrated *in vacuo*

to give the crude isothiocyanate.

An ice-cooled round-bottom flask containing N-Boc protected amino azide (1.10 eq) under N_2 atmosphere was placed behind a blast-shield. TFA (1 mL/mmol) was carefully added dropwise and the resulting solution was stirred at rt for 1 h. TFA was evaporated under a stream of N_2, the residue dissolved in Et_2O and aq. 2 M NaOH solution (5 mL/mmol) was added until pH 14. The aqueous phase was extracted with Et_2O and the combined organics were dried over Na_2SO_4, filtered and concentrated to give the crude aminoazide. This aminoazide (1.1 eq) was added to a solution of the previously made isothiocyanate (1.0 eq) in THF (1 mL/mmol). The reaction mixture was stirred at rt for 16 h. The crude mixture was concentrated *in vacuo*, and was purified by flash chromatography.

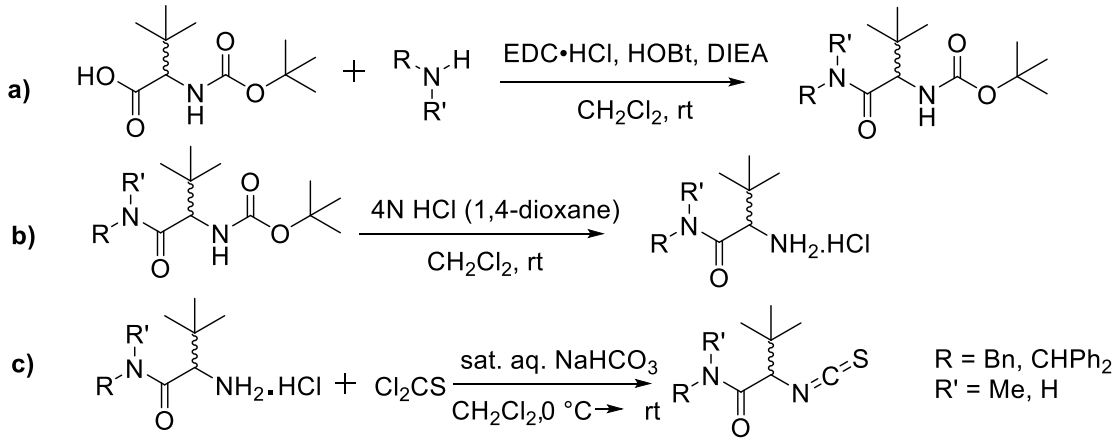
6.2.1.5 General Procedure E for the Synthesis of BIMP Azide Precursors from *N*-Boc Amino Azides



According to a literature procedure[4], to the *N*-Boc protected amino azide (1.0 eq) at 0 °C, behind a blastshield was added dropwise trifluoroacetic acid (1 mL/mmol). Upon completion of addition the reaction mixture was allowed to warm to room temperature and stirring was maintained for 2 hours whereupon the reaction mixture was concentrated under a stream of N_2. The reaction mixture was then diluted with Et_2O (5 mL/mmol) and water (3 mL/mmol). The reaction mixture was

basified to pH 14 by the addition of solid NaOH with cooling over an ice bath. The aqueous phase was extracted with Et_2O (2 x 5 mL/mmol) and the combined organics were washed with brine, dried over $MgSO_4$ and concentrated under a N_2 stream. The crude reaction was diluted with THF (0.3 M) and the iso(thio)cyanate (1.1 eq) [or acyl chloride (1.1 eq) and triethylamine (1.2 eq)] were added. Stirring was maintained for 14 h and the volatiles were removed *in vacuo*. The crude product was purified by FCC to afford the catalyst precursor.

6.2.1.6 General Procedure F for the Formation of Chiral Amido-thiourea Isothiocyanates



According to literature procedure[6],

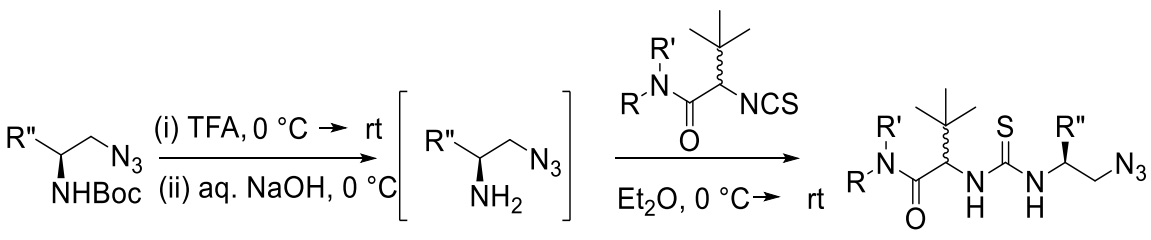
a) To a stirred solution of EDC hydrochloride (1.1 eq) and 1-hydroxybenzotriazole hydrate (1.1 eq) in CH_2Cl_2 (1 mL/mmol) under a N_2 atmosphere at rt was added *N*,*N*-diisopropylethylamine (1.5 eq) and the corresponding amine (1.1 eq) sequentially. Boc-*L*-*tert*-leucine (1.0 eq) was added in one portion and the reaction mixture was stirred for 20 h. The reaction was diluted with Et_2O (1 mL/mmol),

washed with 0.5 N HCl (2 x 1 mL/mmol) and the aqueous phase extracted with Et_2O (1 mL/mmol). The combined organic phase was washed with sat. aq. $NaHCO_3$ (1 mL/mmol) and brine (1 mL/mmol), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the product, which was used crude without further purification.

b) To a vigorously stirred solution of the crude product (1.0 eq) in CH_2Cl_2 (0.5 M) under a N_2 atmosphere at 0 °C was added 4 N HCl in 1,4-dioxane (9.6 eq) over 15 min. The reaction mixture was stirred for 3.5 h and concentrated *in vacuo* to afford the product which was used crude without further purification.

c) To a vigorously stirred solution of the crude product (1.0 eq) in CH_2Cl_2 (1 M) under a N_2 atmosphere at 0 °C was added sat. aq. $NaHCO_3$ (1 M), and the biphasic mixture was stirred for 20 min. Stirring was stopped and thiophosgene (1.5 eq) was added. Immediately, vigorous stirring was restored and the mixture allowed to warm to rt over 30 min. The organic phase was extracted with CH_2Cl_2 (2 x 1 mL/mmol), washed with brine (1 mL/mmol), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude product.

6.2.1.7 General Procedure G for the formation of chiral amido-thiourea scaffold catalyst precursors



To N-Boc-protected amino acid derived amino azide (1.1 eq) at 0 °C was added trifluoroacetic acid (1 mL/mmol) dropwise. The reaction mixture was warmed to rt and stirred for 2 h, and the volatiles removed by N_2 stream. The crude material (1.0 eq) was dissolved in Et_2O/H_2O (1:1 by volume, 1 mL/mmol overall) and adjusted to pH 14 by the addition of NaOH at 0 °C. The organic phase was extracted using Et_2O (2 x 5 mL/mmol), washed with brine (2 mL/mmol), dried over $MgSO_4$, filtered, and concentrated to 2 mL under a N_2 stream. The solution was cooled to 0 °C and chiral amido-thiourea isothiocyanate (1.0 eq) added. The reaction mixture was then warmed to rt and stirred for 24 h. Volatiles were removed by N_2 stream and the crude product was purified by FCC to afford the corresponding azide.

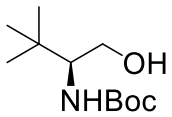
6.2.1.8 General Procedure H for the *in situ* Staudinger reaction to form iminophosphorane catalysts

To the corresponding organoazide (1.0 eq) and phosphine (1.0 eq) under an Ar atmosphere was added Et_2O (0.2 M), and the reaction mixture was stirred at rt for 24 h. The iminophosphorane product was confirmed by LRMS and TLC, and the volatiles were removed by a N_2 stream to yield the crude product, which was used as a catalyst without further purification.

6.2.2 Synthesis of *L-tert*-Leucine Derived azide

6.2.2.1 Synthesis and Characterisation of 2.43

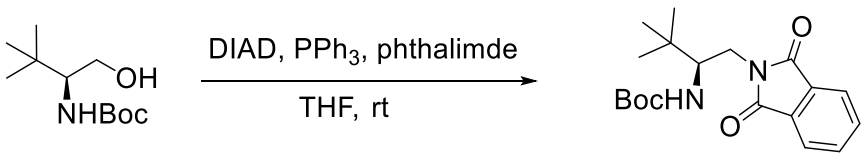
tert-butyl [(2*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]carbamate



According to General Procedure A, sodium borohydride (6.5 g, 171 mmol, 2.4 eq) was reacted with *L-tert*-leucine **2.42** (9.3 g, 70.9 mmol, 1.0 eq) and iodine (18.0 g, 70.9 mmol, 1.00 eq) in THF (250 mL) The crude amino alcohol was dissolved in CH_2Cl_2 (270 mL) and reacted with triethylamine (8.5 mL, 83.7 mmol, 1.18 eq) and Boc anhydride (18.2 g, 83.7 mmol, 1.18 eq). The crude mixture was purified by FCC [4:1 Petrol: EtOAc then 3:2 Petrol: EtOAc] afforded the title compound **2.43** as a colourless solid in 68% yield (10.5 g). **m.p.** = 103 - 104 ˚C, lit. 105 °C[7]; **$[\alpha]_D^{23}$** = -6.2 (*c 1.0*, $CHCl_3$), lit. -5.5 (*c 1.0*, $CHCl_3$)[7]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 4.63 (br. s, 1 H, NH), 3.87 - 3.84 (m, 1 H, one of $CHCH_2$), 3.51 - 3.49 (m, 2 H, one of $CHCH_2$ and $CHCH_2$), 2.64 (br. s, 1 H, OH), 1.46 (s, 9 H, $OC(CH_3)_3$), 0.95 (s, 9 H, $CHC(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 157.2 (C=O), 79.5 ($OC(CH_3)_3$), 63.0 ($CHCH_2$), 60.9 ($CHCH_2$), 33.6 ($C(CH_3)_3$), 28.3 ($OC(CH_3)_3$, 26.8 ($C(CH_3)_3$); Data consistent with that given in the literature.[8]

6.2.2.2 Synthesis and Characterisation of 2.44

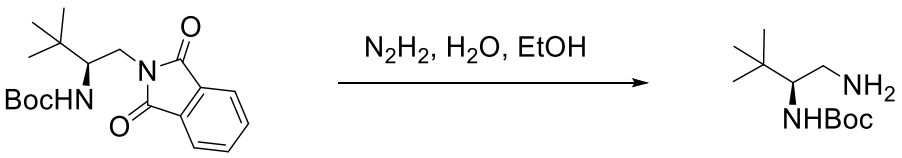
tert-Butyl *N*-[(2*S*)-1-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3,3-dimethylbutan-2-yl]carbamate



To a solution of **2.43** (9.3 g, 43.0 mmol, 1.0 eq), phthalimide (6.3 g, 43.0 mmol, 1.0 eq) and triphenylphosphine (11.3 g, 43.0 mmol, 1.0 eq) in THF (300 mL) under a N_2 atmosphere at rt was added DIAD (9.3 mL, 47.3 mmol, 1.1 eq) dropwise, and the reaction mixture was stirred for 72 h. The reaction was concentrated *in vacuo* and purified by FCC (petroleum ether/EtOAc = 19/1 to 4/1) to afford the title compound **2.44** as a colourless solid in 80% yield (11.8 g). **m.p.** = 149 - 150 °C, lit. 146 - 147 °C[7]; **$[\alpha]_D^{23}$** = +50.2 (*c 0.8*, $CHCl_3$), lit. +48.7 (*c 0.5*, $CHCl_3$)[7]; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.83 (dd, *J* = 5.5, 3.0 Hz, 2 H, Ar<u>H</u>), 7.68 (dd, *J* = 5.5, 3.0 Hz,, 2 H, Ar<u>H</u>), 4.47 (d, *J* = 10.5 Hz, 1 H, CHN<u>H</u>C=O), 3.89 - 3.75 (m, 2 H, C<u>H</u>NHC=O and CHC<u>H$_A$</u>H$_B$N), 3.65 (dd, *J* = 14.0, 1.5 Hz, 1 H, CHCH$_A$<u>H$_B$</u>N), 1.11 (s, 9 H, OC(C<u>H</u>$_3$)$_3$), 1.03 (s, 9 H, CHC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 168.5 (N<u>C</u>=O), 156.1 (NH<u>C</u>=O), 133.7 (Ar<u>C</u>H), 132.2 (Ar<u>C</u>), 123.2 (Ar<u>C</u>H), 78.9 (O<u>C</u>(CH$_3$)$_3$), 57.5 (<u>C</u>HNHC=O), 38.7 (CH<u>C</u>H$_2$N), 33.7 (CH<u>C</u>(CH$_3$)$_3$), 27.9 (OC(<u>C</u>H$_3$)$_3$), 26.4 (CHC(<u>C</u>H$_3$)$_3$); All characterisation data agree with those published in the literature.[7]

6.2.2.3 Synthesis and Characterisation of 2.45

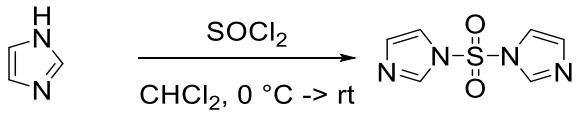
<u>*tert*-Butyl *N*-[(2*S*)-1-amino-3,3-dimethylbutan-2-yl]carbamate</u>



To a solution of **2.44** (11.8 g, 34.2 mmol, 1.0 eq) in EtOH (170 mL) under a N_2 atmosphere at rt was added hydrazine monohydrate (2.5 mL, 51.3 mmol, 1.5 eq). The reaction mixture was heated to reflux and stirred for 2.5 h. The reaction was then cooled to rt and filtered. The precipitate was washed with CH_2Cl_2 (3 x 100 mL), and the filtrate concentrated *in vacuo*. The crude product was purified by FCC (CH_2Cl_2/MeOH = 9/1) to afford the title compound **2.45** as a colourless solid in 99% yield (7.4 g). **m.p.** = 80 - 84 °C, lit. 84 °C[7]; **$[\alpha]_D^{23}$** = +8.5 (*c 0.4*, $CHCl_3$), lit. +9.8 (*c 0.5*, $CHCl_3$)[7]; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 4.49 (d, *J* = 10.0 Hz, 1 H, CHN<u>H</u>C=O), 3.34 (td, *J* = 10.5, 3.0 Hz, 1 H, C<u>H</u>NHC=O), 2.96 (dd, *J* = 13.5, 3.0 Hz, 1 H, CHC<u>H</u>$_A$H$_B$NH$_2$), 2.41 (dd, *J* = 13.0, 11.0 Hz, 1 H, CHCH$_A$<u>H</u>$_B$NH$_2$), 1.83 (br. s, 2 H, CHCH$_2$N<u>H</u>$_2$), 1.44 (s, 9 H, OC(<u>C</u>H$_3$)$_3$), 0.90 (s, 9 H, CHC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 156.8 (<u>C</u>=O), 79.1 (O<u>C</u>(CH$_3$)$_3$), 62.3 (<u>C</u>HNHC=O), 42.3 (CH<u>C</u>H$_2$NH$_2$), 34.2 (CH<u>C</u>(CH$_3$)$_3$), 28.4 (OC(<u>C</u>H$_3$)$_3$), 26.5 (CHC(<u>C</u>H$_3$)$_3$); All characterisation data agree with those published in the literature.[7]

6.2.2.4 Synthesis and Characterisation of 2.48

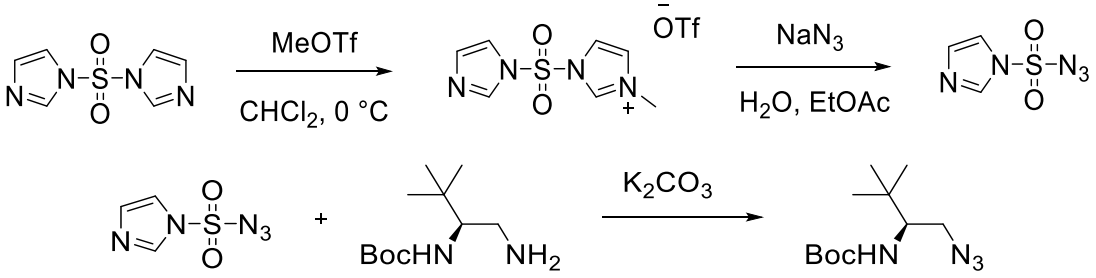
<u>1-(1*H*-Imidazole-1-sulfonyl)-1*H*-imidazole</u>



According to a literature procedure[10], to a solution of imidazole (20 g, 300 mmol,

4.7 eq) in CH_2Cl_2 (160 mL) under a N_2 atmosphere at 0 °C was added dropwise sulfuryl chloride (5.0 mL, 62 mmol, 1.0 eq) over 20 min. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was filtered, and the filtrate concentrated *in vacuo*. The crude product was purified by recrystallisation in refluxing isopropanol to afford the title compound **2.48** as a colourless solid in 80% yield (9.8 g). **m.p.** = 140 - 141 °C, lit. 143 - 144 °C[9]; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 8.07 (s, 2 H, ArH), 7.34 (t, *J* = 1.5 Hz, 2 H, ArH), 7.20 (dd, *J* = 1.5, 1.0 Hz, 2 H, ArH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 136.5 (Ar<u>C</u>H), 132.4 (Ar<u>C</u>H), 117.4 (Ar<u>C</u>H); All characterisation data agree with those published in the literature.[10]

6.2.2.5 Synthesis and Characterisation of 2.46



According to a literature procedure[10], to a solution of **2.48** (10 g, 50 mmol, 1.0 eq) in CH_2Cl_2 (80 mL) under a N_2 atmosphere at 0 °C was added methyl triflate (5.1 mL, 45 mmol, 0.9 eq) dropwise. The reaction mixture was stirred at 0 °C for 2.5 h and then filtered. The solid was dried under high vacuum to afford the title compound **2.49** as a colourless solid in 16 g.

To a stirred solution of **2.49** (15.8 g, 43.7 mmol, 1.0 eq) in H_2O/EtOAc (1:1 v/v,

160 mL) under a N_2 atmosphere at 0 °C was added sodium azide (3.4 g, 52.4 mmol, 1.2 eq). The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was then diluted with H_2O (50 mL) and EtOAc (50 mL), the organic layer extracted and the aqueous layer washed with EtOAc (25 mL). The combined organic layers were dried ($MgSO_4$) and filtered. The diazotransfer reagent – title compound **2.50** – has not been characterised to prevent isolation of an explosive compound.[10,11] The crude compound, with an assumed 80% yield (lit. 88% yield),4 was dissolved in EtOAc (100 mL) and used without further purification.

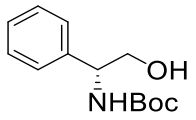
To compound **2.50** (estimated 1.2 eq in EtOAc) under a N_2 atmosphere at 0 °C was added a pre-dissolved solution of compound **2.45** (6.8 g, 31.5 mmol, 1.0 eq) in MeOH (50 mL). Potassium carbonate (7.1 g, 51 mmol, 1.7 eq) and copper sulfate pentahydrate (149 mg, 0.63 mmol, 2 mol%) were added sequentially, and the reaction mixture was stirred at 0 °C for 30 min before warming to rt. After stirring at rt for 3 d, the volatiles were removed under a stream of N_2 and the resulting crude mixture dissolved in H_2O/Et_2O (1:1 v/v, 100 mL). The organic phase was extracted using Et_2O (2 x 100 mL), washed with brine (60 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by FCC (petroleum ether/Et_2O = 9/1) to afford the title compound **2.46** as a colourless solid in 61% yield (4.65 g). **m.p.** = 64 - 65 °C, lit. 58 - 60 °C[4]; $\mathbf{[\alpha]_D^{23}}$ = -26.1 (*c 1.1*, $CHCl_3$), lit. - 46.6 (*c* 0.9, $CHCl_3$)[4]; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 4.54 (d, *J* = 9.5 Hz, 1 H, CHN<u>H</u>C=O), 3.64 - 3.59 (m, 1 H, C<u>H</u>NHC=O), 3.48 (dd, *J* = 12.5, 3.0

Hz, 1 H, CHC$\underline{H_A}H_BN_3$), 3.23 (dd, *J* = 12.5, 8.0 Hz, 1 H, CHC$H_A\underline{H_B}N_3$), 1.46 (s, 9 H, OC(C$\underline{H_3}$)$_3$), 0.94 (s, 9 H, CHC(C$\underline{H_3}$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 155.8 ($\underline{C}$=O), 79.6 (O$\underline{C}$(CH$_3$)$_3$), 58.2 ($\underline{C}$HNHC=O), 52.0 (CH$\underline{C}H_2N_3$), 34.2 (CH$\underline{C}$(CH$_3$)$_3$), 28.4 (OC($\underline{C}$H$_3$)$_3$), 26.6 (CHC($\underline{C}$H$_3$)$_3$); All characterisation data agree with those published in the literature.[4]

6.2.3 Synthesis of *D*-phenyl glycine derived azide

6.2.3.1 Synthesis and Characterisation of 2.68

tert-butyl N-[(1*R*)-2-hydroxy-1- phenylethyl]carbamate

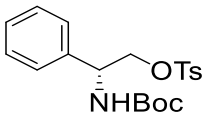


According to General Procedure A, sodium borohydride (3.0 g, 87.1 mmol, 2.4 eq) was reacted with *D*-phenyl glycine **2.67** (5.0 g, 33.1 mmol, 1.0 eq) and iodine (8.41 g, 33.1 mmol, 1.0 eq) in THF (180 mL). The crude amino alcohol was dissolved in CH_2Cl_2 (100 mL) and reacted with triethylamine (5.44 mL, 39.1 mmol, 1.2 eq) and di-*tert*-butyl dicarbonate (8.53 g, 39.1 mmol, 1.20 eq). The crude product was purified by FCC (petroleum ether/EtOAc = 4/1) to afford the title compound **2.68** as a white solid in 38% yield (3.01 g). **m.p.** = 137 - 139 °C, lit. 133 - 135 °C[12]; **$[\alpha]_D^{23}$** = -37.7 (*c 1.0*, $CHCl_3$), lit -35 (*c 1.67* $CHCl_3$)[12]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.34 - 7.27 (m, 5 H, Ar$\underline{H}$), 5.43 (br. s, 1H, CHN$\underline{H}$), 4.76 - 4.71 (m, 1 H, C$\underline{H}CH_2$), 3.78 - 3.65 (m, 2 H, CHC$\underline{H_2}$), 2.94 (br. s, 1 H, O$\underline{H}$), 1.43 (s, 9 H,

OC($C\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 156.0 ($\underline{C}$=O), 137.5 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$H), 127.6 (Ar$\underline{C}$H), 126.6 (Ar$\underline{C}$H), 79.9 (O$\underline{C}$(CH_3)$_3$), 66.8 ($\underline{C}H_2$OH), 54.2 ($\underline{C}$HCH$_2$), 30.9 (OC($\underline{C}H_3$)$_3$); Data are consistent with those published in the literature.[12]

6.2.3.2 Synthesis and Characterisation of 2.69

tert-butyl N-[(1*R*)-2-{[(4- methylbenzene)sulfonyl]oxy}-1- phenylethyl]carbamate

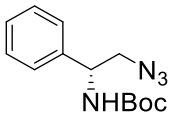


According to General Procedure B, *p*-toluenesulfonyl chloride (2.66 g, 14.0 mmol, 1.1 eq) and triethylamine (3.51 mL, 25.4 mmol, 2.0 eq) were reacted with a solution of **2.68** (3.01 g, 12.7 mmol, 1.0 eq) in CH_2Cl_2 (100 ml). The resulting mixture was purified by FCC (petroleum ether/EtOAc = 4/1) to afford the title compound **2.69** as a colourless solid in 69% yield (3.75 g). **m.p.** = 122 - 123 °C, lit. 123 - 124 °C[13]; **$[\alpha]_D^{23}$** = -2.3 (*c 1.0*, $CHCl_3$), lit -2.2, (*c* 3.0, $CHCl_3$)[3]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.68 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}$), 7.31 - 7.28 (m, 5 H, Ar$\underline{H}$), 7.23 - 7.20 (m, 2 H, Ar$\underline{H}$), 5.24 (d, *J* = 8.0 Hz, 1 H, CHN$\underline{H}$), 4.94 (br. s, 1H, C$\underline{H}$CH$_2$), 4.26 (dd, *J* = 10.0, 4.5 Hz, 1 H, CHC$\underline{H}_A$H$_B$), 4.17 (dd, *J* = 10.0, 5.5 Hz, 1 H, CHCH$_A\underline{H}_B$), 2.44 (s, 3 H, C$\underline{H}_3$), 1.43 (s, 9 H, CH(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 155.0 ($\underline{C}$=O), 145.0 (Ar$\underline{C}$), 137.8 (Ar$\underline{C}$), 132.4 (Ar$\underline{C}$), 129.9 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 128.0 (Ar$\underline{C}$H), 127.9 (Ar$\underline{C}$H), 126.6 (Ar$\underline{C}$H), 80.1 (O$\underline{C}$(CH_3)$_3$), 71.6

(CHCH$_2$), 53.4 (CHCH$_2$), 28.3 (C(CH$_3$)$_3$), 21.7 (ArCH$_3$); Data are consistent with those published in the literature.[3]

6.2.3.3 Synthesis and Characterisation of 2.70

tert-butyl [(1*R*)-2-azido-1-phenylethyl]carbamate

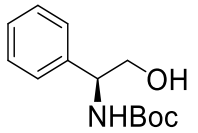


According to General Procedure C, tosylate **2.69** (3.75 g, 9.6 mmol, 1.0 eq) in DMF (47 mL) was reacted with sodium azide (690 mg, 10.6 mmol, 1.1 eq). The crude product was purified by FCC [petrol then 9:1 petrol: EtOAc] to afford the title compound **2.70** as a white solid in 76% yield (1.92 g). **m.p**. = 82 - 83 °C, lit. 82 - 84 °C[4]; **[α]$_D^{23}$** = -8.5 (*c 1.0*, CHCl$_3$), lit. -8.7, (*c* 1.0, CHCl$_3$)[14]; **^{1}H NMR** (400 MHz, CDCl$_3$) δ (ppm): 7.43 - 7.28 (m, 5 H, ArH), 5.15 (d, *J* = 7.5 Hz, 1 H, CHNH), 4.89 (br. s, 1 H, CHCH$_2$), 3.69 - 3.55 (m, 2 H,CHCH$_2$N$_3$), 1.45 (s, 9 H, OC(CH$_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ (ppm): 155.1 (C=O), 139.3 (ArC), 128.8 (ArCH), 128.0 (ArCH), 126.5 (ArCH), 80.1 (OC(CH$_3$)$_3$), 55.6 (CHCH$_2$N$_3$), 54.1 (CHNH), 28.3 (OC(CH$_3$)$_3$); Data consistent with that those reported in the literature.[14]

6.2.4 Synthesis of *L*-phenyl glycine derived azide

6.2.4.1 Synthesis and Characterisation of 2.99

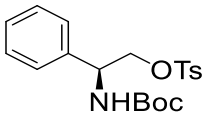
tert-butyl N-[(1*S*)-2-hydroxy-1- phenylethyl]carbamate



According to General Procedure A, sodium borohydride (1.2 g, 31.8 mmol, 2.4 eq) was reacted with *L*-phenyl glycine **2.98** (2.0 g, 13.2 mmol, 1.0 eq) and iodine (3.36 g, 13.2 mmol, 1.0 eq). The crude amino alcohol was then reacted with triethylamine (2.2 mL, 15.8 mmol, 1.2 eq) and di-*tert*-butyl dicarbonate (3.45 g, 15.8 mmol, 1.2 eq). The product was purified by FCC (petroleum ether/EtOAc = 4/1) to afford the title compound **2.99** as a colourless solid in 54% yield (1.68 g). **m.p.** = 138 - 139°C; $[\alpha]_D^{23}$ = +36.8 (*c 1.0*, $CHCl_3$); Other characterisation data agree with **2.68**.

6.2.4.2 Synthesis and Characterisation of 2.100

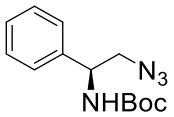
tert-butyl N-[(1*S*)-2-{[(4- methylbenzene)sulfonyl]oxy}-1- phenylethyl]carbamate



According to General Procedure B, *p*-toluenesulfonyl chloride (1.49 g, 7.80 mmol, 1.10 eq) and triethylamine (1.99 mL, 14.2 mmol, 2.00 eq) were reacted with **2.99** (3.01 g, 7.09 mmol, 1.00 eq) in CH_2Cl_2 (50ml) at room temperature. The crude mixture was purified by FCC (petroleum ether/EtOAc = 4/1) to afford the title compound **2.100** as a colourless solid in 71% yield (1.96 g). **m.p.** = 125 - 128 °C; $[\alpha]_D^{23}$ = +1.5 (*c 1.0*, $CHCl_3$); Other characterisation data agree with **2.69**.

6.2.4.3 Synthesis and Characterisation of 2.101

tert-butyl [(1*S*)-2-azido-1-phenylethyl]carbamate

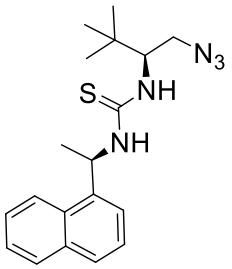


According to General Procedure C, **2.100** (1.95 g, 5.0 mmol, 1.0 eq) in DMF (20 mL) was reacted with sodium azide (358 mg, 5.5 mmol, 1.1 eq) at 45 °C and stirring was maintained for 14 h. The crude product was purified by FCC [petrol then 9:1 petrol: EtOAc] to afford the title compound **2.101** as a colourless solid in 70% yield (920 mg). **m.p. =** 83 - 84 ˚C; **$[\alpha]_D^{23}$** = +7.5 (*c 1.3*, $CHCl_3$); Other characterisation data agree with **2.70**.

6.2.5 Synthesis of chiral amine scaffold catalyst precursors

6.2.5.1 Synthesis and Characterisation of 2.56

3-[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]-1-[(1R)-1- (naphthalen-1-yl)ethyl]thiourea

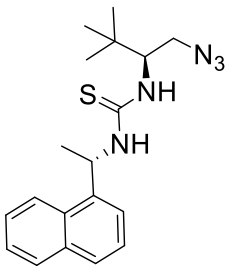


According to General Procedure D, **2.46** (143 mg, 0.68 mmol, 1.1 eq) and *(R)*-1-(1-Naphthyl)-ethylamine (106 mg, 0.62 mmol, 1.0 eq) were reacted with TFA (0.50 mL) and $CSCl_2$ (0.095 mL, 1.24 mmol, 2.0 eq) respectively. Then the deprotected

amino azide was added into a solution of the isothiocyanate in THF. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.56** as a colourless solid in 79% yield (174 mg). **m.p.** = 128 - 130 °C; **$[\alpha]_D^{23}$** = -58.9 (c *1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 8.10 (d, *J* = 8.0 Hz, 1 H, ArH), 7.95-7.84 (m, 2 H, ArH), 7.69-7.53 (m, 4 H, ArH), 5.53 (br. s, 1 H, CHCH$_3$), 4.36 (br. s, 1 H, CHCH$_3$), 3.48 (dd, *J* = 12.5, 4.0 Hz, 1 H, CHCH$_A$H$_B$N$_3$), 3.14 (dd, *J* = 12.5, 6.0 Hz, 1 H, CHCH$_A$H$_B$N$_3$), 1.64 (d, *J* = 6.5 Hz, 3 H, CHCH$_3$), 0.37 (s, 9 H, C(CH$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 181.1 (C=S), 137.2 (ArC), 134.1 (ArC), 130.0 (ArC), 129.3 (ArCH), 128.8 (ArCH), 127.1 (ArCH), 126.2 (ArCH), 125.8 (ArCH), 123.4 (ArCH), 121.8 (ArCH), 62.1 (CHCH$_2$N$_3$), 51.6 (CHCH$_2$N$_3$), 50.2 (CHCH$_3$), 33.9 (C(CH$_3$)$_3$), 26.2 (C(CH$_3$)$_3$), 22.6 (CHCH$_3$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{19}H_{25}N_5NaS$) requires *m/z* 378.1723, found *m/z* 378.1729; **IR** (film) ν_{max}/cm^{-1}: 2360, 2185, 2160, 2022, 2009, 1739, 722, 669, 631, 612.

6.2.5.2 Synthesis and Characterisation of 2.57

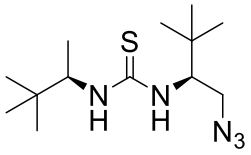
3-[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]-1-[(1*S*)-1-(naphthalen-1-yl)ethyl]thiourea



According to General Procedure D, **2.46** (143 mg, 0.68 mmol, 1.10 eq) and *(S)*-1-(1-Naphthyl)ethylamine (106 mg, 0.62 mmol, 1.00 eq) were reacted with TFA (0.50 mL) and $CSCl_2$ (0.095 mL, 1.24 mmol, 2 eq) respectively. Then the deprotected amino azide was added into a solution of the crude isothiocyanate in THF. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.57** as a white solid in 70% yield (154 mg). **m.p.** = 54 - 56 °C; $\mathbf{[\alpha]_D^{23}}$ = +7.5 (*c 1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 8.04 (d, *J* = 8.5 Hz, 1 H, Ar<u>H</u>), 7.84 (d, *J* = 8.0 Hz, 1 H, Ar<u>H</u>), 7.78 (d, *J* = 8.0 Hz, 1 H, Ar<u>H</u>), 7.43 - 7.54 (m, 4 H, Ar<u>H</u>), 5.39 (m, 1 H, C<u>H</u>CH_3), 4.12 (m, 1 H, C<u>H</u>CH_2N_3), 3.30 (dd, *J* = 12.5, 3.5 Hz, 1 H, CHC<u>H_A</u>H_BN_3), 2.98 (dd, *J* = 12.5, 4.5 Hz, 1 H, $CHCH_A$<u>H_B</u>N_3), 1.64 (d, *J* = 7.0 Hz, 3 H, C<u>H_3</u>), 0.68 (s, 9 H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** ($CDCl_3$, 400 MHz) δ (ppm): 181.7 (<u>C</u>=S), 134.1 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 123.4 (Ar<u>C</u>H), 61.5 (<u>C</u>HCH_2N_3), 51.3 (CH<u>C</u>H_2N_3), 50.5 (<u>C</u>HCH_3), 34.3 (<u>C</u>$(CH_3)_3$), 26.8 (C(<u>C</u>H_3)$_3$), 22.5 (CH<u>C</u>H_3); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{19}H_{25}N_5NaS$) requires *m/z* 378.1723, found *m/z* 378.1717; **IR** (film) ν_{max}/cm^{-1}: 2962, 2094, 1532, 1263, 1108, 801, 777, 714, 658.

6.2.5.3 Synthesis and Characterisation of 2.58

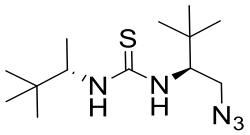
<u>3-[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]-1-[(2*R*)-3,3-dimethylbutan-2-yl] thiourea</u>



According to modified General Procedure D, **2.46** (200 mg, 0.83 mmol, 1.0 eq) and *(S)*-3,3-dimethyl-2-butylamine (92 mg, 0.91 mmol, 1.1 eq) were reacted with TFA (0.50 mL) and $CSCl_2$ (0.14 mL, 1.82 mmol, 2.0 eq) respectively. Then the deprotected amino azide was added into a solution of isothiocyanate in THF. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.58** as a white solid in 62% yield (146 mg). **m.p.** = 110 - 111 °C; $\mathbf{[\alpha]_D^{23}}$ = -81.3 (*c 0.9*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 6.15 (d, 1 H, *J* = 9.0 Hz, C<u>H</u>CH_3), 5.85 (m, 1 H, C<u>H</u>CH_2N_3), 3.67 (dd, *J* = 12.0, 3.5 Hz, 1 H, CH_A<u>H_B</u>N_3), 3.39 (dd, *J* = 12.0, 7.5 Hz, 1 H, C<u>H_A</u>H_BN_3), 1.16 (d, *J* = 7.0 Hz, 3 H, CHC<u>H_3</u>), 0.99 (s, 9 H, C(C<u>H_3</u>)$_3$), 0.95 (s, 9 H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** ($CDCl_3$, 400 MHz) δ (ppm): 181.8 (<u>C</u>=S), 62.0 (one of <u>C</u>HCH_3 or <u>C</u>HCH_2), 58.7 (one of <u>C</u>HCH_3 or <u>C</u>HCH_2), 52.2 (CH<u>C</u>H_2), 34.7 (<u>C</u>$(CH_3)_3$), 35.6 (<u>C</u>$(CH_3)_3$), 26.7 (C(<u>C</u>$H_3)_3$), 26.3 (C(<u>C</u>$H_3)_3$), 16.2 (CH<u>C</u>H_3); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{13}H_{27}N_5NaS$) requires *m/z* 308.1987, found *m/z* 308.1879. **IR** (film) ν_{max}/cm^{-1}: 3290, 2961, 2104, 1533, 712, 669.

6.2.5.4 Synthesis and Characterisation of 2.59

<u>3-[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]-1-[(2*S*)-3,3-dimethylbutan-2-yl] thiourea</u>

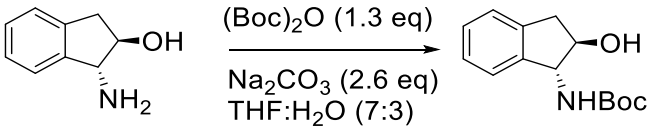


According to modified General Procedure D, **2.46** (104 mg, 0.41 mmol, 1.0 eq) and *(R)*-3,3-dimethyl-2-butylamine (46 mg, 0.45 mmol, 1.1 eq) were reacted with TFA (0.5 mL) and $CSCl_2$ (0.07 mL, 0.9 mmol, 2.0 eq) respectively. Then the deprotected amino azide was added into a solution of isothiocyanate in THF. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.59** as a colourless solid in 56% yield (66 mg). **m.p.** = 116 - 120 °C; $\mathbf{[\alpha]_D^{23}}$ = -94.5 (*c 1.5*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 6.17 (d, *J* = 8.0 Hz, 1 H, C<u>H</u>CH_3), 5.95 (m, 1 H, C<u>H</u>CH_2N_3), 3.64 (dd, *J* = 12.0, 3.5 Hz, 1 H, CH_A<u>H_B</u>N_3), 3.39 (dd, *J* = 12.0, 7.5 Hz, 1 H, C<u>H_A</u>H_BN_3), 1.13 (d, *J* = 7.0 Hz, 3 H, CHC<u>H_3</u>), 0.99 (s, 9 H, C(C<u>H_3</u>)$_3$), 0.95 (s, 9 H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** ($CDCl_3$, 400 MHz) δ (ppm): 181.8 (<u>C</u>=S), 62.0 (one of <u>C</u>HCH_3 or <u>C</u>HCH_2), 58.7 (one of <u>C</u>HCH_3 or <u>C</u>HCH_2), 52.2 (CH<u>C</u>H_2), 34.7 (<u>C</u>$(CH_3)_3$), 35.6 (<u>C</u>$(CH_3)_3$), 26.7 (C(<u>C</u>H_3)$_3$), 26.3(C(<u>C</u>H_3)$_3$), 16.2 (CH<u>C</u>H_3); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{13}H_{27}N_5NaS$) requires *m/z* 378.1987, found *m/z* 378.1879. **IR** (film) ν_{max}/cm^{-1}: 3278, 2962, 2098, 1531, 1359, 720, 659.

6.2.6 Synthesis of Cooperative H-Bond Donor Scaffold Catalyst Precursors

6.2.6.1 Synthesis and Characterisation of 2.61

tert-butyl N-[(1*R*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamate



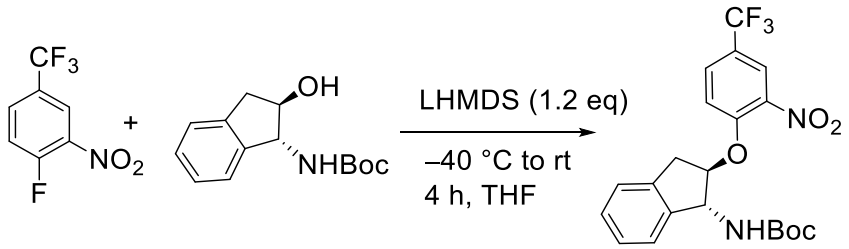
According to a general procedure[5], a solution of Boc_2O (952 mg, 4.36 mmol, 1.3 eq) in THF (10 mL) was added dropwise to a suspension of (*R,R*)-*trans*-aminoindanol **2.60** (500 mg, 3.35 mmol, 1.0 eq) and Na_2CO_3 (924 mg, 8.72 mmol, 2.6 eq) in a mixture of THF and water (7:3, 40 mL) at 0 °C. The reaction mixture was allowed to warm up to rt and stirred overnight. The volatiles were removed under vacuum and the resulting oil extracted with Et_2O (3 × 20 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by FCC (30% EtOAc/Hexane) afforded the title compound **2.61** as a white solid in 96% yield (801 mg). **m.p.** = 136 - 138 °C, lit. 138 - 139 °C[5]; **$[\alpha]_D^{23}$** = +19.2 (*c 1.1,* $CHCl_3$), lit. +52.7 (*c 1.0* $CHCl_3$)[5]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.35 - 7.14 (m, 4 H, Ar<u>H</u>), 5.09 (br, s, 1 H, CHN<u>H</u>), 4.91 (t, *J* = 6.0 Hz, 1 H, C<u>H</u>NH), 4.49 - 4.31 (m, 1 H, C<u>H</u>OH), 3.28 (dd, *J* = 15.5, 7.5 Hz, 1 H, CHC<u>H</u>$_A$H$_B$), 2.91 (dd, *J* = 15.5, 8.0 Hz, 1 H, CHCH$_A$<u>H</u>$_B$), 1.50 (s, 9 H, OC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) 157.4 (<u>C</u>=O), 140.2 (Ar<u>C</u>), 139.3 (Ar<u>C</u>), 128.5 (Ar<u>C</u>H), 127.2 (Ar<u>C</u>H), 125.2 (Ar<u>C</u>H), 123.0 (Ar<u>C</u>H), 82.0 (<u>C</u>HOH), 80.5 (O<u>C</u>(CH$_3$)$_3$), 64.0 (<u>C</u>HNH), 38.3 (CHC<u>H</u>$_2$), 28.4 (OC(<u>C</u>H$_3$)$_3$); Data

agree with those published in the literature.[5]

6.2.6.2 Synthesis and Characterisation of 2.62

tert-butyl N-[(1*R*,2*R*)-2-[2-nitro-4-(trifluoromethyl)phenoxy]

-2,3-dihydro-1H-inden-1-yl]carbamate



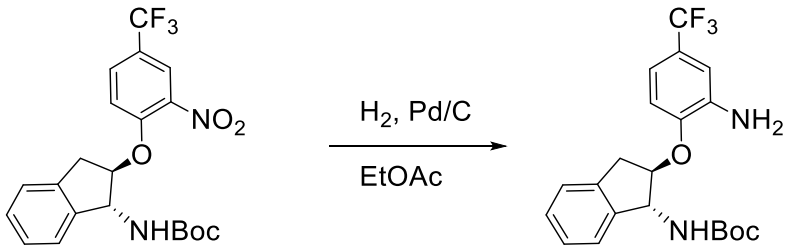
According to a general procedure[5], a solution of LiHMDS (1 M in THF, 3.75 mL, 3.75 mmol, 1.2 eq) was added *via* a syringe to a solution of **2.61** (780 mg, 3.13 mmol, 1.0 eq) and 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (1.29 mL, 9.39 mmol, 3.0 eq) in THF (30 mL) at −40 °C. The reaction mixture was progressively warmed up to rt over 3 h then stirred for an hour at RT. An aqueous saturated solution of NH_4Cl (20 mL) was added and the reaction mixture was concentrated, and extracted with Et_2O (3 × 20 mL), then dried over Na_2SO_4 and concentrated. The crude orange residue was triturated with hexane (40 mL), filtered and washed with hexane (20 mL), then dried under reduced pressure to afford **2.62** as a white solid in 96% yield (1.32 g). **m.p.** = 158 - 160 °C, lit. 154 - 155 °C[5]; $\mathbf{[\alpha]_D^{23}}$ = -55.7 (*c 1.0,* $CHCl_3$), lit. -61 (*c 1.0* $CHCl_3$)[5]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.09 (br. s, 1 H, ArH), 7.92 - 7.85 (m, 2 H, ArH), 7.37 - 7.29 (m, 4 H, ArH), 5.22 - 5.17 (m, 2 H, CHCH$_2$ and CHNH), 4.76 (d, *J* = 6.0 Hz, 1 H, CHNH), 3.57 (dd, *J* = 17.0, 6.0 Hz,

1 H, $CHCH_A\underline{H_B}$,), 3.23 - 3.19 (d, *J* = 17.0 Hz, 1 H, $CHC\underline{H_A}H_B$), 1.49 (s, 9 H, $OC(C\underline{H_3})_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 155.2 (<u>C</u>=O), 153.7 (Ar<u>C</u>), 140.2 (Ar<u>C</u>), 139.9 (Ar<u>C</u>), 139.3 (Ar<u>C</u>), 130.9 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 125.2 (Ar<u>C</u>H), 124.9 (Ar<u>C</u>H), 123.2 (Ar<u>C</u>H), 123.5 (Ar<u>C</u>F_3, q, *J* = 271.8 Hz), 123.0 (Ar<u>C</u>, q, *J* = 35.3 Hz), 117.0 (Ar<u>C</u>H), 85.1 (<u>C</u>HCH_2) , 80.3 (O<u>C</u>$(CH_3)_3$), 61.0 (<u>C</u>HNH), 37.2 (CH<u>C</u>H_2), 28.3 (C(<u>C</u>$H_3)_3$); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -61.5; Data agree with those published in the literature.[5]

6.2.6.3 Synthesis and Characterisation of 2.63

<u>*tert*-butyl N-[(1*R*,2*R*)-2-[2-amino-4-(trifluoromethyl)phenoxy]</u>

<u>-2,3-dihydro-1H-inden-1-yl]carbamate</u>

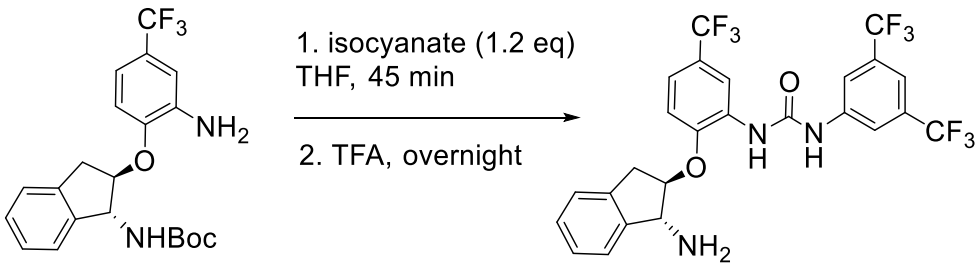


According to a general procedure[5], the nitro compound **2.62** (1.30 g, 2.97 mmol, 1.0 eq) was suspended in EtOAc (50 mL) in the presence of palladium on charcoal (5% w/w, 95 mg) and hydrogen filled balloon, then stirred overnight to afford, after filtration under celite and removal of the solvent, afforded **2.63** as an off-white solid in quantitative yield (1.21 g). **m.p.** = 185 - 186 °C, lit. 185 - 186 °C[5]; **$[\alpha]_D^{23}$** = -92.8 (*c 1.0,* $CHCl_3$), lit. -95.2 (*c 1.0* $CHCl_3$)[5]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.35 - 7.24 (m, 4 H, Ar<u>H</u>), 7.03 - 6.93 (m, 3 H, Ar<u>H</u>), 5.40 (br. s, 1 H, CHN<u>H</u>), 4.83 - 4.81

(m, 2 H, C<u>H</u>CH_2 and C<u>H</u>NH), 3.52 (dd, *J* = 16.0, 6.5 Hz, 1 H, $CHCH_A\underline{H_B}$), 3.07 (dd, *J* = 16.0, 5.5 Hz, 1 H, $CHC\underline{H_A}H_B$), 1.48 (s, 9 H, $OC(C\underline{H_3})_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 155.6 (<u>C</u>=O), 147.8 (Ar<u>C</u>), 139.6 (Ar<u>C</u>), 139.4 (Ar<u>C</u>), 137.4 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 125.2 (Ar<u>C</u>H), 124.4 (Ar<u>C</u>F_3, q, *J* = 271.8 Hz), 124.3 (Ar<u>C</u>H), 124.0 (Ar<u>C</u>, q, *J* = 32.6 Hz), 115.2 (Ar<u>C</u>H), 112.7 (Ar<u>C</u>H), 111.5 (Ar<u>C</u>H), 85.8 (<u>C</u>HCH_2), 80.3 ($O\underline{C}(CH_3)_3$), 61.2 (<u>C</u>HNH), 37.0 ($CH\underline{C}H_2$), 28.3 ($OC(\underline{C}H_3)_3$); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -61.7; Data agree with those published in the literature.[5]

6.2.6.4 Synthesis and Characterisation of 2.64

<u>3-(2-{[(1*R*,2*R*)-1-amino-2,3-dihydro-1H-inden-2-yl]oxy}-5-(trifluoromethyl)phenyl)-1-[3,5-bis(trifluoromethyl)phenyl]urea</u>

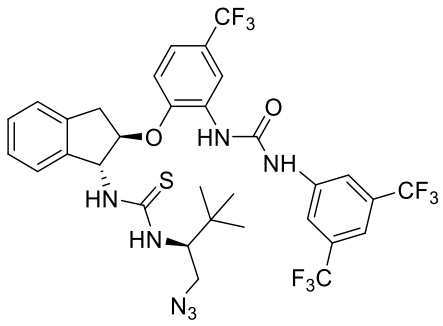


According to a general procedure[5], 3,5-bis(trifluoromethylphenyl) isocyanate (3.9 mL, 3.5 mmol, 1.2 eq) was added dropwise to a solution of **2.63** (1.19 g, 2.92 mmol, 1.0 eq) in THF (25 mL) at 0 °C and stirred at rt for 45 min. TFA (4 mL) was added in the reaction mixture at 0 °C then stirred overnight at rt. The reaction mixture was concentrated under vacuum to afford an oil which was treated with a saturated solution of $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL),

dried over Na_2SO_4 and concentrated. The crude solid was triturated with chloroform and hexane, filtered, and washed with hexane, then dried under vacuum to afford **2.64** as an off-white solid in 93% yield (1.53 g). **m.p.** = 172 - 174 °C, lit. 170 - 171 °C[5]; **$[\alpha]_D^{23}$** = -60.4 (*c 0.9,* DMSO-d_6), lit. -62.2 (*c 1.0* DMSO-d_6)[5]; **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 10.32 (s, 1 H, ArH), 8.53 (s, 1 H, ArH), 8.12 (s, 2 H, ArH), 7.67 - 7.63 (m, 2 H, ArH), 7.42 - 7.38 (m, 4 H, ArH), 5.31 - 5.29 (m, 1 H, CHCH$_2$), 5.19 (m, 1 H, CHNH$_2$), 3.79 (dd, *J* = 17.0, 7.0 Hz, 1 H, CHCH$_A$H$_B$), 3.05 (dd, *J* = 17.0, 4.0 Hz, 1 H, CHCH$_A$H$_B$); **^{13}C NMR** (100 MHz, DMSO-d_6) δ ppm: 152.3 (ArC), 148.9 (ArC), 141.5 (ArC), 141.2 (ArC), 139.5 (ArC), 130.9 (ArC, q, *J* = 30.9 Hz), 129.0 (ArCH), 127.7 (ArCH), 125.5 (ArCF$_3$, q, *J* = 271.0 Hz), 125.4 (ArCH), 125.0 (ArCH), 124.3 (ArC), 123.3 (ArCF$_3$, q, *J* = 272.6 Hz), 121.2 (ArC, q, *J* = 31.8 Hz), 120.1 (ArCH), 118.3 (ArCH, q, *J* = 3.2 Hz), 115.7 (ArCH), 115.1 (ArCH, q, *J* = 4.0 Hz), 113.5 (ArCH), 88.4 (CHCH$_2$), 62.4 (CHNH), 36.3 (CHCH$_2$); **^{19}F NMR** (DMSO-d_6, 376 MHz) (ppm): -61.7, 60.2; Data agree with those published in the literature.[5]

6.2.6.5 Synthesis and Characterisation of 2.65

3-(2-{[(1*R*,2*R*)-1-({[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]carbamothioyl}amino)-2,3-dihydro-1H-inden-2-yl]oxy}-5-(trifluoromethyl)phenyl)-1-[3,5-bis(trifluoromethyl)phenyl]urea



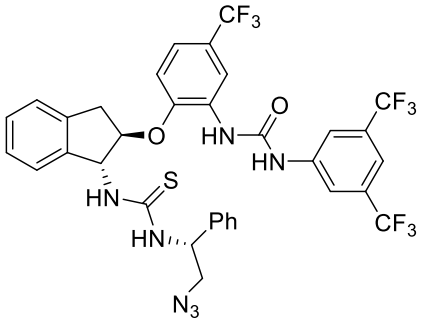
According to General Procedure D, **2.46** (117 mg, 0.83 mmol, 1.1 eq) and **2.64** (422 mg, 0.75 mmol, 1.0 eq) were reacted with TFA (0.50 mL) and $CSCl_2$ (0.115 mL, 1.5 mmol, 2.0 eq) respectively. Then the deprotected amino azide was added into a solution of the previously made isothiocyanate in THF. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.65** as a yellow solid in 77% yield (430 mg). **m.p.** = 138 - 140 °C; **$[\alpha]_D^{23}$** = -156.9 (*c 0.6,* $CHCl_3$); **^{1}H NMR** (400 MHz, $CHCl_3$) δ (ppm): 9.07 (br. s, 1 H, NH), 8.68 (s, 1 H, ArH), 8.35 (br. s, 1 H, NH), 8.14 (s, 2 H, ArH), 7.51 (s, 1 H, ArH), 7.32 - 7.25 (m, 4 H, ArH), 7.19 (d, *J* = 6.5 Hz, 1 H, ArH), 6.98 (d, *J* = 6.5 Hz, 1 H, ArH), 6.84 (m, 1 H, CHNH), 6.28 (m, 1 H, $CHCH_2N_3$), 4.51 (d, *J* = 7.5 Hz, 1 H, CH_2CHO), 3.64 (dd, *J* = 15.0, 7.5 Hz, 1 H, CH_AH_BCHO), 3.36 (m, 1 H, CH_AH_BCHO), 3.24-3.32 (m, 2 H, $CHCH_2N_3$), 0.94 (s, 9 H, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$)[xiv] δ (ppm): 151.5 (ArC), 148.1 (ArC), 139.6 (ArC), 136.4 (ArC), 136.1 (ArC), 131.0 (ArC, q, *J* = 33.4 Hz), 129.0 (ArCH), 127.8 (ArCH), 125.4 (ArCH), 123.0 ($ArCF_3$, q, *J* = 271.8 Hz), 122.7 (ArCH), 122.2 ($ArCF_3$, q, *J* = 272.6 Hz), 121.6 (ArC, q, *J* = 32.0 Hz), 119.2 (ArCH), 118.2 (ArCH), 115.8 (ArCH), 114.6

[xiv] Quaternary carbon C=S and C=O was not found in the ^{13}C NMR.

(Ar<u>C</u>H), 112.7 (Ar<u>C</u>H), 88.5 ($CH_2\underline{C}HO$), 63.5 (<u>C</u>HNH), 62.1 ($\underline{C}HCH_2N_3$), 50.7 ($\underline{C}H_2N_3$), 36.0 ($\underline{C}H_2CHO$), 33.5 ($\underline{C}(CH_3)_3$), 25.3 ($C(\underline{C}H_3)_3$); **^{19} NMR** (100 Hz, $CDCl_3$) δ (ppm): 62.8, 61.7; **HRMS** (EI+): calcd. for $[M+Na]^+$ ($C_{32}H_{30}F_9N_7NaOS$) required 770.1930, found 770.1934; **IR** (film) ν_{max}/cm^{-1}: 1546, 1215, 1133, 746, 668.

6.2.6.6 Synthesis and Characterisation of 2.66

<u>3-(2-{[(1R,2R)-1-({[(1R)-2-azido-1-phenylethyl]carbamothioyl}amino)-2,3-dihydro-1H-inden-2-yl]oxy}-5-(trifluoromethyl)phenyl)-1-[3,5-bis(trifluoromethyl)phenyl]urea</u>



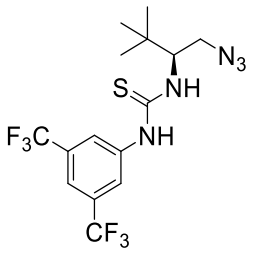
According to General Procedure D, **2.70** (100 mg, 0.33 mmol, 1.1 eq) and **2.64** (163mg, 0.3 mmol, 1.0 eq) were reacted with TFA (0.50 mL) and $CSCl_2$ (0.045 mL, 0.60 mmol, 2.00 eq) respectively. Then the deprotected amino azide was added into a solution of isothiocyanate in THF. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.66** as an off white solid in 67% yield (155 mg). **m.p. =** 100 - 104 °C; **$[\alpha]_D^{23}$ = -**106.5 (*c 1.5*, $CHCl_3$); **^{1}H NMR** (400 MHz, MeOD-d_4) δ (ppm): 8.51 (s, 1 H, Ar<u>H</u>), 8.11 (br s, 1 H, N<u>H</u>), 7.79 (m, 2 H, Ar<u>H</u>), 7.35 (s, 2 H, Ar<u>H</u>), 7.20 - 7.11 (m, 9 H, Ar<u>H</u>), 6.85 (d, *J* =

8.5 Hz, 1 H, ArH), 6.60 (m, 1 H, CHCHNH), 6.21 (m, 1 H, CHCH$_2$N$_3$), 4.35 (q, *J* = 8.5, 1 H, CH$_2$CHO), 3.63 (m, 2 H, CH$_2$N$_3$), 3.51 (dd, *J* = 15.0, 8.0 Hz, 1 H, CH$_A$H$_B$CHO), 3.10 (dd, *J* = 15.0, 9.5 Hz, 1 H, CH$_A$H$_B$CHO); **^{13}C NMR** (100 MHz, MeOD-d$_4$)[xv] δ (ppm): 152.5 (ArC), 149.2 (ArC), 141.4 (ArC), 140.1 (ArC), 138.9 (ArC), 138.5 (ArC), 131.8 (ArC, q, *J* = 33.4 Hz), 128.4 (ArCH) 128.3 (ArCH), 127.6 (ArCH), 127.2 (ArCH), 126.2 (ArCH), 124.8 (ArCH), 125.8 (ArCF$_3$, q, *J* = 273.4 Hz), 123.4 (ArCF$_3$, q, *J* = 271.8 Hz), 123.1 (ArC, q, *J* = 31.8 Hz), 119.2 (ArCH), 117.7 (ArCH), 117.6 (ArCH), 115.1 (ArCH), 114.7 (ArCH), 112.7 (ArCH), 89.8 (CH$_2$CHO), 65.0 (CHNH), 57.7 (CHCH$_2$N$_3$), 55.7 (CH$_2$N$_3$), 36.9 (CH$_2$CHO); **^{19}F NMR** (MeOD-d$_4$, 376 Hz) δ (ppm): -64.4, 63.2; **HRMS** (EI+): calcd. for [M+Na]$^+$ (C$_{34}$H$_{26}$F$_9$N$_7$NaOS) required 790.1617, found 790.1616; **IR** (film) ν_{max}/cm^{-1}: 3320, 2110, 1740, 1544, 1385, 1277, 1171, 1128, 752, 699, 681, 662.

6.2.7 Synthesis of Various H-Bond Donor L-*tert* Leucine Derived Catalyst Precursors

6.2.7.1 Synthesis and Characterisation of 1.61

1-[(2*S*)-1-Azido-3-methylbutan-2-yl]-3-[3,5-bis(trifluoromethyl)phenyl]thiourea

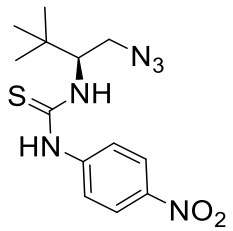


[xv] Quaternary carbon C=S and C=O was not found in the ^{13}C NMR.

Azide **2.46** (484 mg, 2.0 mmol, 1.0 eq) was reacted with TFA (1.0 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.44 mL, 2.4 mmol, 1.2 eq) was added according to General Procedure E. Purification by FCC [Petrol then 9:1 Petrol: Et_2O] afforded the title compound **1.61** as a colourless solid (650 mg, 79% yield). **m.p.** 166 - 168 °C lit. 164 - 166 °C[4]; **$[\alpha]_D^{23}$** = -26.7 (*c 1.0*, $CHCl_3$) lit. - 29.9 (*c 0.9*, $CHCl_3$)[4]; **^{1}H NMR** (400 MHz, MeOD-d4) δ (ppm): 8.23 (s, 2 H, ArC<u>H</u>), 7.64 (s, 1 H, ArC<u>H</u>), 4.73 (d, *J* = 4.5 Hz, 1 H, C<u>H</u>NH), 3.62 (dd, *J* = 13.0, 4.0 Hz, 1 H, CHC<u>H</u>$_A$H$_B$N$_3$), 3.42 (dd, *J* = 14.0, 8.0 Hz, 1 H, CHCH$_A$<u>H</u>$_B$N$_3$), 1.03 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, MeOD-d4) δ (ppm): 180.6 (<u>C</u>=S), 143.4 (Ar<u>C</u>), 133.0 (Ar<u>C</u>, q, *J* = 33.3 Hz), 125.9 (Ar<u>C</u>F$_3$, q, *J* = 271.9 Hz), 123.8 (Ar<u>C</u>H), 118.0 (Ar<u>C</u>H), 62.9 (<u>C</u>HCH$_2$N$_3$), 52.7 (CH<u>C</u>H$_2$N$_3$), 35.8 (<u>C</u>(CH$_3$)$_3$), 27.3 (C(<u>C</u>H$_3$)$_3$). **^{19}F NMR** (MeOD-d$_4$, 376 MHz) δ (ppm): -64.5. All spectroscopic data is consistent with that given in the literature.[4]

6.2.7.2 Synthesis and Characterisation of 3.61

<u>*(S)*-1-(1-azido-3,3-dimethylbutan-2-yl)-3-(4-nitrophenyl)thiourea</u>

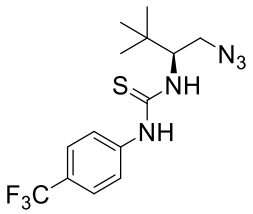


Azide **2.46** (242 mg, 1.0 mmol, 1.0 eq) was reacted with TFA (0.5 mL) then 1-isothiocyanato-4-nitrobenzene (216 mg, 1.2 mmol, 1.2 eq) was added according

to General Procedure E. Purification by FCC [Petrol then 3:2 Petrol: Et_2O] afforded the title compound **3.61** as a yellow solid (255 mg, 79 % yield). **m.p.** 114 - 115 °C, lit 107 - 110 °C[4]; **$[\alpha]_D^{23}$** = +18.1 (*c 1.0*, $CHCl_3$), lit. +10.9 (*c 1.2*, $CHCl_3$)[4]; **^{1}H NMR** (400 MHz, MeOD-d4) δ (ppm): 8.17 (d, *J* = 9.0 Hz, 2 H, ArC<u>H</u>), 7.90 (d, *J* = 9.0 Hz, 2 H, ArC<u>H</u>), 4.71 (dd, *J* = 8.0, 4.0 Hz, 1 H, C<u>H</u>NH), 3.60 (dd, *J* = 13.0, 4.0 Hz, 1 H, CHC<u>H</u>$_A$H$_B$N$_3$), 3.39 (dd, *J* = 13.0, 8.0 Hz, 1 H, CHCH$_A$<u>H</u>$_B$N$_3$), 1.01 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, MeOD-d4) δ (ppm): 183.5 (<u>C</u>=S), 147.7 (Ar<u>C</u>), 144.5 (Ar<u>C</u>), 125.4 (Ar<u>C</u>H), 122.5 (Ar<u>C</u>H), 62.6 (<u>C</u>HCH$_2$N$_3$), 52.7 (CH<u>C</u>H$_2$N$_3$), 35.8 (<u>C</u>(CH$_3$)$_3$), 27.3 (C(<u>C</u>H$_3$)$_3$). All spectroscopic data is consistent with that given in the literature.[4]

6.2.7.3 Synthesis and Characterisation of 3.62

<u>*(S)*-1-(1-azido-3,3-dimethylbutan-2-yl)-3-(4-(trifluoromethyl)phenyl)thiourea</u>



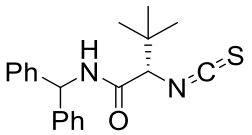
Azide **2.46** (242 mg, 1.0 mmol, 1.0 eq) was reacted with TFA (0.5 mL) then 1-isothiocyanato-4-(trifluoromethyl)benzene (244 mg, 1.2 mmol, 1.2 eq) and Et_3N was added according to General Procedure E. Purification by FCC [Petrol then 3:2 Petrol: Et_2O] afforded the title compound **3.62** as a colourless solid (270 mg, 78 % yield). **m.p.** 122 - 123 °C; **$[\alpha]_D^{23}$** = +28.0 (*c 0.9*, $CHCl_3$) lit **$[\alpha]_D^{23}$** = + 27.1 (*c 0.9*, $CHCl_3$)[4]; **^{1}H NMR** (400 MHz, MeOD-d$_4$) δ (ppm): 7.77 (d, *J* = 8.5 Hz, 2 H, Ar<u>H</u>),

7.59 (d, *J* = 8.5 Hz, 2 H, ArC<u>H</u>), 4.73 (m, 1 H, C<u>H</u>CH_2), 3.64 (dd, *J* = 13.0, 4.0 Hz, 2 H, CHC<u>H_A</u>$H_B$$N_3$), 3.44 (dd, *J* = 13.0, 8.0 Hz, 1 H, CHCH_A<u>H_B</u>N_3), 1.01 (s, 9 H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** (100 MHz, MeOD-d_4) δ (ppm): 183.9 (<u>C</u>=S), 144.6 (Ar<u>C</u>), 126.8 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>F_3, q, *J* = 271.3 Hz), 124.0 (Ar<u>C</u>H), 62.8 (<u>C</u>H$CH_2$$N_3$), 52.7 (CH<u>C</u>$H_2$$N_3$), 35.8 (<u>C</u>($CH_3$)$_3$), 27.4 (C(<u>C</u>$H_3$)$_3$). **^{19}F NMR** (MeOH-$d_4$, 376 MHz) δ (ppm): -63.6. All spectroscopic data is consistent with that given in the literature.[4]

6.2.8 Synthesis of Chiral Amido-thiourea Isothiocyanates

6.2.8.1 Synthesis and Characterisation of 2.80

<u>(2*S*)-*N*-(Diphenylmethyl)-2-isothiocyanato-3,3-dimethylbutanamide</u>

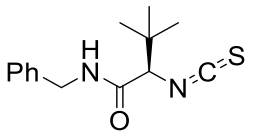


Boc-*L*-*tert*-leucine (1.16 g, 5.0 mmol, 1.0 eq) was reacted with benzhydrylamine (0.57 mL, 5.5 mmol, 1.1 eq) according to General Procedure F to afford the title compound **2.80** as a pale yellow solid in 62% yield (1.05 g). **m.p.** = 150 - 152 °C, lit. 162 - 166°C[15]; **[α]$_D^{23}$** = +39.2 (*c 1.01*, $CHCl_3$), lit. +47.5 (*c 0.7*, $CHCl_3$)[15]; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 7.37 - 7.22 (m, 10 H, Ar<u>H</u>), 6.71 (d, *J* = 8.0 Hz, 1 H, N<u>H</u>), 6.25 (d, *J* = 8.0 Hz, 1 H, Ph_2C<u>H</u>NH), 4.08 (s, 1 H, C<u>H</u>(^{t}Bu)), 1.07 (s, 9 H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm)[xvi]: 165.5 (<u>C</u>=O), 140.8 (Ar<u>C</u>), 140.5 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 70.9 (<u>C</u>H(^{t}Bu)), 57.3 (Ph_2<u>C</u>HNH), 37.1 (<u>C</u>(CH_3)$_3$), 26.7 (C(<u>C</u>H_3)$_3$);

All characterisation data agree with that published in literature.[15]

6.2.8.2 Synthesis and Characterisation of 2.81

(2*R*)-*N*-benzyl-2-isothiocyanato-3,3-dimethylbutanamide

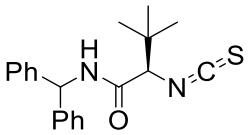


Boc-*D*-*tert*-leucine (324 mg, 1.4 mmol, 1.0 eq) was reacted with benzylamine (168 µL, 1.54 mmol, 1.1 eq) according to General Procedure F to afford the title compound **2.81** as a yellow solid in 95% yield (347 mg). **m.p.** = 110 - 114 °C; **$[\alpha]_D^{23}$** = -15.7 (*c 1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.38 - 7.27 (m, 5 H, ArH), 6.34 (br. s, 1 H, NH), 4.48 (dd, *J* = 15.0, 6.0 Hz, 1 H, $PhCH_AH_BNH$), 4.42 (dd, *J* = 15.0, 5.5 Hz, 1 H, $PhCH_AH_BNH$), 4.09 (s, 1 H, CH(^{t}Bu)), 1.10 (s, 9 H, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz)[xvi] δ (ppm): 166.2 (C=O), 137.4 (ArC), 128.8 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 70.8 (CH(^{t}Bu)), 43.8 ($PhCH_2NH$), 37.0 ($C(CH_3)_3$), 26.7 ($C(CH_3)_3$); **HRMS** (EI+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}N_2NaOS$) requires *m/z* 285.1032, found *m/z* 285.1032; **IR** (film) ν_{max}/cm^{-1}: 3293, 2965, 2072 (NCS), 1658 (C=O), 1548, 1247, 698.

6.2.8.3 Synthesis and Characterisation of 2.83

(2*R*)-*N*-(Diphenylmethyl)-2-isothiocyanato-3,3-dimethylbutanamide

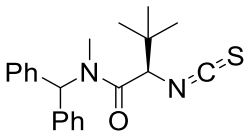
[xvi] Quaternary carbon C=S not found in spectrum



Boc-*D-tert*-leucine (323 mg, 1.4 mmol, 1.0 eq) was reacted with benzhydrylamine (282 µL, 1.54 mmol, 1.11 eq) according to General Procedure F to afford the title compound **2.83** as a pale yellow solid in 89% yield (421 mg). $\mathbf{[\alpha]_D^{23}}$ = -40.5 (*c 1.0*, $CHCl_3$); All other characterisation data agree with the enantiomer **2.80**.

6.2.8.4 Synthesis and Characterisation of 2.84

(2*R*)-*N*-(diphenylmethyl)-2-isothiocyanato-*N*,3,3 - trimethylbutanamide



Boc-*D-tert*-leucine (324 mg, 1.4 mmol, 1.0 eq) was reacted with *N*-benzylmethylamine (303 mg, 1.54 mmol, 1.1 eq) according to General Procedure F to afford the title compound **2.84** as a pale yellow solid in 23% yield (110 mg). **m.p**. = 96 - 100 °C; $\mathbf{[\alpha]_D^{23}}$ = -150.4 (c *1.1*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz, compound exists as ~3:1 mixture of rotamers, major rotamer identified by *) δ ppm: 7.36 - 7.34 (m, 6 H, Ar<u>H</u>* and Ar<u>H</u>), 7.20 - 7.18 (m, 5 H, Ar<u>H</u>* and Ar<u>H</u> and C<u>H</u>NCH_3 and C<u>H</u>*NCH_3), 4.34 (s, 1 H, C<u>H</u>*$(CH_3)_3$), 4.21 (s, 1 H, C<u>H</u>$(CH_3)_3$), 2.89 (s, 3 H, Ph_2CHN(C<u>H</u>$_3$*)), 2.76 (s, 3 H, Ph_2CHN(C<u>H</u>$_3$)), 1.13 (s, 9 H, C(C<u>H</u>$_3$*)$_3$), 1.11 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$, major rotamer identified by *) [xvii] δ ppm:

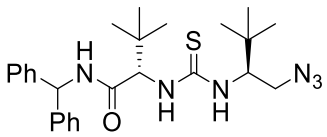
[xvii] Quaternary carbon N<u>C</u>S not found in the spectrum, some of the Ar<u>C</u>Hs are missing, probably due to overlap of signals

167.2 (C=O), 167.0 (C*=O), 138.6 (ArC*), 138.3 (ArC), 138.2 (ArC), 138.0 (ArC*), 128.9 (ArC*H and ArCH), 128.7 (ArC*H), 128.6 (ArC*H), 128.5 (ArCH), 128.4 (ArC*H), 128.3 (ArCH), 127.8 (ArC*H), 127.6 (ArC*H), 65.0 (CH(^{t}Bu)), 64.4 (C*H(^{t}Bu)), 63.9 (Ph_2CHN), 61.2 (Ph_2C*HN), 37.8 (CHC*(CH_3)$_3$), 37.3 (CHC(CH_3)$_3$), 33.0 ($PhCH_2N$(C*H_3)), 31.7 ($PhCH_2N$(CH_3)), 26.5 (C(C*H_3)$_3$ and C(CH_3)$_3$); **HRMS** (EI+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}N_2NaOS$) requires *m/z* 375.1507, found *m/z* 375.1493; **IR** (film) ν_{max}/cm^{-1}: 2966, 2068 (NCS), 1651 (C=O), 908, 729, 701.

6.2.9 Synthesis of Chiral Amido-thiourea H-Bond Donor Scaffold Catalyst Precursors

6.2.9.1 Synthesis and Characterisation of 2.87

(S)-2-(3-(*(S)*-1-azido-3,3-dimethylbutan-2-yl)thioureido)-N-benzhydryl-3,3-dimethylbutanamide

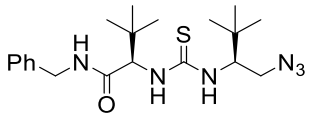


L-tert-leucine boc-protected amino azide **2.46** (242 mg, 1.0 mmol, 1.0 eq) was reacted with Jacobsen isothiocyanate **2.80** (374 mg, 1.1 mmol, 1.1 eq) according to General Procedure G. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.87** as a colourless solid in 64% yield (307 mg). **m.p.** = 196 - 198 °C; **$[\alpha]_D^{23}$** = -36.1 (c *0.9*, $CHCl_3$); ^{1}H NMR (MeOD-d_4, 500 MHz) δ (ppm): 7.35 - 7.19 (m, 10 H, ArH), 6.18 (s, 1 H, Ph_2CHNH),

5.02 (s, 1 H, C(=O)C<u>H</u>$(CH_3)_3$), 4.67 (dd, *J* = 8.0, 3.5 Hz, 1 H, C<u>H</u>CH_2N_3), 3.52 (dd, *J* = 13.0, 3.5 Hz, 1 H, CHC<u>H_A</u>H_BN_3), 3.26 (dd, *J* = 12.5, 8.5 Hz, 1 H, CHCH_A<u>H_B</u>N_3), 1.01 (s, 9 H, one of C(=O)CHC(C<u>H</u>$_3)_3$ or NHCHC(C<u>H</u>$_3)_3$), 0.98 (s, 9 H, one of C(=O)CHC(C<u>H</u>$_3)_3$ or NHCHC(C<u>H</u>$_3)_3$); **^{13}C NMR** (MeOD-d_4, 125 MHz) δ (ppm): 186.0 (<u>C</u>=S), 172.8 (<u>C</u>=O), 143.4 (Ar<u>C</u>), 142.9 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 129.4 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 66.8 (C(=O)<u>C</u>H(^{t}Bu)), 63.6 (<u>C</u>HCH_2N_3), 58.5 (Ph_2<u>C</u>HNH), 53.0 (CH<u>C</u>H_2N_3), 35.7 (one of C(=O)CH<u>C</u>$(CH_3)_3$ or NHCH<u>C</u>$(CH_3)_3$), 35.7 (one of C(=O)CH<u>C</u>$(CH_3)_3$ or NHCH<u>C</u>$(CH_3)_3$), 27.6 (one of C(=O)CHC(<u>C</u>$H_3)_3$ or NHCHC(<u>C</u>$H_3)_3$), 27.4 (one of C(=O)CHC(<u>C</u>$H_3)_3$ or NHCHC(<u>C</u>$H_3)_3$); **HRMS** (EI+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{36}N_6NaOS$) requires m/z 503.2564, found m/z 503.2559; **IR** (film) ν_{max}/cm^{-1}: 2963, 2099, 1650, 1530, 752, 699.

6.2.9.2 Synthesis and Characterisation of 2.88

<u>(2*R*)-2-({[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]carbamothioyl}amino)-*N*-benzyl-3,3-dimethylbutanamide</u>

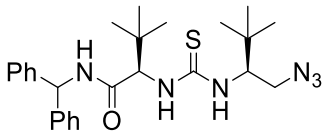


L-tert-leucine Boc-protected amino azide **2.46** (185 mg, 0.77 mmol, 1.1 eq) was reacted with Jacobsen isothiocyanate **2.81** (183 mg, 0.7 mmol, 1.0 eq) according to General Procedure G. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 9/1 to 4/1) to afford the title compound **2.88** as a pale white solid in

50% yield (154 mg). **m.p.** = 164 - 166 °C; **$[\alpha]_D^{23}$** = -26.0 (*c 1.0*, $CHCl_3$); **^{1}H NMR** (MeOD-d_4, 400 MHz) δ (ppm): 8.31 (br. s, 1 H, $PhCH_2N\underline{H}$), 7.23 - 7.11 (m, 5 H, Ar$\underline{H}$), 4.87 (s, 1 H, C(=O)C$\underline{H}$(^{t}Bu)), 4.53 (m, 1 H, C$\underline{H}CH_2N_3$), 4.27 - 4.28 (m, 2 H, $PhC\underline{H}_2NH$), 3.51 (dd, *J* = 12.5, 4.0 Hz, 1 H, $CHC\underline{H}_AH_BN_3$), 3.23 (dd, *J* = 12.5, 8.0 Hz, 1 H, $CHCH_A\underline{H}_BN_3$), 0.92 (s, 9 H, one of C(=O)CHC($C\underline{H}_3$)$_3$ or NHCHC($C\underline{H}_3$)$_3$), 0.88 (s, 9 H, one of C(=O)CHC($C\underline{H}_3$)$_3$ or NHCHC($C\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, MeOD-d_4) δ (ppm): 184.5 ($\underline{C}$=S), 171.7 ($\underline{C}$=O), 138.4 (Ar$\underline{C}$), 128.0 (Ar$\underline{C}$H), 127.4 (Ar$\underline{C}$H), 126.7 (Ar$\underline{C}$H), 65.3 (C(=O)$\underline{C}$H(^{t}Bu)), 61.5 ($\underline{C}HCH_2N_3$), 51.6 ($CH\underline{C}H_2N_3$), 42.6 ($Ph\underline{C}H_2NH$), 34.5 (one of C(=O)CH$\underline{C}$(CH_3)$_3$ or NHCH$\underline{C}$(CH_3)$_3$), 34.3 (one of C(=O)CH$\underline{C}$(CH_3)$_3$ or C(=O)CH$\underline{C}$(CH_3)$_3$), 26.0 (one of C(=O)CHC($\underline{C}H_3$)$_3$ or NHCHC($\underline{C}H_3$)$_3$), 25.8 (one of C(=O)CHC($\underline{C}H_3$)$_3$ or NHCHC($\underline{C}H_3$)$_3$); **HRMS** (EI+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{32}N_6NaOS$) requires *m/z* 427.2258, found *m/z* 427.2234; **IR** (film) ν_{max}/cm^{-1}: 3272, 2963, 2095, 1644, 1532, 697.

6.2.9.3 Synthesis and Characterisation of 2.90

(2R)-2-({[(2S)-1-azido-3,3-dimethylbutan-2-yl]carbamothioyl}amino)-N-(diphenylmethyl)-3,3-dimethylbutanamide



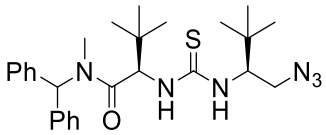
L-tert-leucine boc-protected amino azide **2.46** (185 mg, 0.77 mmol, 1.1 eq) was reacted with Jacobsen isothiocyanate **2.83** (237 mg, 0.70 mmol, 1.0 eq) according

to General Procedure G. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.90** as a colourless solid in 60% yield (202 mg). **m.p.** = 227 - 230 °C; **$[\alpha]_D^{23}$** = +4.1 (*c 1.0*, $CHCl_3$); **^{1}H NMR** (MeOD-d_4, 400 MHz) δ (ppm): 8.76 (d, *J* = 8.0 Hz, 1 H, $Ph_2CHN\underline{H}$), 7.42 - 7.04 (m, 10 H, Ar$\underline{H}$), 6.19 (d, *J* = 8.0 Hz, 1 H, $Ph_2C\underline{H}NH$), 5.01 (s, 1 H, C(=O)C$\underline{H}$(^{t}Bu)), 4.66 (m, 1 H, $C\underline{H}CH_2N_3$), 3.55 (dd, *J* = 13.0, 4.0 Hz, 1 H, $CHC\underline{H_A}H_BN_3$), 3.32 (dd, *J* = 13.0, 8.0 Hz, 1 H, $CHCH_A\underline{H_B}N_3$), 1.01 (s, 18 H, C(=O)CHC($C\underline{H_3}$)$_3$ and NHCHC($C\underline{H_3}$)$_3$); **^{13}C NMR** (MeOD-d_4, 100 MHz))[xviii] δ (ppm): 171.6 (C=O), 142.0 (Ar$\underline{C}$), 141.8 (Ar$\underline{C}$), 128.5 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 128.2 (Ar$\underline{C}$H), 127.7 (Ar$\underline{C}$H), 127.4 (Ar$\underline{C}$H), 127.1 (Ar$\underline{C}$H), 65.9 (C(=O)$\underline{C}$H(^{t}Bu)), 65.5 ($\underline{C}HCH_2N_3$), 61.9 ($Ph_2\underline{C}HNH$), 57.3 ($CH\underline{C}H_2N_3$), 35.0 (one of C(=O)CH$\underline{C}$(CH$_3$)$_3$ or NHCH$\underline{C}$(CH$_3$)$_3$), 34.7 (one of C(=O)CH$\underline{C}$(CH$_3$)$_3$ or NHCH$\underline{C}$(CH$_3$)$_3$), 26.3 (one of C(=O)CHC($\underline{C}$H$_3$)$_3$ or NHCHC($\underline{C}$H$_3$)$_3$), 26.2 (one of C(=O)CHC($\underline{C}$H$_3$)$_3$ or NHCHC($\underline{C}$H$_3$)$_3$); **HRMS** (EI+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{36}N_6NaOS$) requires *m/z* 503.2569, found *m/z* 503.2556; **IR** (film) ν_{max}/cm^{-1}: 3304, 2960, 2099, 1637, 1533, 756, 698.

6.2.9.4 Synthesis and Characterisation of 2.91

(2*R*)-2-({[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]carbamothioyl}amino)-*N*-(diphenylmethyl)-*N*,3,3-trimethylbutanamide

[xviii] Quaternary carbon N$\underline{C}$S not found in the spectrum

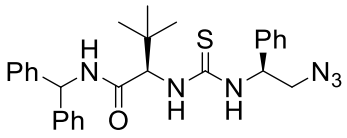


L-tert-leucine boc-protected amino azide **2.46** (26 mg, 0.11 mmol, 1.1 eq) was reacted with Jacobsen isothiocyanate **2.84** (35 mg, 0.10 mmol, 1.0 eq) according to General Procedure G. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.91** as a white solid in 69% yield (34 mg). **m.p.** = 68 - 72 °C; **$[\alpha]_D^{23}$** = -2.5 (*c 0.6*, $CHCl_3$); **^{1}H NMR** (400 MHz, MeOD-d_4) δ (ppm): 7.39 - 7.18 (m, 10 H, Ar<u>H</u>), 7.05 (s, 1 H, $Ph_2C\underline{H}N$), 5.63 (s, 1 H, C(=O)C<u>H</u>(^{t}Bu)), 4.67 (m, 1 H, $C\underline{H}CH_2N_3$), 3.55 (dd, *J* = 13.0, 4.0 Hz, 1 H, $CHC\underline{H}_AH_BN_3$), 3.30 (m, 1 H, $CHCH_A\underline{H}_BN_3$), 3.15 (s, 3 H, $NC\underline{H}_3$), 1.06 (s, 9 H, one of C(=O)CHC($C\underline{H}_3$)$_3$ or CHC($C\underline{H}_3$)$_3CH_2N_3$), 1.01 (s, 9 H, one of C(=O)CHC($C\underline{H}_3$)$_3$ or CHC($C\underline{H}_3$)$_3CH_2N_3$); **^{13}C NMR** (100 MHz, MeOD-d_4) δ (ppm): 171.1 (<u>C</u>=O), 140.5 (Ar<u>C</u>), 138.4 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 61.5 ($Ph_2\underline{C}HNCH_3$), 60.7 (C(=O)<u>C</u>H(^{t}Bu), 58.8 ($\underline{C}HCH_2N_3$), 52.0 ($CH\underline{C}H_2N_3$), 34.7 (C(=O)CH<u>C</u>(CH_3)$_3$ and CH<u>C</u>(CH_3)$_3CH_2N_3$), 33.2 (NCH_3), 26.3 (C(=O)CHC($\underline{C}H_3$)$_3$ and CHC($\underline{C}H_3$)$_3CH_2N_3$); **HRMS** (EI+) exact mass calculated for $[M+Na]^+$ ($C_{27}H_{38}N_6NaOS$) requires *m/z* 517.2726, found *m/z* 517.2725; **IR** (film) ν_{max}/cm^{-1}: 2964, 2098, 1612, 1446, 1216, 755.

6.2.9.5 Synthesis and Characterisation of 2.102

<u>(2*R*)-2-({[(1*S*)-2-azido-1-phenylethyl]carbamothioyl}amino)-*N*-(diphenylmethyl)-</u>

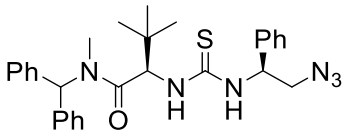
3,3-dimethylbutanamide



tert-butyl [(1*S*)-2-azido-1-phenylethyl]carbamate **2.101** (403 mg, 1.54 mmol, 1.1 eq) was reacted with Jacobsen isothiocyanate **2.83** (237 mg, 1.4 mmol, 1.0 eq) according to General Procedure G. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.102** as a colourless solid in 60% yield (420 mg). **m.p.** = 188 - 190 °C; **$[\alpha]_D^{23}$** = +23.4 (*c 1.0*, $CHCl_3$); **^{1}H NMR** (MeOD-d_4, 400 MHz) δ (ppm): 8.87 (d, *J* = 8.5 Hz, 1H, $Ph_2CHN\underline{H}$), 7.43 - 7.20 (m, 15 H, Ar$\underline{H}$), 6.22 (d, *J* = 8.5 Hz, 1 H, $Ph_2C\underline{H}NH$), 5.73 (t, *J* = 6.0 Hz, 1 H, $C\underline{H}CH_2N_3$), 4.95 (s, 1 H, C(=O)C$\underline{H}$(^{t}Bu)), 3.74 (dd, *J* = 12.5, 6.0 Hz, 1 H, $CHC\underline{H}_AH_BN_3$), 3.66 (dd, *J* = 12.5, 6.0 Hz, 1 H, $CHCH_A\underline{H}_BN_3$), 0.98 (s, 9 H, $C(=O)CHC(C\underline{H}_3)_3$); **^{13}C NMR** (MeOD-$d_4$, 100 MHz) δ (ppm): 181.6 ($\underline{C}$=S), 171.6 ($\underline{C}$=O), 139.9 (Ar$\underline{C}$), 139.0 (Ar$\underline{C}$), 138.0 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$H), 128.5 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 127.8 (Ar$\underline{C}$H), 127.7 (Ar$\underline{C}$H), 127.5 (Ar$\underline{C}$H), 127.1 (Ar$\underline{C}$H), 127.0 (Ar$\underline{C}$H), 65.4 (C(=O)$\underline{C}$H(^{t}Bu)), 57.6 ($\underline{C}HCH_2N_3$), 57.3 ($Ph_2\underline{C}HNH$), 55.4 ($CH\underline{C}H_2N_3$), 34.7 ($C(=O)CH\underline{C}(CH_3)_3$), 26.3 ($C(=O)CHC(\underline{C}H_3)_3$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{28}H_{32}N_6NaOS$) requires *m/z* 523.2256, found *m/z* 523.2237; **IR** (film) ν_{max}/cm^{-1}: 3236, 2107, 1666 (C=O), 1532, 1508, 1339, 751, 699, 644.

6.2.9.6 Synthesis and Characterisation of 2.103

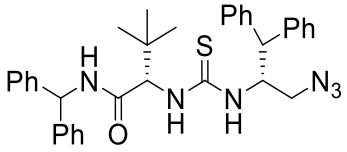
(R)-2-(3-((S)-2-azido-1-phenylethyl)thioureido)-N-benzhydryl-N,3,3-trimethylbutanamide



tert-butyl [(1*S*)-2-azido-1-phenylethyl]carbamate **2.101** (144 mg, 0.55 mmol, 1.1 eq) was reacted with Jacobsen isothiocyanate **2.84** (176 mg, 0.5 mmol, 1.0 eq) according to General Procedure G. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **2.103** as a colourless solid in 68% yield (300 mg). **m.p.** = 73 - 74 °C; **$[\alpha]_D^{23}$** = +17.5 (*c 0.6*, $CHCl_3$); **^{1}H NMR** (MeOD-d_4, 400 MHz) δ (ppm): 7.40 - 7.23 (m, 15 H, Ar<u>H</u>), 7.10 (s, 1 H, $Ph_2C\underline{H}N$), 5.76 (t, *J* = 5.0 Hz, 1 H, $C\underline{H}CH_2N_3$), 5.46 (s, 1 H, C(=O)C<u>H</u>(^{t}Bu)), 3.75 (dd, *J* = 12.5, 5.5 Hz, 1 H, $CHC\underline{H}_AH_BN_3$), 3.69 (dd, *J* = 12.5, 6.0 Hz, 1 H, $CHCH_A\underline{H}_BN_3$), 3.16 (s, 3 H, $NC\underline{H}_3$), 1.05 (s, 9 H, C(=O)CHC($C\underline{H}_3$)$_3$); **^{13}C NMR** (MeOD-d_4, 100 MHz) δ (ppm): 173.4 (<u>C</u>=O), 139.5 (Ar<u>C</u>), 139.2 (Ar<u>C</u>), 138.1 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 61.3 ($Ph_2\underline{C}HN$), 60.7 (C(=O)<u>C</u>H(^{t}Bu)), 57.3 ($\underline{C}HCH_2N_3$), 55.1 ($CH\underline{C}H_2N_3$), 35.3 (C(=O)CH<u>C</u>(CH_3)$_3$), 32.8 ($NC\underline{H}_3$), 25.8 (C(=O)CHC($C\underline{H}_3$)$_3$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{28}H_{32}N_6NaOS$) requires *m/z* 514.2515, found *m/z* 514.2513; **IR** (film) ν_{max}/cm^{-1}: 3317, 2979, 2103, 1616 (C=O), 1530, 1277, 751, 700.

6.2.9.7 Synthesis and Characterisation of 4.22

(S)-2-(3-(*(R)*-3-azido-1,1-diphenylpropan-2-yl)thioureido)-N-benzhydryl-3,3-dimethylbutanamide



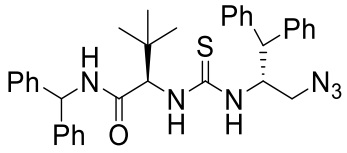
Amino azide **3.59** (352 mg, 1.0 mmol, 1.0 eq) was reacted with Jacobsen isothiocyanate **2.80** (380 mg, 1.1 mmol, 1.1 eq) according to General Procedure G. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **4.22** as a colourless solid in 73% yield (430 mg). **m.p.** = 120 - 122 °C; $\mathbf{[\alpha]_D^{23}}$ = -103.4 (*c 1.2*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.38 - 7.13 (m, 20 H, ArC<u>H</u>), 6.88 (d, *J* = 9.5 Hz, 1 H, (^{t}Bu)CHN<u>H</u>), 6.75 (d, *J* = 8.5 Hz, 1 H, Ph_2CHN<u>H</u>), 6.57 (d, *J* = 8.5 Hz, 1 H, CH_2CHN<u>H</u>), 6.25 (d, *J* = 8.5 Hz, 1 H, Ph_2C<u>H</u>NH), 5.48 (m, 1 H, C<u>H</u>CH_2N_3), 5.02 (d, *J* = 8.5 Hz, 1 H, C(=O)C<u>H</u>(^{t}Bu)), 4.08 (d, *J* = 11.5 Hz, 1 H, Ph_2C<u>H</u>CH), 3.70 (dd, *J* = 12.0, 2.0 Hz, 1 H, CHC<u>H_A</u>H_BN_3), 3.11 (dd, *J* = 12.0, 2.5 Hz, 1 H, CHCH_A<u>H_B</u>N_3), 0.84 (s, 9 H, C(=O)CHC(C<u>H_3</u>)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 182.8 (<u>C</u>=S), 170.6 (<u>C</u>=O), 141.4 (Ar<u>C</u>), 141.3 (Ar<u>C</u>), 140.8 (Ar<u>C</u>), 140.5 (Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 65.7 (C(=O)<u>C</u>H(^{t}Bu)), 57.0 (Ph_2<u>C</u>HNH), 56.3 (<u>C</u>HCH_2N_3), 53.0 (Ph_2<u>C</u>HCH), 52.8 (CH<u>C</u>H_2N_3), 35.4 (C(=O)CH<u>C</u>$(CH_3)_3$),

26.8 (C(=O)CHC(<u>C</u>H_3)$_3$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{35}H_{39}N_6OS$) requires *m/z* 591.2901, found *m/z* 591.2903; **IR** (film) ν_{max}/cm^{-1}: 3289, 2101, 1647 (C=O), 1530, 749, 699.

6.2.9.8 Synthesis and Characterisation of 4.23

<u>*(R)*-2-(3-(*(R)*-3-azido-1,1-diphenylpropan-2-yl)thioureido)

-N-benzhydryl-3,3-dimethylbutanamide</u>



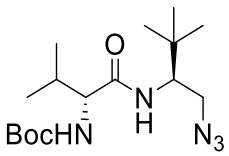
tert-Butyl *(S)*-(3-azido-1,1-diphenylpropan-2-yl)carbamate **3.59** (352 mg, 1.0 mmol, 1.0 eq) was reacted with Jacobsen isothiocyanate **2.83** (380 mg, 1.1 mmol, 1.1 eq) according to the General Procedure G. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **4.23** as a colourless solid in 69% yield (410 mg). **m.p.** = 203 - 204 °C; **$[\alpha]_D^{23}$** = -80.9 (*c 0.9*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.38 - 7.12 (m, 20 H, ArC<u>H</u>), 6.62 (d, *J* = 7.5 Hz, 1 H, Ph_2CHN<u>H</u>), 6.42 (d, *J* = 4.5 Hz, 1 H, (^{t}Bu)CHN<u>H</u>), 6.18 (d, *J* = 7.5 Hz, 1 H, Ph_2C<u>H</u>NH), 5.95 (m, 1 H, CH_2CHN<u>H</u>), 5.35 (m, 1 H, C<u>H</u>CH_2N_3), 4.79 (m, 1 H, C(=O)C<u>H</u>(^{t}Bu)), 4.23 (d, *J* = 11.0 Hz, 1 H, Ph_2C<u>H</u>CH), 3.82 (d, *J* = 11.0 Hz, 1 H, CHC<u>H_A</u>$H_B$$N_3$), 3.15 (d, *J* = 11.0 Hz, 1 H, $CHCH_A$<u>H_B</u>N_3), 0.93 (s, 9 H, C(=O)CHC(C<u>H_3</u>)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 182.9 (<u>C</u>=S), 169.7 (<u>C</u>=O), 141.2 (Ar<u>C</u>), 141.1 (Ar<u>C</u>), 140.7 (Ar<u>C</u>), 140.3 (Ar<u>C</u>), 129.0 (Ar<u>C</u>H), 128.8

(ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.5 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 65.8 (C(=O)CH(^{t}Bu)), 57.2 (Ph_2CHNH), 56.7 (CHCH$_2$N$_3$), 52.7 (Ph_2CHCH), 52.5 (CHCH$_2$N$_3$), 34.9 (C(=O)CHC(CH$_3$)$_3$), 26.7 (C(=O)CHC(CH$_3$)$_3$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{35}H_{39}N_6OS$) requires *m/z* 591.2901, found *m/z* 591.2903; **IR** (film) ν_{max}/cm^{-1}: 3314, 2101, 1639, 1537, 753, 699.

6.2.10 Synthesis of other BIMP Catalyst Precursors

6.2.10.1 Synthesis and Characterisation of 4.27

tert-butyl (*(R)*-1-((*(S)*-1-azido-3,3-dimethylbutan-2-yl) amino)-3-methyl-1-oxobutan-2-yl)carbamate

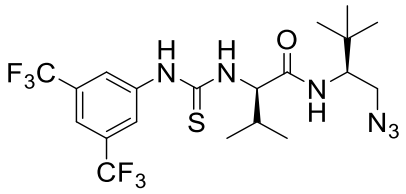


According to a modified literature procedure[16], to a stirred solution of *N*-Boc *L*-valine (432 mg, 2.0 mmol, 1.0 eq) in THF (10 mL) at 0 °C was added sequentially triethylamine (0.70 mL, 5.0 mmol, 2.5 eq) and then ethyl chloroformate (210 µL, 2.2 mmol, 1.1 eq) dropwise. Stirring was maintained for 1 h and then the crude amino azide [obtained according to General Procedure D using azide **2.46** (528 mg, 2.2 mmol, 2.0 eq)] was added as a solution in Et_2O (4 mL) was added dropwise. The reaction mixture was warmed to rt and stirring was maintained overnight whereupon the volatiles were removed *in vacuo*. The crude material was

partitioned in H_2O (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL), the combined organics were washed (brine), dried ($MgSO_4$) and the volatiles concentrated *in vacuo*. Purification by FCC [Petroleum ether to petroleum ether/EtOAc 4/1] afforded the title compound **4.27** as a colourless solid in 88% yield (600 mg). **m.p.** = 140 - 141 °C; **$[\alpha]_D^{25}$** = +25.8 (c *1.0*, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 6.08 (d, *J* = 10.0 Hz, 1 H, N<u>H</u>CHC<u>H</u>$_2$N$_3$), 4.90 (s, 1 H, N<u>H</u>Boc), 3.89 (ddd, *J* = 10.0, 8.0, 4.0 Hz, 1 H, C<u>H</u>CH$_2$N$_3$), 3.82 (t, *J* = 7.0 Hz, 1 H,C<u>H</u>CH(CH$_3$)$_2$), 3.49 (dd, *J* = 12.5, 4.0 Hz, 1 H, CHC<u>H$_A$</u>H$_B$N$_3$), 3.20 (dd, *J* = 12.5, 8.0 Hz, 1 H,CHCH$_A$<u>H$_B$</u>N$_3$), 2.21 - 2.20 (m, 1 H, (CH$_3$)C<u>H</u>(CH$_3$)), 1.37 (s, 9 H,OC(C<u>H</u>$_3$)$_3$), 0.93 (d, *J* = 7.0 Hz, 3 H, (CH$_3$)CH(C<u>H</u>$_3$)), 0.90 (d, *J* = 7.0 Hz, 3 H, (C<u>H</u>$_3$)CH(CH$_3$)), 0.87 (s, 9 H, CHC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 171.6 (<u>C</u>ONH), 156.1 (<u>C</u>OONH), 79.9 (O<u>C</u>(CH$_3$)$_3$), 60.8 (<u>C</u>HCH(CH$_3$)$_2$), 56.0 (<u>C</u>HCH$_2$N$_3$), 51.9 (CH<u>C</u>H$_2$N$_3$), 34.0 (CH<u>C</u>(CH$_3$)$_3$), 29.9 ((CH$_3$)<u>C</u>H(CH$_3$)), 28.3 (OC(<u>C</u>H$_3$)$_3$), 26.7 (CHC(<u>C</u>H$_3$)$_3$), 19.6 ((<u>C</u>H$_3$)CH(CH$_3$)), 18.1 ((CH$_3$)CH(<u>C</u>H$_3$)); **HRMS** (EI+): calcd. for $[M+Na]^+$ ($C_{16}H_{31}N_5NaO_3$) 364.2319, found 364.2316; **IR** ν_{max}/cm^{-1} 3318, 3275, 2965, 2092, 1686 (C=O), 1650 (C=O), 1522.

6.2.10.2 Synthesis and Characterisation of 4.28

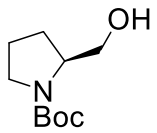
<u>*(R)*-N-(*(S)*-1-azido-3,3-dimethylbutan-2-yl)-2-(3-(3,5-bis(trifluoromethyl)phenyl) thioureido)-3-methylbutanamide</u>



Azide **4.27** (273 mg, 0.8 mmol, 1.0 eq) was reacted with TFA (0.8 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.24 mL, 0.88 mmol, 1.1 eq) was added according to a modified General Procedure E using Et_2O (3 mL). Purification by FCC [Petroleum ether to petroleum ether/EtOAc 4/1] afforded the title compound **4.28** as a colourless solid in 85% yield (350 mg). **m.p.** = 187 - 190 °C; **$[\alpha]_D^{25}$** = +64.0 (c *1.3*, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1 H, ArN<u>H</u>C=S), 8.29 (d, *J* = 9.0 Hz, 1H, (C=S)N<u>H</u>CHCH), 8.16 (s, 2 H, Ar<u>H</u>), 7.62 (s, 1 H, Ar<u>H</u>), 6.81 (d, *J* = 10.5 Hz, 1 H, N<u>H</u>CHCH$_2$N$_3$), 4.99 (t, *J* = 9.0 Hz, 1 H, C<u>H</u>C=O), 3.78 (td, *J* = 10.0, 3.0 Hz, 1 H, C<u>H</u>CH$_2$N$_3$), 3.48 (dd, *J* = 13.0, 3.0 Hz, 1 H, CHC<u>H$_A$</u>H$_B$N$_3$), 3.31 (dd, *J* = 13.0, 9.5 Hz, 1 H, CHCH$_A$<u>H$_B$</u>N$_3$), 2.27 (dt, *J* = 10.0, 7.0 Hz, 1 H, (CH$_3$)C<u>H</u>(CH$_3$)), 1.17 (d, *J* = 7.0 Hz, 3 H, (CH$_3$)CH(C<u>H$_3$</u>)), 1.13 (d, *J* = 7.0 Hz, 3 H, (C<u>H$_3$</u>)CH(CH$_3$)), 0.96 (s, 9 H, CHC(C<u>H$_3$</u>)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 182.0 (<u>C</u>=S), 173.5 (<u>C</u>=O), 140.4 (Ar<u>C</u>), 131.5 (q, J_{FC} = 33.8 Hz, Ar<u>C</u>CF$_3$), 124.5 (Ar<u>C</u>H), 124.1 (q, J_{FC} = 272.8 Hz, <u>C</u>F$_3$), 118.2 (ArCH), 64.5 (<u>C</u>HCH(CH$_3$)$_2$), 58.4 (<u>C</u>HCH$_2$N$_3$), 52.0 (CH<u>C</u>H$_2$N$_3$), 33.5 (CH<u>C</u>(CH$_3$)$_3$), 29.9 ((CH$_3$)<u>C</u>H(CH$_3$)), 26.7 (CHC(<u>C</u>H$_3$)$_3$), 19.7 ((<u>C</u>H$_3$)CH(CH$_3$)), 18.5 ((CH$_3$)CH(<u>C</u>H$_3$)); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -62.9; **HRMS** (EI+): calcd. for $[M+Na]^+$ ($C_{20}H_{26}ON_6F_6NaS$) 535.1696, found 535.1684; **IR** ν_{max}/cm^{-1}: 3310, 3238, 3016, 2970, 2112, 1738 (C=O), 1366, 1229, 1217.

6.2.10.3 Synthesis and Characterisation of 4.32

tert-butyl *(S)*-2-(hydroxymethyl)pyrrolidine-1-carboxylate

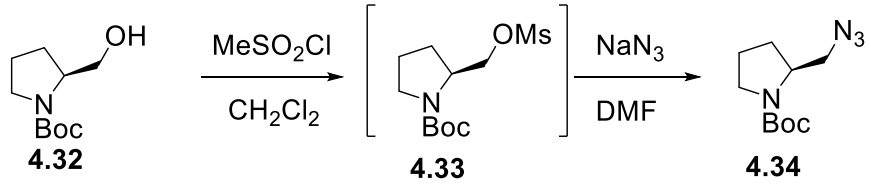


According to a literature procedure[17], to a heterogeneous mixture of $NaBH_4$ powder (605 mg, 16 mmol, 1.6 eq) in anhydrous THF (60 mL) was added N-Boc-protected *L*-proline **4.31** (2.15 g, 10 mmol, 1.0 eq) at 0 °C during 1 h (evolution of H_2). $BF_3{\cdot}OEt_2$ (2.47 mL, 20 mmol, 2.0 eq) was then added and stirring was continued for 4 h, followed by addition of 1 N aq NaOH (80 mL). Stirring was continued for 30 min and then the solvent was removed *in vacuo*. EtOAc (60 mL) was added to the residue and the organic layer was washed with 1 N HCl (60 mL) and H_2O (40 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by FCC (PE:EtOAc, 3:1) to afford the title compound **4.32** as a colourless oil in 95% yield (1.9 g); $\mathbf{[\alpha]_D^{25}}$ = -42.0 (c *0.5*, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 4.76 (d, *J* = 6.0 Hz, 1 H, O$\underline{H}$), 3.98 - 3.97 (m, 1 H, C$\underline{H}CH_2OH$), 3.65 - 3.58 (m, 2 H, CHC$\underline{H_2}$OH), 3.48 - 3.43 (m, 1 H, C$\underline{H_A}H_BN$), 3.34 - 3.27 (m, 1 H, $CH_A\underline{H_B}N$), 2.06 - 1.97 (m, 1 H, C$\underline{H_A}H_BCHN$), 1.84 - 1.77 (m, 2 H, C$\underline{H_2}CH_2N$), 1.56 - 1.53 (m, 1 H, $CH_A\underline{H_B}CHN$), 1.48 (s, 9 H, C(C$\underline{H_3}$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 157.1 ($\underline{C}$=O), 80.2 ($\underline{C}(CH_3)_3$), 67.8 (CH$\underline{C}H_2OH$), 60.2 ($\underline{C}HCH_2OH$), 47.6 ($\underline{C}H_2N$), 28.8

($\underline{C}H_2CHN$), 28.5 ($C(\underline{C}H_3)_3$), 24.1 ($\underline{C}H_2CH_2N$); All data consistent with those reported in literature.[18]

6.2.10.4 Synthesis and Characterisation of 4.34

tert-butyl *(S)*-2-(azidomethyl)pyrrolidine-1-carboxylate



4.32 **4.33** **4.34**

According to a literature procedure[18]**,** alcohol **4.32** (1.87 g, 9.3 mmol,1.0 eq) was dissolved in anhydrous CH_2Cl_2 (25 ml) and cooled to 0°C under N_2. After 5 min stirring, Et_3N (1.11 ml, 14.0 mmol, 1.5 eq) and $MeSO_2Cl$ (0.57 ml, 14.0 mmol, 1.5 eq) were added dropwise, the reaction mixture was stirred 2 h at 0 °C. The solvent was removed *in vacuo* and the resulting oil was diluted with EtOAc and sat. $NaHCO_3$ solution. The organic layer was washed with sat. $NaHCO_3$ solution, water, 1M $KHSO_4$ aqueous solution and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give **4.33** as a yellow oil in 2.8 g which was used in next step without further purification.

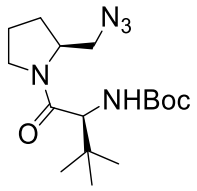
According to a literature procedure[18]**,** tosylate **4.33** (2.8 g, 9.3 mmol, 1.0 eq) was dissolved in DMF (20 ml) and heated to 60 °C. NaN_3 (1.5 g, 23.3 mmol, 2.5 eq) was added and the reaction mixture was stirred at 60 °C for 24 h. The mixture was diluted with EtOAc. The organic layer was washed with 1 M $KHSO_4$ aqueous solution, water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. FCC

(PE:EtOAc, 4:6) over silica gel gave **4.34** as a yellow oil in 81% yield over two steps (1.7 g). **$[\alpha]_D^{25}$** = -46.0 (c *0.7*, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 3.93 - 3.86 (m, 1 H, C<u>H</u>CH_2N_3), 3.56 - 3.28 (m, 4 H, CHC<u>H_2</u>N_3 and C<u>H_2</u>N), 1.97 - 1.84 (m, 4 H, C<u>H_2</u>CHN and C<u>H_2</u>CH_2N), 1.48 (s, 9 H, C(C<u>H_3</u>)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 154.5 (<u>C</u>=O), 79.8 (<u>C</u>$(CH_3)_3$), 56.5 (<u>C</u>HCH_2N_3), 53.7 (CH<u>C</u>H_2N_3), 47.0 (<u>C</u>H_2N), 29.4 (<u>C</u>H_2CHN), 28.5 (C(<u>C</u>H_3)$_3$), 23.0 (<u>C</u>H_2CH_2N); All data consistent with those reported in literature.[18]

6.2.10.5 Synthesis and Characterisation of 4.37

<u>*tert*-butyl (*(S)*-1-(*(S)*-2-(azidomethyl)pyrrolidin-1-yl)</u>

<u>-3,3-dimethyl-1-oxobutan-2-yl)carbamate</u>



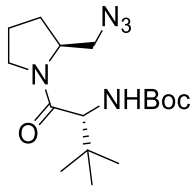
Under N_2 atmosphere, TFA (1 mL) was added into azide **4.34** (249 mg, 1.1 mmol, 1.1 eq) at 0°C. The reaction was followed by TLC and quenched with NaOH (aq). The aqueous layer was extracted with Et_2O (20 mL× 3). The organic layers were combined, dried over $MgSO_4$ and concentrated under a stream of N_2. According to General Procedure F, EDC hydrochloride (210 mg, 1.1 mmol, 1.1 eq) and 1-hydroxybenzotriazole hydrate (149 mg, 1.1 mmol, 1.1 eq) in CH_2Cl_2 (10 mL) was reacted with Boc-*L*-*tert* leucine (231 mg, 1.0 mmol, 1.0 eq) and the free amine (1.1 mmol, 1.1 eq) sequentially. The crude product was purified with FCC to afford the

title compound **4.37** as a colourless oil in >99% yield (340 mg). **$[\alpha]_D^{25}$** = +21.4 (c *0.4*, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm; 5.26 (d, *J* = 10.0 Hz, 1 H, CHNHBoc), 4.28 (d, *J* = 10.0 Hz, 1 H, CHNHBoc), 4.20 - 4.16 (m, 1 H, $CHCH_2N_3$), 3.82 - 3.78 (m, 1 H, CH_AH_BN), 3.63 - 3.46 (m, 3 H, $CHCH_2N_3$ and CH_AH_BN), 2.07 - 1.88 (m, 4 H, CH_2CHN and CH_2CH_2N), 1.42 (s, 9 H, $(C=O)OC(CH_3)_3$), 0.99 (s, 9 H, $CHC(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 171.1 (NC=O), 155.8 (NHC=O), 79.5 ($(C=O)OC(CH_3)_3$), 58.5 (CHNHBoc), 56.7 ($CHCH_2N_3$), 51.6 (CH_2N), 48.1 ($CHCH_2N_3$), 35.3 ($CHC(CH_3)_3$), 29.3 (CH_2CHN), 28.3 ($COC(CH_3)_3$), 26.4 ($CHC(CH_3)_3$), 23.9 (CH_2CH_2N); **HRMS** (EI+): calcd. for $[M+Na]^+$ ($C_{16}H_{29}O_3N_5Na$) 362.2163, found 362.2164; **IR** ν_{max}/cm^{-1}: 2970, 2101, 1707 (C=O), 1636 (C=O),1423, 1169, 752.

6.2.10.6 Synthesis and Characterisation of 4.38

tert-butyl (*(R)*-1-(*(S)*-2-(azidomethyl)pyrrolidin-1-yl)

-3,3-dimethyl-1-oxobutan-2-yl)carbamate

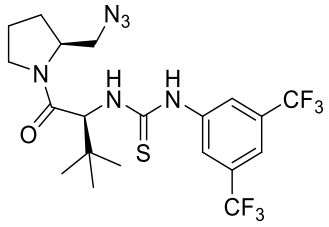


Under N_2 atmosphere, TFA (1 mL) was added into azide **4.34** (249 mg, 1.1 mmol, 1.1 eq) at 0°C. The reaction was followed by TLC and quenched with NaOH (aq). The aqueous layer was extracted with Et_2O (20 mL× 3). The organic layers were combined, dried over $MgSO_4$ and concentrated under a stream of N_2. According

to General Procedure F, EDC hydrochloride (210 mg, 1.1 mmol, 1.1 eq) and 1-hydroxybenzotriazole hydrate (149 mg, 1.1 mmol, 1.1 eq) in CH_2Cl_2 (10 mL) was reacted with Boc-L-*tert* leucine (231 mg, 1.0 mmol, 1.0 eq) and the free amine (1.1 mmol, 1.1 eq) sequentially. The crude product was purified with FCC to afford the title compound **4.38** as a colourless oil in 96% yield (325 mg). $\mathbf{[\alpha]_D^{25}}$ = -42.1 (c *1.4*, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 5.20 (d, *J* = 10.0 Hz, 1 H, CHN<u>H</u>Boc), 4.25 (d, *J* = 10.0 Hz, 1 H, C<u>H</u>NHBoc), 4.21 - 4.20 (m, 1 H, C<u>H</u>CH_2N_3), 3.75 - 3.72 (m, 1 H, C<u>H_A</u>H_BN), 3.57 - 3.48 (m, 3 H, CHC<u>H_2</u>N_3 and CH_A<u>H_B</u>N), 2.00 - 1.83 (m, 4 H, C<u>H_2</u>CHN and C<u>H_2</u>CH_2N), 1.39 (s, 9 H, (C=O)OC(C<u>H_3</u>)$_3$), 0.99 (s, 9 H, CHC(C<u>H_3</u>)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 171.3 (N<u>C</u>=O), 155.9 (NH<u>C</u>=O), 79.6 ((C=O)O<u>C</u>$(CH_3)_3$), 58.6 (<u>C</u>HNHBoc), 56.3 (<u>C</u>HCH_2N_3), 52.6 (<u>C</u>H_2N), 48.6 (CH<u>C</u>H_2N_3), 35.5 (CH<u>C</u>$(CH_3)_3$), 28.4 (<u>C</u>H_2CHN), 27.8 ((C=O)OC(<u>C</u>H_3)$_3$), 26.4 (CHC(<u>C</u>H_3)$_3$), 24.4 (<u>C</u>H_2CH_2N); **HRMS** (EI+): calcd. for $[M+Na]^+$ ($C_{16}H_{29}O_3N_5Na$) 362.2163, found 362.2164; **IR** ν_{max}/cm^{-1}: 2970, 2101, 1712 (C=O), 1638 (C=O), 1423, 1170, 755.

6.2.10.7 Synthesis and Characterisation of 4.39

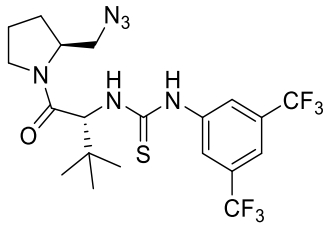
<u>1-((*S*)-1-((*S*)-2-(azidomethyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea</u>



Azide **4.37** (289 mg, 0.8 mmol, 1.0 eq) was reacted with TFA (0.8 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.2 mL, 0.96 mmol, 1.2 eq) was added according to a modified General Procedure E using Et_2O (3 mL). Addition of petroleum ether (3.0 mL) to the reaction mixture gave a precipitate which was dried *in vacuo* to afford the title compound **4.39** as a colourless solid in 49% yield (200 mg). **m.p.** = 66 - 68 °C; **$[\alpha]_D^{25}$** = -89.8 (c *0.6*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 8.95 (s, 1 H, ArC<u>H</u>), 7.88 (s, 2 H, ArC<u>H</u>), 7.79 (d, *J* = 8.6 Hz, 1 H, CHN<u>H</u>), 7.58 (s, 1 H, ArN<u>H</u>), 5.34 (d, *J* = 9.0 Hz, 1 H, C<u>H</u>NH), 4.33 - 4.27 (m, 1 H, C<u>H</u>$_A$H$_B$N), 4.15 (dd, *J* = 5.5, 3.0 Hz, 1 H, C<u>H</u>CH$_2$N$_3$), 3.76 (dd, *J* = 12.0, 5.5 Hz, 1 H, CHC<u>H</u>$_A$H$_B$N$_3$), 3.59 (dt, *J* = 10.0, 7.0 Hz, 1 H, CH$_A$<u>H</u>$_B$N), 3.47 (dd, *J* = 12.0, 3.0 Hz, 1 H, CHC<u>H</u>$_A$H$_B$N$_3$), 2.06-1.85 (m, 4 H, C<u>H</u>$_2$CHN and C<u>H</u>$_2$CH$_2$N), 1.15 (s, 9 H, CHC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 181.6 (<u>C</u>=S), 172.4 (<u>C</u>=O), 142.6 (Ar<u>C</u>), 132.5 (q, *J* = 33.8 Hz, Ar<u>C</u>CF$_3$), 124.1 (q, *J* = 272.8 Hz, <u>C</u>F$_3$), 123.7 (Ar<u>C</u>H), 118.0 (Ar<u>C</u>H), 63.8 (<u>C</u>HNH), 57.1 (<u>C</u>HCH$_2$N$_3$), 52.6 (CH<u>C</u>H$_2$N$_3$), 49.5 (<u>C</u>H$_2$N), 35.5 (CH<u>C</u>(CH$_3$)$_3$), 27.6 (<u>C</u>H$_2$CHN), 27.2 (C(<u>C</u>H$_3$)$_3$), 24.5 (<u>C</u>H$_2$CH$_2$N); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -63.0; **HRMS** (EI+): calcd. for $[M+Na]^+$ ($C_{20}H_{24}ON_6F_6NaS$) 533.1529, found 533.1527; **IR** ν_{max}/cm^{-1}: 3248, 2968, 2105, 1619 (C=O), 1525, 1380, 1277, 1176, 1134, 758.

6.2.10.8 Synthesis and Characterisation of 4.40

1-((*R*)-1-((*S*)-2-(azidomethyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea



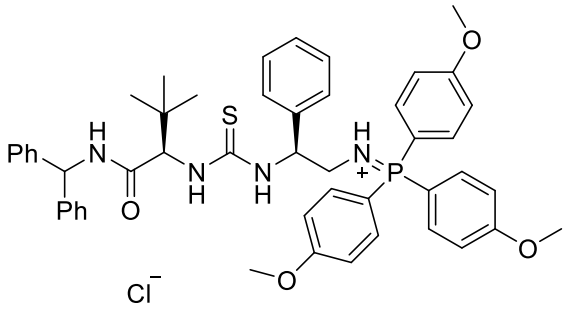
Azide **4.38** (304 mg, 0.84 mmol, 1.0 eq) was reacted with TFA (0.8 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.27 mL, 1.0 mmol, 1.2 eq) was added according to a modified General Procedure E using Et_2O as solvent (3 mL). The crude product was purified with FCC to afford the title compound **4.40** as a colourless solid in 51% yield (220 mg). **m.p.** = 77 - 80 °C; **$[\alpha]_D^{25}$** = +90.1 (c 0.*6*, $CHCl_3$); **^{1}H NMR** (MeOD-d_4, 400 MHz) δ (ppm); 8.17 (s, 2 H, ArC$\underline{H}$), 7.53 (s, 1 H, ArC$\underline{H}$), 5.02 (s, 1 H, C$\underline{H}$NH), 4.22 - 4.18 (m, 1 H, C$\underline{H_A}H_BN$), 4.14 - 4.09 (m, 1 H, $CH_A\underline{H_B}N$), 3.59 - 3.54 (m, 1 H, CHC$\underline{H_A}H_BN_3$), 3.49-3.43 (m, 2 H, C$\underline{H}CH_2N_3$ and $CHCH_A\underline{H_B}N_3$), 2.00-1.75 (m, 4 H, C$\underline{H_2}$CHN and C$\underline{H_2}CH_2N$), 1.02 (s, 9 H, CHC(C$\underline{H_3}$)$_3$); **^{13}C NMR** (MeOD-d_4, 100 MHz) δ (ppm): 181.7 ($\underline{C}$=S), 170.9 ($\underline{C}$=O), 141.7 (Ar$\underline{C}$), 131.3 (q, *J* = 33.8 Hz, Ar$\underline{C}CF_3$), 124.0 (q, *J* = 272.8 Hz, $\underline{C}F_3$), 122.0 (Ar$\underline{C}$H), 116.5 (Ar$\underline{C}$H), 62.6 (C$\underline{H}$NH), 56.8 (C$\underline{H}CH_2N_3$), 52.3 (CH$\underline{C}H_2N_3$), 48.8 (C$\underline{H_2}$N), 34.7 ($\underline{C}$(CH$_3$)$_3$), 27.4 ($\underline{C}H_2$CHN), 25.8 (C($\underline{C}$H$_3$)$_3$), 24.1 ($\underline{C}H_2CH_2N$); **^{19}F NMR** (MeOD-d_4, 376 MHz) δ (ppm): -64.5; **HRMS** (EI+): calcd. for $[M+Na]^+$

($C_{20}H_{24}ON_6F_6NaS$) 533.1529, found 533.1527; **IR** ν_{max}/cm^{-1}: 3320, 2971, 2104, 1606 (C=O), 1532, 1383, 1276, 1176, 1130, 618.

6.2.11 Synthesis of BIMP Catalyst HCl Salt

6.2.11.1 Synthesis and Characterisation of 2.118

(S)-2-(3-(*(R)*-1-(benzhydrylamino)-3,3-dimethyl-1-oxobutan-2-yl)thioureido)-2-phenyl-N-(tris(4-methoxyphenyl)-l5-phosphanylidene)ethan-1-aminium chloride



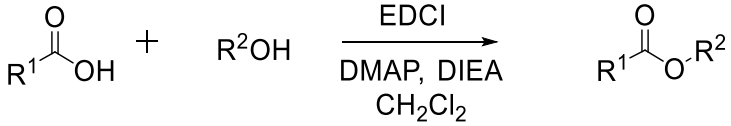
Et_2O (1 mL) was added into a vial containing azide **2.104** (50 mg, 0.1 mmol, 1.0 eq) and tri (4-methoxyphenyl) phosphine (35.2 mg, 0.1 mmol, 1.0 eq) under N_2. The reaction was stirred for 24 h and then a solution of HCl (0.1 mL, 2 M in Et_2O, 0.2 eq) was added into the mixture at 0 °C. The reaction was stirred for 2 h and then filtered, washed with Et_2O (5 mL). White solid was collected from filter cake (78 mg, 91%). **m.p.** = 120 - 124 °C; $\mathbf{[\alpha]_D^{25}}$ = -22.6 (c *0.8*, $CHCl_3$); **^{1}H NMR** (MeOD-d_4, 400 MHz) δ (ppm): 9.06 (d, *J* = 8.5 Hz, 1 H, $Ph_2CHN\underline{H}$), 7.67 - 7.60 (m, 6 H, Ar$\underline{H}$), 7.38 - 7.29 (m, 10 H, Ar$\underline{H}$), 7.24 - 7,12 (m, 11 H, Ar$\underline{H}$), 6.33 (d, *J* = 8.5 Hz, 1 H, $Ph_2C\underline{H}NH$), 5.64 (dd, *J* = 8.0, 5.5 Hz, 1 H, $C\underline{H}CH_2$), 4.84 (s, 1 H, $C\underline{H}C(CH_3)_3$), 3.95 - 3.88 (m, 1 H, $CHCH_2N\underline{H}$), 3.87 (s, 9 H, $OC\underline{H}_3$), 3.45 (ddd, *J* = 13.5, 11.0,

9.0 Hz, 1 H, CHC$\underline{H_A}H_B$), 3.25 (ddd, *J* = 13.0, 10.0, 5.5 Hz, 1 H, CHC$H_A\underline{H_B}$), 0.96 (s, 9 H, CHC($C\underline{H_3}$)$_3$); **^{13}C NMR** (MeOD-d$_4$, 100 MHz) δ (ppm): 185.6 ($\underline{C}$=S), 164.5 ($\underline{C}$=O), 142.5 (Ar$\underline{C}$), 142.5 (Ar$\underline{C}$), 141.8 (Ar$\underline{C}$), 141.8 (Ar$\underline{C}$), 141.6 (Ar$\underline{C}$), 141.4 (Ar$\underline{C}$), 141.3 (Ar$\underline{C}$), 141.1 (Ar$\underline{C}$), 140.0 (Ar$\underline{C}$), 137.1 (Ar$\underline{C}$H), 137.0 (Ar$\underline{C}$H), 130.1 (Ar$\underline{C}$H), 129.8 (Ar$\underline{C}$H), 129.6 (Ar$\underline{C}$H), 129.4 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 128.1 (Ar$\underline{C}$H), 116.9 (Ar$\underline{C}$H), 116.8 (Ar$\underline{C}$H), 113.8 (Ar$\underline{C}$H), 112.7 (Ar$\underline{C}$H), 67.2 (C(=O)$\underline{C}$H(^{t}Bu)), 58,3 ($\underline{C}$HCH$_2$), 56.5 (Ph$_2\underline{C}$HNH), 54.6 (O$\underline{C}$H$_3$), 48.2 (CH$\underline{C}$H$_2$), 35.7 (C(=O)CH$\underline{C}$(CH$_3$)$_3$), 27.6 (C(=O)CHC($\underline{C}$H$_3$)$_3$); **^{31}P NMR** (MeOD-d$_4$, 162 MHz) δ (ppm): 36.8; **^{19}F NMR** (MeOD-d$_4$, 376 MHz) δ (ppm): -62.7; **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{49}H_{54}O_4N_4PS$) requires m/z 825.3598, found m/z 825.3588; **IR** (film) ν_{max}/cm^{-1}: 3224, 2966, 1659 (C=O), 1595, 1504, 1266, 1117, 751, 700.

6.3 Sulfa-Michael Addition of Thiols to α,β-Unsaturated Ester

6.3.1 General Procedures

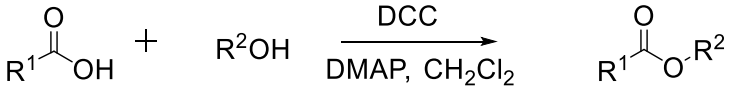
6.3.1.1 General Procedure I: Coupling of Different Ester Groups with EDCI



Carboxylic acid (1.0 eq) and alcohol (1.0 eq) were added into a solution of 4-dimethylaminopyridine (0.2 eq) and N,N-diisopropylethylamine (0.1 eq) in CH_2Cl_2 (0.2 M). The mixture was cooled to 0 °C and 1-ethyl-3-(3-dimethylaminopropyl)

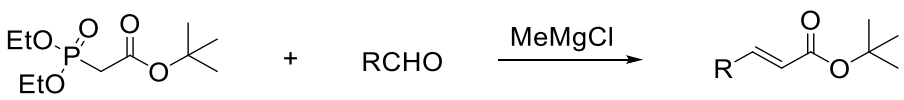
carbodiimide (1.0 eq) was added into the mixture. The reaction was allowed to warm to rt and stirred overnight. Water (5 mL/mmol) was then added into the mixture and the mixture was extracted with CH_2Cl_2 (3 × 2 mL/mmol). The combined organic layers were then washed with brine (2 mL/mmol), dried and concentrated *in vacuo*. The crude mixture was then purified by FCC to afford the pure compound.

6.3.1.2 General Procedure J: Coupling of Different Ester Groups with DCC



According to a literature procedure,[35] N,N'-Dicyclohexylcarbodiimide (DCC, 1.2 eq) was added into a solution of carboxylic acid (1.0 eq), alcohol (2.0 eq) and 4-Dimethylaminopyridine (DMAP, 0.2 eq) in CH_2Cl_2 (0.2 M) at 0 °C. The reaction was allowed to warm to rt and stirred overnight. The solid was filtered. The filtrate was washed with water (2 mL/mmol) and brine (2 mL/mmol). The organic layer was dried and concentrated *in vacuo*. The crude mixture was then purified by FCC to afford the pure compound.

6.3.1.3 General Procedure K for the Synthesis of α, β-Unsaturated Esters



MeMgCl (.0 eq) was added dropwise to a stirred solution of the requisite

phosphonate (1.0 eq) in THF (0.5 M) at rt and stirred for 15 min. Aldehyde (1.1 eq) dissolved in THF (1 M) was added via cannula and the reaction mixture heated at reflux for 18 h. The reaction was quenched with sat aq NH_4Cl (1 mL/mmol) and extracted with Et_2O (3 × 1 mL/mmol). The combined organic layers were then washed with brine (2 mL/mmol), dried and concentrated *in vacuo*. The crude mixture was then purified by FCC to afford the pure compound.

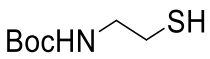
6.3.1.4 General Procedure L for the Organocatalytic Michael Addition of Thiols to α,*β*-Unsaturated Ester[xix]

To a solution of the *β*-substituted, α,*β*-unsaturated ester (1.0 eq) and BIMP catalyst (0.1 eq) in solvent (0.5 M) under a N_2 atmosphere was added the desired thiol (3.0 eq). The reaction mixture was stirred at certain temperature and monitored by TLC and quenched with 1.0 M AcOH (0.1 mL/mmol). The volatiles were removed under a stream of N_2 and the reaction mixture was purified by FCC to afford the product.

6.3.2 Synthesis of Substrates

6.3.2.1 Synthesis and Characterisation of 2.121

tert-butyl (2-mercaptoethyl)carbamate

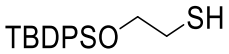


[xix] The racemic compounds were prepared using 0.2 mmol ester, 0.6 mmol thiol and 10 mol% BEMP in 0.5 M Et_2O.

According to a literature procedure[19], Boc anhydride (4.36 g, 20 mmol, 1.0 eq) was added into a solution of 2-aminoethane-1-thiol (1.54 g, 20 mmol, 1.0 eq) and Et_3N (5.56 mL, 40 mmol, 2.0 eq) in CH_2Cl_2 (200 mL) at 0 °C. The mixture was stirred overnight and then water was added in. The mixture was extracted with CH_2Cl_2 (50 mL × 3) and the organic layers combined, dried over $MgSO_4$ concentrated *in vacuo*. The crude was purified by FCC to afford the title compound **2.121** as a colourless oil in 84% yield (2.97 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 5.00 (br. s, 1 H, NHBoc), 3.31 - 3.28 (q, *J* = 6.0 Hz, 2 H, CH_2NHBoc), 2.67 - 2.62 (m, 2 H, CH_2SH), 1.44 (s, 9 H, OC(CH_3)$_3$). 1.36 (t, *J* = 8.5 Hz, 1 H, SH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 155.8 (C=O), 79.5 (OC(CH_3)$_3$), 43.6 (CH_2NHBoc), 28.4 (OC(CH_3)$_3$), 25.1 (CH_2SH); Data is consistent with that reported in literature.[19]

6.3.2.2 Synthesis and Characterisation of 2.122

2-((*tert*-butyldiphenylsilyl)oxy)ethane-1-thiol

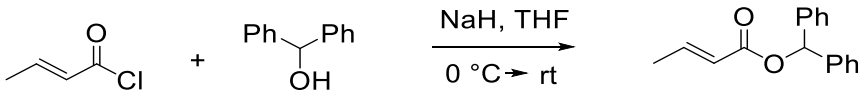


According to a literature procedure[20], *tert*-butyldiphenylsilyl chloride (5.15 mL, 20 mmol, 1.0 eq) was added into a solution of 2-mercaptoethan-1-ol (1.4 mL, 20 mmol, 1.0 eq) and imidazole (1.36 g, 20 mmol, 2.0 eq) in DMF (10 mL) at 0 °C. The mixture was stirred overnight and then water (20 mL) was added in. The mixture was extracted with CH_2Cl_2 (50 mL × 3) and the organic layers combined, dried over $MgSO_4$ concentrated *in vacuo*. The crude was purified by FCC to afford the title compound **2.122** as a colourless oil in 78% yield (4.93 g). **^{1}H NMR** ($CDCl_3$,

400 MHz) δ (ppm): 7.74 (d, *J* = 6.0 Hz, 4 H, ArH), 7.48 - 7.42 (m, 6 H, ArH), 3.83 (t, *J* = 6.5 Hz, 2 H, CH_2CH_2SH), 2.74 - 2.68 (m, 2 H, CH_2SH), 1.63 (t, *J* = 8.0 Hz, 1 H, SH), 1.13 (s, 9 H, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 135.5 (ArCH), 133.4 (ArC), 129.7 (ArCH), 127.7 (ArCH), 65.7 (CH_2CH_2SH), 27.1 (CH_2SH), 26.8 ($C(CH_3)_3$), 19.3 ($SiC(CH_3)_3$); Data is consistent with that reported in literature.[20]

6.3.2.3 Synthesis and Characterisation of 2.13g

Diphenylmethyl (2*E*)-but-2-enoate

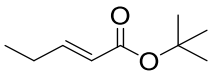


Sodium hydride (60% dispersion in mineral oil, 140 mg, 3.5 mmol, 1.0 eq) was added into a solution of diphenylmethanol (709 mg, 3.85 mmol, 1.1 eq) in THF (5 mL) at 0 °C. After the gas generation stopped, the mixture was added into crotonoyl chloride (0.4 mL, 4.2 mmol, 1.2 eq) in THF (5 mL) dropwise at 0°C. The reaction was allowed to warm to rt and stirred overnight. The mixture was then concentrated under a N_2 stream and the resulting mixture was purified by FCC (9:1 PE:CH_2Cl_2) to give **2.13g** as a colourless solid in 45% yield (400 mg). **m.p.** = 34 - 36 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 7.39 - 7.27 (m, 10 H, ArH), 7.08 (dq, *J* = 15.5, 7.0 Hz, 1 H, $CHCH_3$), 6.95 (s, 1 H, $OCHPh_2$), 5.98 (dq, *J* = 15.5, 1.5 Hz, 1 H, CHC=O), 1.91 (dd, *J* = 7.0, 1.5 Hz, 3 H, $CHCH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz)

δ (ppm): 165.5 (C=O), 145.5 ($\underline{C}HCH_3$), 140.4 (Ar$\underline{C}$), 128.5 (Ar$\underline{C}$H), 127.8 (Ar$\underline{C}$H), 127.1 (Ar$\underline{C}$H), 122.6 ($\underline{C}$HC=O), 76.5 (O$\underline{C}$HPh$_2$), 18.1 (CH$\underline{C}H_3$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{16}NaO_2$) requires *m/z* 275.1043, found *m/z* 275.1042; **IR** (film) ν_{max}/cm^{-1}: 1715 (C=O), 1645, 1170, 746, 695, 644.

6.3.2.4 Synthesis and Characterisation of 2.107a

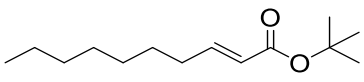
tert-butyl *(E)*-pent-2-enoate



According to General Procedure K, reaction of phosphonate (1.15 mL, 5.0 mmol) with propionaldehyde (2.40 mL, 5.5 mmol) gave title compound **2.107a** as a colourless oil in 92% yield (720 mg) after column; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 6.95 - 6.86 (dt, *J* = 15.5, 6.5 Hz, 1 H, C$\underline{H}CH_2$), 5.74 - 5.69 (dt, *J* = 15.5, 2.0 Hz, 1 H, C$\underline{H}$C=O), 2.22 – 2.14 (m, 2 H, C$\underline{H}_2CH_3$), 1.47 (s, 9 H, C(C$\underline{H}_3$)$_3$), 1.04 (t, *J* = 7.5 Hz, 3 H, $CH_2C\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 166.4 ($\underline{C}$=O), 149.5 ($\underline{C}$H=CHC=O), 122.2 ($\underline{C}$HC=O), 80.1 ($\underline{C}$(CH$_3$)$_3$), 28.3 (C(C$\underline{H}_3$)$_3$), 25.2 (C$\underline{H}_2$CH$_3$), 12.3 ($CH_2\underline{C}H_3$); All data consistent with those reported in literature.[21]

6.3.2.5 Synthesis and Characterisation of 2.107b

tert-butyl *(E)*-dec-2-enoate

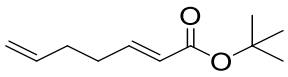


According to General Procedure K, reaction of phosphonate (1.15 mL, 5.0 mmol)

with octanal (0.86 mL, 5.5 mmol) gave the title compound **2.107b** as a colourless oil in 33% yield (370 mg) after column; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 6.86 - 6.79 (m, 1 H, C<u>H</u>=CHC=O), 5.69 (d, *J* = 15.5 Hz, 1 H, C<u>H</u>C=O), 2.13 (q, *J* = 7.0 Hz, 2 H, C<u>H</u>$_2$CH=CH), 1.47 - 1.40 (m, 11 H, C<u>H</u>$_2$CH$_2$CH=CH and C(C<u>H</u>$_3$)$_3$), 1.28 - 1.20 (m, 8 H, CH$_3$(C<u>H</u>$_2$)$_4$CH$_2$), 0.84 (t, *J* = 6.5 Hz, 3 H, C<u>H</u>$_3$CH$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 166.3 (<u>C</u>=O), 148.3 (<u>C</u>H=CHC=O), 123.0 (<u>C</u>HC=O), 80.0 (<u>C</u>(CH$_3$)$_3$), 32.1 (C<u>H</u>$_2$CH=CH), 31.8 (C<u>H</u>$_2$), 29.2 (C<u>H</u>$_2$), 29.1 (C<u>H</u>$_2$), 28.3 (C<u>H</u>$_2$), 28.2 (C(C<u>H</u>$_3$)$_3$), 22.7 (C<u>H</u>$_2$), 14.2 (CH$_2$<u>C</u>H$_3$); All data consistent with those reported in literature.[22]

6.3.2.6 Synthesis and Characterisation of 2.107c

<u>*tert*-butyl *(E)*-hepta-2,6-dienoate</u>

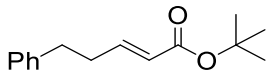


According to General Procedure K, reaction of phosphonate (1.27 mL, 5.5 mmol) with pent-4-enal (0.59 mL, 6 mmol) gave a colourless oil **2.107c** in 44% yield (437 mg) after column; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 6.87 - 6.80 (dt, *J* = 15.5, 6.5 Hz, 1 H, C<u>H</u>=CHCO), 5.81 - 5.71 (m, 2 H, CH$_2$=C<u>H</u> and C<u>H</u>C=O), 4.97 (dd, *J* = 17.0, 1.5 Hz, 1 H, C<u>H$_A$H$_B$</u>=CH), 4.97 (dd, *J* = 10.0, 1.0 Hz, 1 H, CH$_A$<u>H$_B$</u>=CH), 2.28 - 2.22 (m, 2 H, CH$_2$=CHCH$_2$C<u>H</u>$_2$), 2.20-2.17 (m, 2 H, CH$_2$=CHC<u>H</u>$_2$), 1.45 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 166.1 (<u>C</u>=O), 147.1(<u>C</u>H=CHC=O), 137.3 (<u>C</u>H=CH$_2$), 123.5 (<u>C</u>HC=O), 115.5 (CH=<u>C</u>H$_2$), 80.1

(C(CH$_3$)$_3$), 32.2 (CH$_2$=CHCH$_2$), 31.4 (CH$_2$=CHCH$_2$CH$_2$), 28.2 (C(CH$_3$)$_3$); Data is consistent with that reported in literature.[23]

6.3.2.7 Synthesis and Characterisation of 2.107d

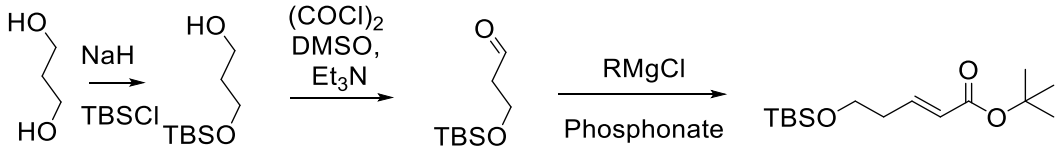
tert-butyl (*E*)-5-phenylpent-2-enoate



According to General Procedure K, reaction of phosphonate (1.73 mL, 7.5 mmol) with 3-phenylpropanal (1.11 g, 8.25 mmol) gave the title compound **2.107d** as a colourless oil in 22% yield (390 mg) after column. **^{1}H NMR** (CDCl$_3$, 400 MHz) δ (ppm): 7.23 - 7.19 (m, 2 H, ArH), 7.13 - 7.09 (m, 3 H, ArH), 6.83 (dt, *J* = 15.5, 7.0 Hz, 1 H, CHCHC=O), 5.70 (dt, *J* = 15.5, 1.5 Hz, 1 H, CHC=O), 2.70 - 2.66 (m, 2 H, PhCH$_2$CH$_2$), 2.43 - 2.38 (m, 2 H, PhCH$_2$CH$_2$), 1.40 (s, 9 H, C(CH$_3$)$_3$); **^{13}C NMR** (CDCl$_3$, 100 MHz) δ (ppm): : 166.1 (C=O), 146.9 (CHCHC=O), 141.1 (ArC), 128.6 (ArCH), 126.2 (ArCH), 123.6 (ArCH), 120.3 (CHC=O), 80.2 (C(CH$_3$)$_3$), 34.5 (PhCH$_2$CH$_2$), 33.9 (PhCH$_2$CH$_2$), 28.2 (C(CH$_3$)$_3$); Data consistent with that reported in literature.[24]

6.3.2.8 Synthesis and Characterisation of 2.107e

tert-butyl (*E*)-5-((tert-butyldimethylsilyl)oxy)pent-2-enoate



Sodium hydride (1.05 g, 26.3 mmol, 1.0 eq) was suspended in THF (50 mL) after being washed with hexane. Propane-1,3-diol (2.0 g, 26.3 mmol, 1.0 eq) was added to this mixture at room temperature and stirred for 45 min at which time a large amount of an opaque white precipitate had formed. *tert*-Butyldimethylsilyl chloride (3.96 g, 26.3 mmol, 1.0 eq) was then added, and vigorous stirring was continued for 45 min. The mixture was poured into ether (100 mL), washed with 10% aqueous K_2CO_3 (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude was used without further purification.

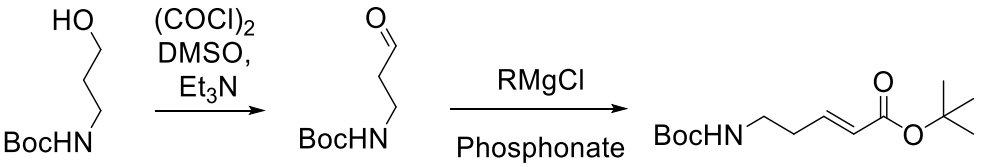
According to a literature procedure[25], oxalyl chloride (2.07 mL, 24.42 mmol, 1.16 eq) in CH_2Cl_2 (50 mL) was cooled to –60 ˚C and DMSO (3.58 mL, 50.5 mmol, 2.4 eq) in CH_2Cl_2 (5mL) was added and the reaction mixture stirred. After 5 min, 3-((tert-butyldimethylsilyl)oxy)propan-1-ol (4 g, 21.05 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) was added dropwise. After 2 h, water (50 mL) was added and the phases separated. The aqueous phase was back-extracted with further CH_2Cl_2 (50 mL) and the combined organic layers were washed with brine (50 mL), water (50 mL) and further brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the product as a colourless oil (3.65 g), which was used in the next step without further purification.

According to General Procedure K, reaction of phosphonate (1.04 mL, 4.5 mmol) with 3-((tert-butyldimethylsilyl)oxy)propanal (940 mg, 5.0 mmol) gave the title compound **2.107e** as a colourless oil in 51% yield (660 mg) after column. **^{1}H NMR**

($CDCl_3$, 400 MHz) δ (ppm): 6.83 (dt, *J* = 15.5, 7.0 Hz, 1 H, C<u>H</u>=CHC=O), 5.76 (d, *J* = 15.5 Hz, 1 H, C<u>H</u>C=O), 3.69 (t, *J* = 6.5 Hz, 2 H, C<u>H</u>$_2$OTBS), 2.36 (qd, *J* = 6.5, 1.5 Hz, 2 H, C<u>H</u>$_2$CH$_2$OTBS), 1.46 (s, 9 H, OC(C<u>H</u>$_3$)$_3$), 0.87 (s, 9 H, SiC(C<u>H</u>$_3$)$_3$), 0 (s, 6 H, Si(C<u>H</u>$_3$)$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 165.8 (<u>C</u>=O), 144.4 (<u>C</u>H=CHCO), 124.7 (<u>C</u>HC=O), 80.0 (O<u>C</u>(CH$_3$)$_3$), 61.6 (<u>C</u>H$_2$OTBS), 35.5 (<u>C</u>H$_2$CH$_2$OTBS), 28.1 (OC(<u>C</u>H$_3$)$_3$), 25.8 (SiC(<u>C</u>H$_3$)$_3$), 18.3 (Si<u>C</u>(CH$_3$)$_3$), -5.4 (Si(<u>C</u>H$_3$)$_2$) ; Data consistent with that reported in literature.[26]

6.3.2.9 Synthesis and Characterisation of 2.107f

<u>*tert*-butyl (E)-5-((tert-butoxycarbonyl)amino)pent-2-enoate</u>



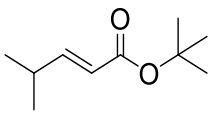
According to a literature procedure[25], oxalyl chloride (1.86 mL, 22.0 mmol, 1.25 eq) in CH_2Cl_2 (50mL) was cooled to –60 ˚C and DMSO (3.12 mL, 44.0 mmol, 2.5 eq) in CH_2Cl_2 (10 mL) was added and the reaction mixture stirred. After 5 min, *tert*-butyl (3-hydroxypropyl) carbamate (3.08 g, 17.6 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) was added dropwise. After 2h, water (50 mL) was added and the phases separated. The aqueous phase was back-extracted with CH_2Cl_2 (50 mL) and the combined organic layers were washed with brine (50 mL), water (50 mL) and brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the product as a colourless oil (2.9 g), which was used in the next step without further

purification.

According to General Procedure K, reaction of phosphonate (0.87 mL, 3.75 mmol) with *tert*-butyl (3-oxopropyl) carbamate (712 mg, 4.1 mmol) gave the title compound **2.107f** as a colourless oil in 49% yield (500 mg) after column; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 6.82 - 6.75 (m, 1 H, C<u>H</u>=CHC=O), 5.80 (d, *J* = 15.5 Hz, 1 H, C<u>H</u>C=O), 4.60 (br. s, 1 H, N<u>H</u>), 3.25 (m, 2 H, C<u>H</u>$_2$NH), 2.37 (q, *J* = 6.5 Hz, 2 H, C<u>H</u>$_2$CH$_2$NH), 1.46 (s, 9 H, one of CHCOOC(C<u>H</u>$_3$)$_3$ and NHCOOC(C<u>H</u>$_3$)$_3$), 1.44 (s, 9 H, one of CHCOOC(C<u>H</u>$_3$)$_3$ and NHCOOC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 165.5 (CH<u>C</u>=O), 155.7 (NH<u>C</u>=O) 143.9 (<u>C</u>H=CHC=O), 125.0 (C<u>H</u>C=O), 80.2 (one of CHCOO<u>C</u>(CH$_3$)$_3$ and NHCOO<u>C</u>(CH$_3$)$_3$), 79.3 (one of CHCOO<u>C</u>(CH$_3$)$_3$ and NHCOO<u>C</u>(CH$_3$)$_3$), 39.0 (<u>C</u>H$_2$NH), 32.5 (<u>C</u>H$_2$CH$_2$NH), 28.3 (one of CHCOOC(<u>C</u>H$_3$)$_3$ and NHCOOC(<u>C</u>H$_3$)$_3$), 25.8 (one of CHCOOC(<u>C</u>H$_3$)$_3$ and NHCOOC(<u>C</u>H$_3$)$_3$); Data consistent with reported in literature.[27]

6.3.2.10 Synthesis and Characterisation of 2.107g

<u>*tert*-butyl (*E*)-4-methylpent-2-enoate</u>

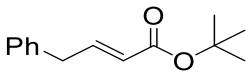


According to General Procedure K, reaction of phosphonate (1.15 mL, 5.0 mmol) with isobutyraldehyde (0.5 mL, 5.5 mmol) gave the title compound **2.107g** as a colourless oil in 80% yield (680 mg) after column; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ

ppm: 6.82 (dd, *J* = 15.5, 6.5 Hz, 1 H, C<u>H</u>CHC=O), 5.67 (dd, *J* = 15.5, 1.5 Hz, 1 H, C<u>H</u>C=O), 2.41 (dqd, *J* = 13.5, 7.0, 1.5 Hz, 1 H, C<u>H</u>(CH_3)$_2$), 1.47 (s, 9 H, C(C<u>H</u>$_3$)$_3$), 1.02 (t, *J* = 7.0 Hz, 6 H, CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 166.5 (<u>C</u>=O), 154.2 (<u>C</u>H=CHC=O), 122.3 (<u>C</u>HC=O), 80.0 (<u>C</u>(CH_3)$_3$), 30.8 (<u>C</u>H(CH_3)$_2$), 28.2 (C(C<u>H</u>$_3$)$_3$), 21.3 (CH(C<u>H</u>$_3$)$_2$); Data consistent with that reported in literature.[28]

6.3.2.11 Synthesis and Characterisation of 2.107h

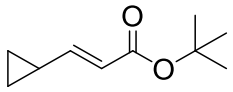
<u>*tert*-butyl (*E*)-4-phenylbut-2-enoate</u>



According to General Procedure K, reaction of phosphonate (1.15 mL, 5 mmol) with 2-phenylacetaldehyde (0.64 mL, 5.5 mmol) gave the title compound **2.107h** as a yellow oil in 68% yield (740 mg) after column. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.37 - 7.29 (m, 2 H, Ar<u>H</u>), 7.29 - 7.25 (m, 1 H, Ar<u>H</u>), 7.21 (d, *J* = 7.5 Hz, 2 H, Ar<u>H</u>), 7.03 (dt, *J* = 15.5, 7.0 Hz, 1 H, C<u>H</u>CHC=O), 5.76 (d, *J* = 15.5 Hz, 1 H, C<u>H</u>C=O), 3.52 (d, *J* = 7.0 Hz, 2 H, PhC<u>H</u>$_2$), 1.50 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): : 165.8 (<u>C</u>=O), 146.0 (<u>C</u>HCHC=O), 137.9 (Ar<u>C</u>), 128.8 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 124.0 (<u>C</u>HC=O), 80.2 (<u>C</u>(CH_3)$_3$), 38.3 (Ph<u>C</u>H$_2$), 28.2 (C(<u>C</u>H$_3$)$_3$); Data consistent with that reported in literature.[29]

6.3.2.12 Synthesis and Characterisation of 2.107i

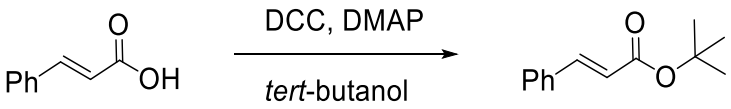
<u>*tert*-butyl (*E*)-3-cyclopropylacrylate</u>



According to General Procedure K, reaction of phosphonate (1.15 mL, 5 mmol) with cyclopropanecarbaldehyde (0.41 mL, 5.5 mmol) gave the title compound **2.107i** as a colourless solid in 30% yield (250 mg) after column. **m.p.** = 40 - 41 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 6.25 (dd, *J* = 15.5, 10.0 Hz, 1 H, C<u>H</u>=CHC=O), 5.74 (d, *J* = 16.0 Hz, 1 H, C<u>H</u>C=O), 1.50-1.41 (m, 1 H, C<u>H</u>CH=CH), 1.40 (s, 9 H, C(C<u>H</u>$_3$)$_3$), 0.86 - 0.82 (m, 2 H, C<u>H</u>$_A$H$_B$C<u>H</u>$_A$H$_B$), 0.56-0.52 (m, 2 H, CH$_A$<u>H</u>$_B$CH$_A$<u>H</u>$_B$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 166.2 (<u>C</u>=O), 152.7 (<u>C</u>HCHC=O), 119.4 (<u>C</u>HC=O), 79.8 (<u>C</u>(CH$_3$)$_3$), 28.2 (C(<u>C</u>H$_3$)$_3$), 14.1 (one of <u>C</u>H$_2$CH$_2$), 8.4 (one of <u>C</u>H$_2$CH$_2$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{16}O_2Na$) requires *m/z* 191.1043, found *m/z* 191.1044; **IR** (film) ν_{max}/cm^{-1}: 2978, 1707 (C=O), 1646, 1142, 713.

6.3.2.13 Synthesis and Characterisation of 2.107j

<u>*tert*-butyl cinnamate</u>

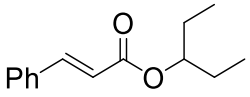


According to modified General Procedure J, to a mixture of cinnamic acid (5 g, 33.8 mmol, 1.0 eq), 2-methylpropan-2-ol (5 g, 67.5 mmol, 2.0 eq) and DMAP (4.95 g, 40.5 mmol, 1.2 eq.) in anhydrous CH_2Cl_2 (30 mL) was added DCC (10.45 g, 50.6 mmol, 1.5 eq). The reaction was refluxed for 16 h. The crude mixture was

purified by FCC to afford the title compound **2.107j** as a colourless oil in 88% yield (6.1 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.66 (d, *J* = 16.0 Hz, 1 H, C<u>H</u>CHC=O), 7.57 - 7.52 (m, 2 H, Ar<u>H</u>), 7.41 - 7.38 (m, 3 H, Ar<u>H</u>), 6.43 (d, *J* = 16.0, 1 H, C<u>H</u>C=O), 1.60 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 166.4 (<u>C</u>=O), 143.7 (<u>C</u>HCHC=O), 134.8 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 120.3 (<u>C</u>HC=O), 80.5 (<u>C</u>(CH$_3$)$_3$), 28.2 (C(<u>C</u>H$_3$)$_3$); Data is consistent with that reported in literature.[30]

6.3.2.14 Synthesis and Characterisation of 2.107k

<u>pentan-3-yl cinnamate</u>

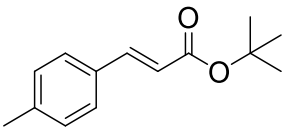


According to General Procedure I, Cinnamic acid (1,48 g, 10 mmol, 1.0 eq) and pentan-3-ol (880 mg, 10 mmol, 1.0 eq) were added into a solution of 4-dimethylaminopyridine (244 mg, 2.0 mmol, 0.2 eq) and N,N-diisopropylethylamine (0.17 mL, 1.0 mmol, 0.1 eq) in CH_2Cl_2 (50 mL). 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.91 g, 10 mmol, 1.0 eq) was then added into the mixture. The crude mixture was then purified FCC (99:1 PE: Et_2O) to afford the title compound **2.107k** as a yellow oil in 94% yield (2.04 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 7.71 (d, *J* = 16.0 Hz, 1 H, C<u>H</u>=CHC=O), 7.57 - 7.54 (m, 2 H, Ar<u>H</u>), 7.41 - 7.39 (m, 3 H, Ar<u>H</u>), 6.48 (d, *J* = 16.0 Hz, 1 H, CH=C<u>H</u>C=O), 4.93 (quin, *J* = 6.0 Hz, 1 H, C<u>H</u>(CH$_2$CH$_3$)$_2$), 1.71 - 1.63 (m, 4 H, CH(C<u>H</u>$_2$CH$_3$)$_2$), 0.95 (t, *J* = 7.0 Hz, 6 H, CH(CH$_2$C<u>H</u>$_3$)$_2$); **^{13}C**

NMR ($CDCl_3$, 100 MHz) δ (ppm): 166.9 (C=O), 144.2 (CH=CHC=O), 134.5 (ArC), 130.1 (ArCH), 128.8 (ArCH), 128.1 (ArCH), 118.6 (CHC=O), 76.7 ($OCH(CH_2CH_3)_2$), 26.5 ($CH(CH_2CH_3)_2$), 9.6 ($CH(CH_2CH_3)_2$); All data consistent with those reported in literature.[31]

6.3.2.15 Synthesis and Characterisation of 2.107l

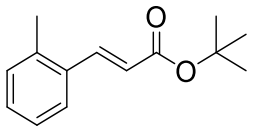
tert-butyl (E)-3-(p-tolyl)acrylate



According to modified General Procedure K, reaction of phosphonate (0.8 mL, 3.5 mmol) with 4-methylbenzaldehyde (416 mg, 3.5 mmol) gave the title compound **2.107l** as a colourless oil in 29% yield (223 mg) after column. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.48 (d, *J* = 16.0 Hz, 1 H, CH=CHC=O), 7.32 (d, *J* = 8.0 Hz, 2 H, ArH), 7.09 (d, *J* = 8.0 Hz, 2 H, ArH), 6.25 (d, *J* = 16.0 Hz, 1 H, CHC=O), 2.28 (s, 3 H, CH_3), 1.45 (s, 9 H, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 166.6 (C=O), 143.6 (CHCHC=O), 140.3 (ArC), 131.9 (ArC), 129.6 (ArCH), 128.0 (ArCH), 119.1 (CHC=O), 80.4 ($C(CH_3)_3$), 28.2 ($C(CH_3)_3$), 21.4 (CH_3); Data consistent with that reported in literature.[32]

6.3.2.16 Synthesis and Characterisation of 2.107m

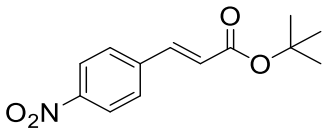
tert-butyl (*E*)-3-(o-tolyl)acrylate



According to modified General Procedure K, reaction of phosphonate (2.05 mL, 9.0 mmol) with 2-methylbenzaldehyde (1.1 mL, 9.5 mmol) gave the title compound **2.107m** as a colourless solid in 47% yield (915 mg) after column. **m.p.** = 40 - 42 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 7.92 (d, *J* = 16.0 Hz, 1 H, C<u>H</u>=CHC=O), 7.58 - 7.56 (m, 1 H, Ar<u>H</u>), 7.28 - 7.20 (m, 3 H, Ar<u>H</u>), 6.32 (d, *J* = 16.0 Hz, 1 H, C<u>H</u>C=O), 2.46 (s, 3 H, C<u>H</u>$_3$), 1.57 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 166.5 (<u>C</u>=O), 141.2 (<u>C</u>HCHC=O), 137.5 (Ar<u>C</u>), 133.6 (Ar<u>C</u>), 130.7 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 126.3 (Ar<u>C</u>H), 121.1 (<u>C</u>HC=O), 80.5 (<u>C</u>(CH$_3$)$_3$), 28.2 (C(<u>C</u>H$_3$)$_3$), 19.8 (<u>C</u>H$_3$); Data consistent with that reported in literature.[32]

6.3.2.17 Synthesis and Characterisation of 2.107n

<u>*tert*-butyl (*E*)-3-(4-nitrophenyl)acrylate</u>



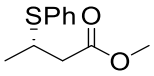
A mixture of 1-iodo-4-nitrobenzene 1 (1.25 g, 5 mmol, 1.0 eq), tert-butyl acrylate (1.1 mL, 7.5 mmol, 1.5 eq), $Pd(OAc)_2$ (11.5 mg, 0.05 mmol, 0.01 eq), DABCO (11.2 mg, 0.1 mmol, 0.02 eq), K_2CO_3 (138 mg, 5.0 mmol, 1.0 eq), and DMF (30 mL) was added to a sealed tube under N_2. The mixture was stirred at 120 °C for 4 h until complete consumption of the starting material (as judged by TLC). After

the mixture was filtered and evaporated, the residue was purified by FCC to afford the title compound **2.107n** as a yellow solid in 39% yield (480 mg). **m.p.** = 138 - 139 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 8.24 (d, *J* = 8.5 Hz, 2 H, ArH), 7.66 (d, *J* = 8.5 Hz, 2 H, ArH), 7.61 (d, *J* = 16.0 Hz, 1 H, CHCHC=O), 6.50 (d, *J* = 16.0 Hz, 1 H, CHC=O), 1.55 (s, 9 H, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 165.3 (C=O), 148.0 (ArC), 140.9 (ArC), 140.6 (ArCH), 128.5 (ArCH), 124.6 (CHC=O), 124.1 (CHCHC=O), 81.4 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$); Data consistent with that reported in literature.[33]

6.3.3 Michael Addition of Thiols to α,β-Unsaturated Ester

6.3.3.1 Synthesis and Characterisation of 2.16d

methyl (*S*)-3-(phenylthio)butanoate

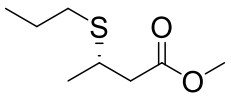


According to General Procedure L, to a solution of methyl crotonate (21.0 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL toluene was added thiophenol (64 µL, 0.6 mmol, 3.0 eq) at rt, and then the reaction mixture was stirred at rt. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.16d** as a colourless oil in 90% yield (37.8 mg) and 41% ee [determined by HPLC, chiralpak OD, hexane/isopropanol 99:1, λ 220nm, 1.0 mL/min, t (minor) = 6.06 min, t (major) = 8.51 min]. **$[\alpha]_D^{23}$** = +19.4 (*c 0.6*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.47-7.28 (m, 5 H, ArH), 3.68 (s, 3 H, OCH_3), 3.63 (m, 1 H, $CHCH_2$), 2.65

(dd, *J* = 15.5, 6.0 Hz, 1 H, CHC$\underline{H_A}H_B$), 2.44 (dd, *J* = 15.5, 8.5 Hz, 1 H, CHC$H_A\underline{H_B}$), 1.33 (d, *J* = 7.0 Hz, 3 H, CHC$\underline{H_3}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.8 ($\underline{C}$=O), 133.7 (Ar$\underline{C}$), 132.9 (Ar$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 127.5 (Ar$\underline{C}$H), 51.7 (O$\underline{C}H_3$), 41.6 (CHC$\underline{H_2}$), 39.4 ($\underline{C}$HCH$_3$), 20.9 (CH$\underline{C}H_3$); Data consistent with that given in the literature.[34]

6.3.3.2 Synthesis and Characterisation of 2.77a

methyl (*S*)-3-(propylthio)butanoate

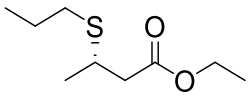


According to General Procedure L, to a solution of methyl crotonate (21 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanolthiol (54 µL, 0.6 mmol, 3.0 eq), and then stirred at rt. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.77a** as a colourless oil in >99% yield (35.2 mg) and 59% ee [determined by HPLC, chiralpak OD-H, hexane/isopropanol 99.5:0.5, λ 220nm, 1.0mL/min, t (minor) = 12.88 min, t (major) = 16.63 min]. **$[\alpha]_D^{23}$** = +4.8 (*c 1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.70 (s, 3 H, OC$\underline{H_3}$), 3.24-3.16 (m, 1 H, C$\underline{H}CH_3$), 2.64 (dd, *J* = 15.5, 6.5 Hz, 1 H, CHC$\underline{H_A}H_B$), 2.53 (t, *J* = 7.5 Hz, 2 H, C$\underline{H_2}$S), 2.46 (dd, *J* = 15.5, 8.5 Hz, 1 H, CHC$H_A\underline{H_B}$), 1.62 (sxt, *J* = 7.5 Hz, 2 H, C$\underline{H_2}CH_2$S), 1.33 (d, *J* = 6.5 Hz, 3 H, CHC$\underline{H_3}$), 0.98 (t, *J* = 7.0 Hz, 3 H, C$\underline{H_3}CH_2CH_2$S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 172.0 ($\underline{C}$=O), 51.7 (O$\underline{C}H_3$), 42.2 (CH$\underline{C}H_2$), 36.1 ($\underline{C}$HCH$_3$), 32.7 (CH$_3$CH$_2\underline{C}H_2$S), 23.0

($CH_3\underline{C}H_2CH_2S$), 21.5 ($\underline{C}H_3CH$), 13.6 ($\underline{C}H_3CH_2CH_2S$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_8H_{16}NaO_2S$) requires *m/z* 199.0763, found *m/z* 199.0757; **IR** (film) ν_{max}/cm^{-1}: 2963, 1738 (C=O), 1437, 1222, 1161, 913, 734.

6.3.3.3 Synthesis and Characterisation of 2.77b

ethyl (*S*)-3-(propylthio)butanoate

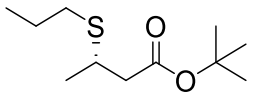


According to General Procedure L, to a solution of ethyl crotonate (24.8 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanolthiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.77b** as a colourless oil in >99% yield (38.0 mg) and 66% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ 220 nm, 1.0 mL/min, t (minor) = 11.27 min, t (major) = 13.45 min]. $\mathbf{[\alpha]_D^{23}}$ = +4.0 (*c 0.6*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 4.15 (q, *J* = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.24 (m, 1 H, $C\underline{H}CH_3$), 2.61 (dd, *J* = 15.5, 6.0 Hz, 1 H, $CHC\underline{H}_AH_B$), 2.55-2.48 (m, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.42 (dd, *J* = 15.5, 8.5 Hz, 1 H, $CHCH_A\underline{H}_B$), 1.60 (sxt, *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 1.31 (d, *J* = 7.0 Hz, 3 H, $CHC\underline{H}_3$), 1.25 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.98 (t, *J* = 7.0 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$); **^{13}C NMR** ($CDCl_3$, 400 MHz) δ (ppm): 171.6 ($\underline{C}$=O), 60.5 ($O\underline{C}H_2CH_3$), 42.4 ($CH\underline{C}H_2$), 36.1 ($\underline{C}HCH_3$), 32.7 ($CH_3CH_2\underline{C}H_2S$), 23.0 ($CH_3\underline{C}H_2CH_2S$), 21.4 ($\underline{C}H_3CH$), 14.2 ($OCH_2\underline{C}H_3$), 13.5 ($\underline{C}H_3CH_2CH_2S$); **HRMS**

(EI+) mass calculated for $[M+Na]^+$ ($C_9H_{18}NaO_2S$) requires *m/z* 213.0920, found *m/z* 213.0922; **IR** (film) ν_{max}/cm^{-1}: 2968, 1729 (C=O), 1216, 1169, 754, 667.

6.3.3.4 Synthesis and Characterisation of 2.77d

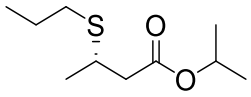
tert-Butyl (*S*)-3-(propylsulfanyl)butanoate



According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanolthiol (54.4 µL, 0.6 mmol, 3.0 eq) at –15 °C, and then stirred at –15 °C. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.77d** as a colourless oil in 94% yield (41.0 mg) and 94% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ 220 nm, 1.0 mL/min, t (major) = 9.45 min, t (minor) = 11.34 min]. $\mathbf{[\alpha]_D^{23}}$ = +5.5 (c *1.9*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.16 (dquin, *J* = 8.5, 6.5 Hz, 1 H, C$\underline{H}$$CH_3$), 2.57-2.51 (m, 3 H, CHC$\underline{H_A}H_B$ and $CH_3CH_2C\underline{H_2}S$), 2.34 (dd, *J* = 15.0, 8.5 Hz, 1 H, $CHCH_A\underline{H_B}$), 1.66-1.57 (m, 2 H, $CH_3C\underline{H_2}CH_2S$), 1.47 (s, 9 H, $OC(C\underline{H_3})_3$), 1.32 (d, *J* = 6.5 Hz, 3 H, $CHC\underline{H_3}$), 0.98 (t, *J* = 7.5 Hz, 3 H, $C\underline{H_3}CH_2CH_2S$); **^{13}C NMR** ($CDCl_3$, 400 MHz) δ (ppm): 171.0 ($\underline{C}$=O), 80.7 ($O\underline{C}(CH_3)_3$), 42.6 ($CH\underline{C}H_2$), 36.3 ($\underline{C}HCH_2$), 32.6 ($\underline{C}H_2S$), 28.0 ($C(\underline{C}H_3)_3$), 23.0 ($\underline{C}H_2CH_2S$), 21.0 ($CH\underline{C}H_3$), 13.4 ($\underline{C}H_3CH_2CH_2S$); **HRMS** (ESI+) mass calculated for $[M]^+$ ($C_{11}H_{22}O_2S$) requires *m/z* 218.1341, found *m/z* 218.1373; **IR** (film) ν_{max}/cm^{-1}: 2966, 1725 (C=O), 1368, 1216, 1148, 753, 667.

6.3.3.5 Synthesis and Characterisation of 2.77e

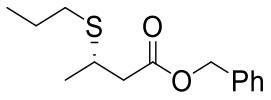
Propan-(*S*)-2-yl 3-(propylsulfanyl)butanoate



According to General Procedure L, to a solution of propan-2-yl (2*E*)-but-2-enoate (25.6 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanolthiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.77e** as a colourless oil in 95% yield (38.6 mg) and 70% ee [determined by HPLC, chiralpak AD-H, hexane/isopropanol 99:1, λ 220 nm, 1.0 mL/min, t (major) = 5.47 min, t (minor) = 5.82 min]. **$[\alpha]_D^{23}$ =** +1.6 (*c 0.5*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 5.04 (sqt, *J* = 6.5 Hz, 1 H, OC<u>H</u>$(CH_3)_2$), 3.19 (dquin, *J* = 8.0, 6.5 Hz, 1 H, C<u>H</u>CH_3), 2.59 (dd, *J* = 15.0, 6.5 Hz, 1 H, CHC<u>H$_A$</u>H$_B$), 2.53 (t, *J* = 7.5 Hz, 2 H, CH_3CH_2C<u>H_2</u>S), 2.40 (dd, *J* = 15.0, 8.5 Hz, 1 H, CHCH$_A$<u>H$_B$</u>), 1.61 (sxt, *J* = 7.5 Hz, 2 H, CH_3<u>CH_2</u>CH_2S), 1.32 (d, *J* = 6.5 Hz, 3 H, CHC<u>H_3</u>), 1.25 (d, *J* = 6.5 Hz, 6 H, OCH(C<u>H_3</u>)$_2$), 0.99 (t, *J* = 7.5 Hz, 3 H, C<u>H_3</u>CH_2CH_2S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.1 (<u>C</u>=O), 67.9 (O<u>C</u>H$(CH_3)_2$), 42.7 (CH<u>C</u>H_2), 36.2 (<u>C</u>HCH_3), 32.6 (<u>C</u>H_2S), 23.0 (<u>C</u>H_2CH_2S), 21.8 (OCH(<u>C</u>H_3)$_2$), 21.4 (CH<u>C</u>H_3), 13.6 (<u>C</u>$H_3CH_2CH_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{10}H_{20}NaO_2S$) requires *m/z* 227.1076, found *m/z* 227.1084; **IR** (film) ν_{max}/cm^{-1}: 2926, 1722 (C=O), 1216, 1106, 755.

6.3.3.6 Synthesis and Characterisation of 2.77f

Benzyl (*S*)-3-(propylsulfanyl)butanoate

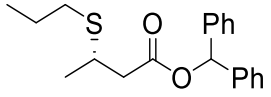


According to General Procedure L, to a solution of benzyl (2*E*)-but-2-enoate (35.2 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanolthiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.77f** as a colourless oil in 96% yield (48.4 mg) and 61% ee [determined by HPLC, chiralpak AD-H, hexane/isopropanol 99:1, λ 220 nm, 1.0 mL/min, t (major) = 11.99 min, t (minor) = 13.93 min]. $\mathbf{[\alpha]_D^{23}}$ = 0 (c *0.6*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.38 - 7.34 (m, 5 H, Ar<u>H</u>), 5.15 (s, 2 H, OC<u>H_2</u>Ph), 3.22 (m, 1 H, C<u>H</u>CH_3), 2.68 (dd, *J* = 15.5, 6.5 Hz, 1 H, CHC<u>H_A</u>H_B), 2.54-2.48 (m, 3 H, CH_3CH_2C<u>H_2</u>S and $CHCH_A$<u>H_B</u>), 1.60 (sxt, *J* = 7.5 Hz, 2 H, CH_3C<u>H_2</u>CH_2S), 1.33 (d, *J* = 7.0 Hz, 3 H, CHC<u>H_3</u>), 0.98 (t, *J* = 7.5 Hz, 3 H, C<u>H_3</u>CH_2CH_2S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.4 (<u>C</u>=O), 135.8 (Ar<u>C</u>), 128.6 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H)[xx], 66.4 (O<u>C</u>H_2Ph), 42.4 (CH<u>C</u>H_2), 36.1 (<u>C</u>HCH_2), 32.7 (CH_3CH_2<u>C</u>H_2S), 23.0 (CH_3<u>C</u>H_2CH_2S), 21.5 (<u>C</u>H_3CH), 15.3 (<u>C</u>$H_3CH_2CH_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_2S$) requires *m/z* 275.1076, found *m/z* 275.1079; **IR** (film) ν_{max}/cm^{-1}: 2962, 1731 (C=O), 1216, 1156, 753, 697, 668.

[xx] One of the Ar<u>C</u>H is missing, probably due to overlap of the aromatic carbon signals.

6.3.3.7 Synthesis and Characterisation of 2.77g

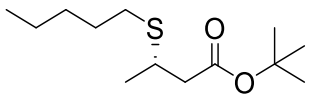
Benzhydryl *(S)*-3-(propylthio)butanoate



According to General Procedure L, to a solution of diphenylmethyl (2*E*)-but-2-enoate (50.4 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanolthiol (54.4 µL, 0.6 mmol, 1.0 eq) at 0 °C, and then stirred at 0 °C. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.77g** as a colourless oil in >99% yield (65.6 mg) and 67% ee [determined by HPLC, chiralpak AD-H, hexane/isopropanol 98:2, λ 220 nm, 1.0 mL/min, t (minor) = 11.04 min, t (major) = 11.75 min]. $\mathbf{[\alpha]_D^{23}}$ = -1.3 (*c 1.2*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.44-7.22 (m, 10 H, ArH), 6.92 (s, 1 H, CHPh$_2$), 3.24 (dquin, *J* = 8.5, 7.0 Hz, 1 H, CHCH$_3$), 2.77 (dd, *J* = 15.5, 7.0 Hz, 1 H, CHCH$_A$H$_B$), 2.58 (dd, *J* = 15.5, 8.5 Hz, 1 H, CHCH$_A$H$_B$), 2.51 (td, *J* = 7.5, 1.5 Hz, 2 H, CH$_3$CH$_2$CH$_2$S), 1.59 (sxt, *J* = 7.5 Hz, 2 H, CH$_3$CH$_2$CH$_2$S), 1.31 (d, *J* = 7.0 Hz, 3 H, CHCH$_3$), 0.98 (t, *J* = 7.5 Hz, 3 H, CH$_3$CH$_2$CH$_2$S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.4 (C=O), 140.0 (ArC), 128.5 (ArCH), 127.9 (ArCH), 127.2 (ArCH), 77.2 (CHPh$_2$), 42.0 (CHCH$_2$), 36.2 (CHCH$_2$), 32.7 (CH$_2$S), 23.0 (CH$_2$CH$_2$S), 21.5 (CHCH$_3$), 13.6 (CH$_3$CH$_2$CH$_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{20}H_{24}NNaO_4$) requires *m/z* 351.1389, found *m/z* 351.1388; **IR** (film) ν_{max}/cm^{-1}: 2971, 1734 (C=O), 1216, 1154, 751, 699, 667.

6.3.3.8 Synthesis and characterisation of 2.106a

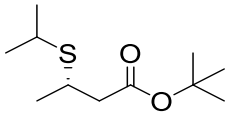
tert-butyl *(S)*-3-(pentylthio)butanoate



According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-pentanethiol (74 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 24 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.106a** as a colourless oil in 98% yield (48 mg) and 90% ee [determined by HPLC, chiralpak IA hexane/isopropanol 100:0, λ 220 nm, 1.0 mL/min, t (major) = 11.09 min, t (minor) = 13.30 min]. $\mathbf{[\alpha]_D^{23}}$ = +4.8 (*c 1.57*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.15 - 3.13 (m, 1 H, C$\underline{H}$$CH_2$), 2.53 (t, *J* = 7.5 Hz, 2 H, C$\underline{H_2}$S), 2.53 (dd, *J* = 15.0, 6.0 Hz, 1 H, CHC$\underline{H_A}H_B$), 2.33 (dd, *J* = 15.0, 8.5 Hz, 1 H, CHC$H_A\underline{H_B}$), 1.57 (quin, *J* = 7.5 Hz, 2 H, C$\underline{H_2}$$CH_2$S), 1.45 (s, 9 H, C(C$\underline{H_3}$)$_3$), 1.38 - 1.34 (m, 2 H, C$\underline{H_2}$$CH_2$$CH_2$S), 1.30 (d, *J* = 7.0 Hz, 3 H, CHC$\underline{H_3}$), 1.27-1.25 (m, 2 H, CH_3C$\underline{H_2}$), 0.88 (t, *J* = 7.0 Hz, 3 H, C$\underline{H_3}$$CH_2$$CH_2$$CH_2$$CH_2$S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.0 ($\underline{C}$=O), 80.8 (O$\underline{C}$(CH_3)$_3$), 43.7 (CH$\underline{C}$$H_2$), 36.5 ($\underline{C}$HCH), 31.3 ($\underline{C}$$H_2$S), 30.7 ($\underline{C}$$H_2$$CH_2$S), 29.5 ($CH_3$$CH_2$$\underline{C}$$H_2$), 28.2 (C($\underline{C}$$H_3$)$_3$), 22.4 ($CH_3$$\underline{C}$$H_2$$CH_2$), 21.5 ($\underline{C}$$H_3$CH), 14.1 ($\underline{C}$$H_3$$CH_2$$CH_2$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{13}H_{26}O_2NaS$) requires *m/z* 269.1546, found *m/z* 269.1546; **IR** (film) ν_{max}/cm^{-1}: 2929, 1727 (C=O), 1368, 1149, 907, 731, 648.

6.3.3.9 Synthesis and characterisation of 2.106b

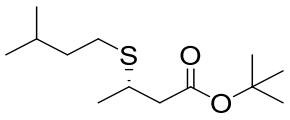
tert-butyl *(S)*-3-(isopropylthio)butanoate



According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 2-propanethiol (55.6 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 24 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.106b** as a colourless oil in 86% yield (37.5 mg) and 90% ee [determined by GC, Supelco β-dex^{TM} 325, 30 m, 0.25 mm, 0.25 µm, carrier gas He (flow rate 30 cm/s); column temperature 80 ˚C ramp 1 ˚C/min to 90 ˚C then 90 ˚C, t (minor) = 60.86 min, t (major) = 61.78 min]. **$[\alpha]_D^{23}$** = +1.6 (c *0.8*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.25 - 3.16 (m, 1 H, C<u>H</u>CH_2), 3.04 – 2.94 (dt, *J* = 13.5, 7.0 Hz, 1 H, $(CH_3)_2C\underline{H}S$), 2.52 (dd, *J* = 15.0, 6.0 Hz, 1 H, $CHC\underline{H}_AH_B$), 2.35 (dd, *J* = 15.0, 8.5 Hz, 1 H, $CHCH_A\underline{H}_B$), 1.45 (s, 9 H, $C(C\underline{H}_3)_3$), 1.29 (d, *J* = 7.0 Hz, 3 H, $CHC\underline{H}_3$), 1.25 (t, *J* = 7.0 Hz, 6 H, $CH(C\underline{H}_3)_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.1 (<u>C</u>=O), 80.8 ($O\underline{C}(CH_3)_3$), 43.9 ($CH\underline{C}H_2$), 35.4 ($\underline{C}HCH_2$), 34.2 ($(CH_3)_2\underline{C}H$), 28.2 ($C(\underline{C}H_3)_3$), 23.9 ($(\underline{C}H_3)_2CH$), 21.9 ($\underline{C}H_3CH$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{11}H_{22}O_2NaS$) requires *m/z* 241.1233, found *m/z* 241.1229; **IR** (film) ν_{max}/cm^{-1}: 2972, 1727 (C=O), 1368, 1149, 909, 731, 648.

6.3.3.10 Synthesis and characterisation of 2.106c

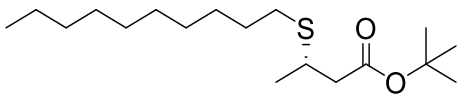
tert-butyl *(S)*-3-(isopentylthio)butanoate



According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 3-methyl-1-butanethiol (74 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 24 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.106c** as a yellow oil in 99% yield (48.8 mg) and 90% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ 210 nm, 1.0 mL/min, t (major) = 10.55 min, t (minor) = 12.41 min]. $\mathbf{[\alpha]_D^{23}}$ = -4.9 (*c 1.5*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.16 - 3.12 (m, 1 H, C$\underline{H}CH_2$), 2.54 (t, *J* = 7.5 Hz, 2 H, C$\underline{H_2}$S), 2.53 (dd, *J* = 15.0, 6.0 Hz, 1 H, CHC$\underline{H_A}H_B$), 2.33 (dd, *J* = 15.0, 8.5 Hz, 1 H, CHC$H_A\underline{H_B}$), 1.69 - 1.61 (m, 1 H, C$\underline{H}(CH_3)_2$), 1.49 - 1.45 (m, 2 H, C$\underline{H_2}CH_2$S), 1.45 (s, 9 H, C(C$\underline{H_3}$)$_3$), 1.30 (d, *J* = 7.0 Hz, 3 H, CHC$\underline{H_3}$), 0.89 (d, *J* = 7.0 Hz, 6 H, CH(C$\underline{H_3}$)$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.0 ($\underline{C}$=O), 80.8 (O$\underline{C}$(CH$_3$)$_3$), 43.7 (CH$\underline{C}H_2$), 38.8 ((CH$_3$)$_2\underline{C}$H), 36.5 ($\underline{C}HCH_2$), 28.7 ($CH_2\underline{C}H_2$S), 28.2 (C($\underline{C}$H$_3$)$_3$), 27.6 ($\underline{C}H_2CH_2$S), 22.4 (($\underline{C}$H$_3$)$_2$CH), 21.4 ($\underline{C}H_3$CH); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{13}H_{26}O_2NaS$) requires *m/z* 269.1546, found *m/z* 269.1541; **IR** (film) ν_{max}/cm^{-1}: 2959, 1729 (C=O), 1368, 1149, 909, 733, 648.

6.3.3.11 Synthesis and characterisation of 2.106d

tert-butyl (S)-3-(decylthio)butanoate

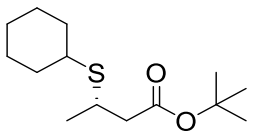


According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added decane-1-thiol (124 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 24 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.106d** as a colourless oil in >99% yield (63.2 mg) and 90% ee [determined by GC, Supelco β-dex^{TM} 325, 30 m, 0.25 mm, 0.25 µm, carrier gas He (flow rate 30 cm/s); column temperature 90 ˚C ramp 1 ˚C/min to 100 ˚C then 100 ˚C, t (minor) = 195.88 min, t (minor) = 197.92 min]. **$[\alpha]_D^{23}$** = +3.5 (*c 1.2*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.19 - 3.10 (m, 1 H, C$\underline{H}CH_2$), 2.53 (t, *J* = 7.5 Hz, 2 H, C$\underline{H_2}$S), 2.53 (dd, *J* = 15.0, 6.0 Hz, 1 H, CHC$\underline{H_A}H_B$), 2.33 (dd, *J* = 15.0, 8.5 Hz, 1 H, CHC$H_A\underline{H_B}$), 1.60 - 1.55 (m, 2 H, C$\underline{H_2}CH_2$S), 1.45 (s, 9 H, C(C$\underline{H_3}$)$_3$), 1.38 - 1.34 (m, 2 H, C$\underline{H_2}CH_2CH_2$S), 1.30 (d, *J* = 7.0 Hz, 3 H, CHC$\underline{H_3}$), 1.28 - 1.25 (m, 12 H, (C$\underline{H_2}$)$_6$CH$_3$), 0.87 (d, *J* = 7.0 Hz, 3 H, CH$_2$C$\underline{H_3}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.0 ($\underline{C}$=O), 80.8 (O$\underline{C}$(CH$_3$)$_3$), 43.7 (CH$\underline{C}$H$_2$), 36.5 ($\underline{C}$HCH$_2$), 32.0 (CH$_2\underline{C}$H$_2$S), 30.7 (one of CH$_3$($\underline{C}$H$_2$)$_8$), 29.9 (one of CH$_3$($\underline{C}$H$_2$)$_8$), 29.7 (one of CH$_3$($\underline{C}$H$_2$)$_8$), 29.5 (one of CH$_3$($\underline{C}$H$_2$)$_8$), 29.4 (one of CH$_3$($\underline{C}$H$_2$)$_8$), 29.2 (one of CH$_3$($\underline{C}$H$_2$)$_8$), 28.7 (one of CH$_3$($\underline{C}$H$_2$)$_8$), 28.2 (C($\underline{C}$H$_3$)$_3$), 22.8 (one of CH$_3$($\underline{C}$H$_2$)$_8$), 21.5 ($\underline{C}$H$_3$CH), 14.3 ($\underline{C}$H$_3$(CH$_2$)$_8$); **HRMS** (EI+) mass calculated for $[M+Na]^+$

($C_{18}H_{36}O_2NaS$) requires *m/z* 339.2328, found *m/z* 339.2320; **IR** (film) ν_{max}/cm^{-1}: 2925, 2855 (C=O), 1730, 1457, 1367, 1148, 908, 733, 648.

6.3.3.12 Synthesis and Characterisation of 2.106e

tert-butyl *(S)*-3-(cyclohexylthio)butanoate

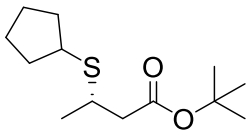


According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added cyclohexanethiol (73 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 96 h. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.106e** as a colourless oil in 68% yield (35.2 mg) and 90% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ 220 nm, 0.5 mL/min, t (major) = 27.64 min, t (minor) = 31.64 min]. $\mathbf{[\alpha]_D^{23}}$ = +1.1 (*c 0.9*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.21 (dquin, *J* = 8.5, 6.5 Hz, 1 H, C<u>H</u>CH_2C=O), 2.71 - 2.66 (m, 1 H, $(CH_2)_2$C<u>H</u>S), 2.48 (dd, *J* = 15.0, 6.0 Hz, 1 H, CHC<u>H_A</u>H_BC=O), 2.31 (dd, *J* = 15.0, 8.5 Hz, 1 H, CHCH_A<u>H_B</u>C=O), 1.96 - 1.93 (m, 2 H, C<u>H_2</u>CHS), 1.74 - 1.72 (m, 2 H, C<u>H_2</u>CHS), 1.60 - 1.57 (m, 1 H, one of C<u>H_2</u>C<u>H_2</u>C<u>H_2</u>CH_2CHS), 1.44 (s, 9 H, C(C<u>H_3</u>)$_3$), 1.32 - 1.22 (m, 5 H, five of C<u>H_2</u>C<u>H_2</u>C<u>H_2</u>CH_2CHS), 1.29 (d, *J* = 7.0 Hz, 3 H, CHC<u>H_3</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.0 (<u>C</u>=O), 80.7 (O<u>C</u>$(CH_3)_3$), 44.1 (CH<u>C</u>H_2C=O), 42.8 (CH_2CH_2C<u>H</u>S), 35.0 (<u>C</u>HCH_3), 34.2, 34.1 (C<u>H_2</u>CHC<u>H_2</u>),

28.2 (C(CH$_3$)$_3$), 26.2 and 25.9 (CH$_2$CH$_2$CH$_2$CH$_2$CHS)[xxi], 22.1 (CH$_3$CH); **HRMS** (EI+) mass calculated for [M+Na]$^+$ ($C_{14}H_{26}O_2NaS$) requires *m/z* 281.1546, found *m/z* 281.1533; **IR** (film) ν_{max}/cm^{-1}: 2928, 2853, 1728 (C=O), 1367, 1145, 844, 732.

6.3.3.13 Synthesis and Characterisation of 2.106f

tert-butyl *(S)*-3-(cyclopentylthio)butanoate



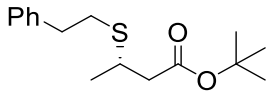
According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added cyclopentanethiol (64 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 24 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.106f** as a colourless oil in 99% yield (48.4 mg) and 90% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ 220 nm, 1.0 mL/min, t (major) = 13.15 min, t (minor) = 16.11 min]; **[α]$_D^{23}$** = +5.3 (*c 1.1*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.22 - 3.09 (m, 2 H, CH_2CH_2CHS and CHCH$_2$C=O), 2.54 (dd, *J* = 15.0, 6.0 Hz, 1 H, CHCH$_A$H$_B$C=O), 2.32 (dd, *J* = 15.5, 8.5 Hz, 1 H, CHCH$_A$H$_B$C=O), 2.03 - 1.96 (m, 2 H, one of CH$_2$CH$_2$CHS), 1.74 - 1.70 (m, 2 H, one of CH$_2$CH$_2$CHS), 1.57 - 1.47 (m, , 4 H, CH$_2$CH$_2$CH$_2$CH$_2$CHS), 1.44 (s, 9 H, C(CH$_3$)$_3$), 1.31 (d, *J* = 6.5 Hz, 3 H, CHCH$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.1 (C=O), 80.8

[xxi] one of CH$_2$CH$_2$CH$_2$CH$_2$CHS carbon is missing, possibly hidden below 26.2 and 25.9 signals.

(O<u>C</u>$(CH_3)_3$), 43.9 (CH<u>C</u>H_2C=O), 42.8 (CH_2CH_2C<u>H</u>S), 36.6 (<u>C</u>HCH_3), 34.4 and 34.2 (C<u>H</u>$_2$CHC<u>H</u>$_2$), 28.2 (C(<u>C</u>$H_3)_3$), 24.9 and 24.8 (CH_2C<u>H</u>$_2$C<u>H</u>$_2CH_2$CHS), 21.8 (<u>C</u>H_3CH); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{13}H_{24}O_2NaS$) requires *m/z* 267.1389, found *m/z* 267.1382; **IR** (film) ν_{max}/cm^{-1}: 2960, 1727 (C=O), 1368, 1147, 907, 843, 730.

6.3.3.14 Synthesis and Characterisation of 2.106g

<u>tert-butyl *(S)*-3-(phenethylthio)butanoate</u>

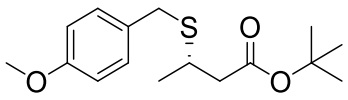


According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 2-penylethanethiol (80 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 24 h. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.106g** as a colourless oil in 94% yield (53 mg) and 88% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ 210 nm, 1.0 mL/min, t (major) = 9.23 min, t (minor) = 10.49 min]. **$[\alpha]_D^{23}$** = +5.6 (*c 1.3*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.23 - 7.20 (m, 2 H, Ar<u>H</u>), 7.15 - 7.12 (m, 3 H, Ar<u>H</u>), 3.15 - 3.09 (dquin, *J* = 8.5, 6.5 Hz, 1 H, C<u>H</u>CH_2C=O), 2.83 - 2.70 (m, 4 H, PhC<u>H</u>$_2$C<u>H</u>$_2$), 2.46 (dd, *J* = 15.0, 6.0 Hz, 1 H, CHC<u>H</u>$_A$H$_B$C=O), 2.27 (dd, *J* = 15.5, 8.5 Hz, 1 H, CHCH$_A$<u>H</u>$_B$C=O), 1.38 (s, 9 H, C(C<u>H</u>$_3)_3$), 1.24 (d, *J* = 6.5 Hz, 3 H, CHC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100

MHz) δ (ppm): 170.9 (C=O), 140.7 (ArC), 128.6 (ArCH), 126.4 (ArCH)[xxii], 80.8 ($OC(CH_3)_3$), 43.6 ($CHCH_2C=O$), 36.7 ($CHCH_3$), 36.4 ($PhCH_2CH_2$), 32.2 ($PhCH_2CH_2$), 28.2 ($C(CH_3)_3$), 21.4 (CH_3CH); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{16}H_{24}O_2NaS$) requires *m/z* 303.1389, found *m/z* 303.1374. **IR** (film) ν_{max}/cm^{-1}: 2976, 1726 (C=O), 1367, 1146, 843, 732, 697.

6.3.3.15 Synthesis and Characterisation of 2.106h

tert-butyl *(S)*-3-((4-methoxybenzyl)thio)butanoate



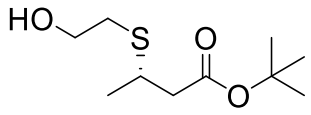
According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 4-Methoxy-α-toluenethiol (84 µL, 0.6 mmol, 3.0 eq) at –15 °C, and then stirred at –15 °C for 24 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.106h** as a colourless oil in 99% yield (58.4 mg) and 90% ee [determined by HPLC, chiralpak AS-H, hexane/isopropanol 99:1, λ 220 nm, 1.0 mL/min, t (major) = 8.27 min, t (minor) = 12.35 min]. $\mathbf{[\alpha]_D^{23}}$ = -1.9 (*c 1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.16 (d, *J* = 8.5 Hz, 2 H, ArCH), 6.76 (d, *J* = 8.5 Hz, 2 H, ArCH), 3.71 (s, 3 H, OCH_3), 3.64 (s, 2 H, $PhCH_2$), 3.02 – 2.98 (m, 1 H, $CHCH_3$), 2.45 (dd, *J* = 15.0, 6.0 Hz, 1 H, $CHCH_AH_BC=O$), 2.25 (dd, *J* = 15.0, 8.5 Hz, 1 H, $CHCH_AH_BC=O$), 1.37 (s, 9 H, $C(CH_3)_3$), 1.21 (d, *J* = 7.0 Hz, 3 H,

[xxii] One of the ArCH is missing, probably due to overlap of the aromatic carbon signals.

$CHC\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.8 ($\underline{C}$=O), 158.7 (Ar$\underline{C}$), 130.3 (Ar$\underline{C}$), 130.0 (Ar$\underline{C}$H), 114.0 (Ar$\underline{C}$H), 80.8 (O$\underline{C}(CH_3)_3$), 55.4 (O$\underline{C}H_3$), 43.4 ($CH\underline{C}H_2C$=O), 36.1 ($\underline{C}HCH_2$), 34.7 (Ph$\underline{C}H_2$), 28.2 ($C(\underline{C}H_3)_3$), 21.2 ($\underline{C}H_3CH$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{16}H_{24}O_3NaS$) requires *m/z* 319.1338, found *m/z* 319.1329. **IR** (film) v_{max}/cm^{-1}: 2976, 1725 (C=O), 1511, 1247, 1147, 833, 730.

6.3.3.16 Synthesis and Characterisation of 2.106i

<u>*tert*-butyl *(S)*-3-((2-hydroxyethyl)thio)butanoate</u>

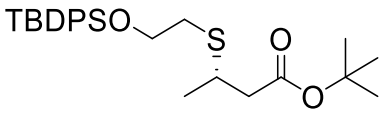


According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 2-mercaptoethan-1-ol (84 µL, 0.6 mmol, 3.0 eq) at 0°C, and then stirred at 0°C for 24 h. The product was purified by FCC (9:1 PE: acetone) to afford the title compound **2.106i** as a colourless oil in 48% yield (21.1 mg) and 31% ee [determined by HPLC, chiralpak OD-H, hexane/isopropanol 98:2, λ 220 nm, 1.0 mL/min, t (major) = 18.04 min, t (minor) = 22.73 min]. **$[\alpha]_D^{25}$** = +7.6 (c *0.9,* $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.78 - 3.74 (q, *J* = 5.0 Hz, 2 H, $C\underline{H}_2OH$), 3.21 (sxt, *J* = 7.0 Hz, 1 H, $C\underline{H}CH_3$), 2.77 (t, *J* = 5.5 Hz, 2 H, $C\underline{H}_2SH$), 2.56 (br. s, 1 H, O$\underline{H}$), 2.50 (dd, *J* = 15.5, 8.0 Hz, 1 H, $CHC\underline{H}_AH_B$), 2.41 (dd, *J* = 15.5, 7.0 Hz, 1 H, $CHCH_A\underline{H}_B$), 1.47 (s, 9 H, $OC(C\underline{H}_3)_3$), 1.34 (d, *J* = 7.0 Hz, 3 H, $CHC\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 400 MHz) δ (ppm): 171.0 ($\underline{C}$=O), 81.1 (O$\underline{C}(CH_3)_3$), 61.0 ($CH_2\underline{C}H_2OH$),

43.5 (CH<u>C</u>H$_2$), 36.2 (<u>C</u>HCH$_2$), 34.0 (CH$_2$<u>C</u>H$_2$S), 28.1 (C(<u>C</u>H$_3$)$_3$), 21.8 (<u>C</u>H$_3$CH); **HRMS** (EI+) mass calculated for [M+Na]$^+$ ($C_{10}H_{20}O_3NaS$) requires *m/z* 243.1036, found *m/z* 243.1026; **IR** (film) ν_{max}/cm^{-1}: 3408 (OH), 2977, 1726 (C=O), 1368, 1150, 754.

6.3.3.17 Synthesis and Characterisation of 2.106j

<u>*tert*-butyl *(S)*-3-((2-((tert-butyldiphenylsilyl)oxy)ethyl)thio)butanoate</u>

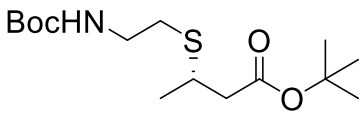


According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.10 eq) in 0.4 mL Et_2O was added 2-((tert-butyldiphenylsilyl)oxy)ethane-1-thiol (108 mg, 0.6 mmol, 3.0 eq) at 0°C, and then stirred at 0°C for 24 h. The product was purified by FCC (9:1 PE: acetone) to afford the title compound **2.106j** as a colourless oil in 44% yield (40 mg) and 75% ee [determined by HPLC, chiralpak OG, hexane/isopropanol 100:0, λ 220 nm, 1.0 mL/min, t (minor) = 15.59 min, t (major) = 16.43 min]. **[α]$_D^{25}$** = +35.0 (c *0.1*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.32 - 7.71 (m, 4 H, ArC<u>H</u>), 7.48 - 7.42 (m, 6 H, ArC<u>H</u>), 3.83 (t, *J* = 7.0 Hz, 2 H, C<u>H</u>$_2$OTBDPS), 3.20 - 3.11 (m, 1 H, C<u>H</u>CH$_3$), 2.73 (t, *J* = 7.0 Hz, 2 H, C<u>H</u>$_2$SH), 2.50 (dd, *J* = 15.0, 6.0 Hz, 1 H, CHC<u>H</u>$_A$H$_B$), 2.41 (dd, *J* = 15.0, 8.5 Hz, 1 H, CHCH$_A$<u>H</u>$_B$), 1.47 (s, 9 H, OC(C<u>H</u>$_3$)$_3$), 1.26 (d, *J* = 7.0 Hz, 3 H, CHC<u>H</u>$_3$), 1.10 (s, 9 H, SiC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 400 MHz) δ (ppm): 170.6 (<u>C</u>=O), 135.6 (Ar<u>C</u>H), 133.6 (Ar<u>C</u>), 129.7 (Ar<u>C</u>H), 127.7

(Ar<u>C</u>H), 80.7 (O<u>C</u>(CH$_3$)$_3$), 64.0 (<u>C</u>H$_2$OTBDPS), 43.6 (CH<u>C</u>H$_2$), 36.6 (<u>C</u>HCH$_2$), 32.6 (CH$_2$<u>C</u>H$_2$S), 28.1 (C(<u>C</u>H$_3$)$_3$), 26.9(SiC(<u>C</u>H$_3$)$_3$), 21.4 (<u>C</u>H$_3$CH), 19.2 (Si<u>C</u>(CH$_3$)$_3$); **HRMS** (EI+) mass calculated for [M+Na]$^+$ ($C_{26}H_{38}O_3NaSSiNa$) requires *m/z* 481.2203, found *m/z* 481.2202; **IR** (film) ν_{max}/cm^{-1}: 2962, 2930, 2858, 1729 (C=O), 1149, 1111, 756, 703.

6.3.3.18 Synthesis and Characterisation of 2.106k

<u>*tert*-butyl *(S)*-3-((2-((tert-butoxycarbonyl)amino)ethyl)thio)butanoate</u>

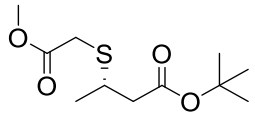


According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.10 eq) in 0.4 mL Et_2O was added tert-butyl (2-mercaptoethyl)carbamate (105 mg, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 24 h. The product was purified by FCC (6:4 PE: Et_2O) to afford the title compound **2.106k** as a colourless oil in 59% yield (37.8 mg) and 21% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 99:1, λ 230 nm, 1.0 mL/min, t (minor) = 17.46 min, t (major) = 18.09 min]. **$[\alpha]_D^{25}$** = +3.4 (c *0.7*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 4.95 (br s, 1 H, N<u>H</u>Boc), 3.27 - 3.24 (m, 2 H, C<u>H</u>$_2$NHBoc), 3.10 (sxt, *J* = 7.0 Hz, 1 H, C<u>H</u>CH$_3$), 2.61 (t, *J* = 6.0 Hz, 2 H, C<u>H</u>$_2$SH), 2.43 (dd, *J* = 15.0, 7.0 Hz, 1 H, CHC<u>H$_A$</u>H$_B$), 2.29 (dd, *J* = 15.0, 7.5 Hz, 1 H, CHCH$_A$<u>H$_B$</u>), 1.39 (s, 9 H, one of COOC(C<u>H</u>$_3$)$_3$ and NHCOC(C<u>H</u>$_3$)$_3$), 1.37 (s, 9 H, one of COOC(C<u>H</u>$_3$)$_3$ and NHCOC(C<u>H</u>$_3$)$_3$), 1.25 (d, *J* = 7.0 Hz, 3 H, CHC<u>H</u>$_3$); **^{13}C**

NMR ($CDCl_3$, 400 MHz) δ (ppm): 170.7 ($CH_2\underline{C}$=O), 155.8 (NH$\underline{C}$=O), 80.9 (one of COO$\underline{C}(CH_3)_3$ and NHCO$\underline{C}(CH_3)_3$), 79.3 (one of O$\underline{C}(CH_3)_3$ and NHCO$\underline{C}(CH_3)_3$), 43.5 (CH$\underline{C}H_2$), 39.9 ($\underline{C}H_2$NHBoc), 36.2 ($\underline{C}HCH_2$), 30.9 ($CH_2\underline{C}H_2S$), 28.4 (one of COOC($\underline{C}H_3)_3$ and NHCOC($\underline{C}H_3)_3$), 28.1 (one of COOC($\underline{C}H_3)_3$ and NHCOC($\underline{C}H_3)_3$), 21.6 ($\underline{C}H_3CH$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{15}H_{29}O_4NNaS$) requires *m/z* 342.1720, found *m/z* 342.1705; **IR** (film) ν_{max}/cm^{-1}: 3368 (NH), 2977, 1715 (C=O), 1511, 1367, 1251, 1151, 754.

6.3.3.19 Synthesis and Characterisation of 2.106l

tert-butyl *(S)*-3-((2-methoxy-2-oxoethyl)thio)butanoate

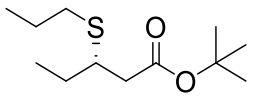


According to General Procedure L, to a solution of *tert*-butyl crotonate (32 µL, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added methyl 2-mercaptoacetate (67 mg, 0.6 mmol, 3.0 eq) at 0°C, and then stirred at 0°C for 2 h. The product was purified by FCC (6:4 PE: Et_2O) to afford the title compound **2.106l** as a colourless oil in 89% yield (44 mg) and 31% ee [determined by HPLC, chiralpak AD, hexane/isopropanol 99:1, λ 220 nm, 1.0 mL/min, t (minor) = 9.00 min, t (major) = 9.62 min]. $\mathbf{[\alpha]_D^{25}}$ = +0.7 (c *1.5*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.74 (s, 3 H, OC$\underline{H}_3$), 3.33 - 3.26 (m, 3 H, C$\underline{H}_2$S and C$\underline{H}CH_3$), 2.57 (dd, *J* = 15.0, 6.0 Hz, 1 H, CHC$\underline{H}_A$H$_B$), 2.38 (dd, *J* = 15.0, 8.0 Hz, 1 H, CHCH$_A\underline{H}_B$), 1.46 (s, 9 H, OC(C$\underline{H}_3)_3$), 1.34 (d, *J* = 7.0 Hz, 3 H, CHC$\underline{H}_3$); **^{13}C NMR**

($CDCl_3$, 400 MHz) δ (ppm): 170.4 (C=O), 170.1 (C=O), 80.9 (OC(CH_3)$_3$), 52.5 (OCH_3), 43.0 (CHCH_2), 37.2 ($CHCH_2$), 32.5 (CH_2S), 28.1 (OC(CH_3)$_3$), 20.9 (CH_3CH); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{11}H_{20}O_4NaS$) requires *m/z* 271.0975, found *m/z* 271.0974; **IR** (film) ν_{max}/cm^{-1}: 2978, 1729 (C=O), 1279, 1149, 754.

6.3.3.20 Synthesis and Characterisation of 2.108a

tert-butyl *(S)*-3-(propylthio)pentanoate

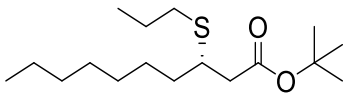


According to General Procedure L, to a solution of *tert*-butyl (*E*)-pent-2-enoate **2.107a** (31.2 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.108a** as a colourless oil in 84% yield (39 mg) and 86% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ = 220 nm, 1.0 mL/min, t (major) = 8.37 min, t (minor) = 9.86 min]. $\mathbf{[\alpha]_D^{23}}$ = -1.2 (*c 1.2*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 2.99 - 2.92 (dq, *J* = 7.0, 5.5 Hz, 1 H, CHCH_3), 2.52 - 2.46 (m, 4 H, CHCH_2C=O and CH_2CH_2S), 1.64 - 1.55 (m, 4 H, CHCH_2CH_3 and $CH_3CH_2CH_2$S), 1.46 (s, 9 H, C(CH_3)$_3$), 1.00 (t, *J* = 7.5 Hz, 3 H, $CHCH_2CH_3$), 0.98 (t, *J* = 7.5 Hz, 3 H, $CH_3CH_2CH_2$S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.3 (C=O), 80.8 (OC(CH_3)$_3$), 43.7 (CHCH_2), 42.0 (CHCH_2C=O), 32.9 (CH_2CH_2S), 28.2

($C(\underline{C}H_3)_3$), 28.1 ($CH\underline{C}H_2CH_3$), 23.3 ($CH_3\underline{C}H_2CH_2S$), 13.7 ($\underline{C}H_3CH_2CH_2S$), 11.4 ($CHCH_2\underline{C}H_3$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{12}H_{24}O_2NaS$) requires *m/z* 255.1389, found *m/z* 255.1384. **IR** (film) ν_{max}/cm^{-1}: 2965, 2931, 1729 (C=O), 1368, 1148, 909, 733.

6.3.3.21 Synthesis and characterisation of 2.108b

tert-butyl *(S)*-3-(propylthio)decanoate

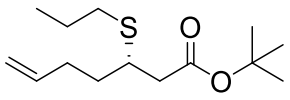


According to General Procedure L, to a solution *tert*-butyl (*E*)-dec-2-enoate **2.107b** (45.2 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.108b** as a colourless oil in 89% yield (54.0 mg) and 84% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ = 240 nm, 1.0 mL/min, t (major) = 15.54 min, t (minor) = 16.75 min]. $\mathbf{[\alpha]_D^{23}}$ = -2.1 (*c 1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.01 - 2.95 (m, 1 H, $C\underline{H}CH_3$), 2.51 - 2.44 (m, 4 H, $CHC\underline{H}_2C{=}O$ and $CH_2C\underline{H}_2S$), 1.64 - 1.52 (m, 5 H, $CHC\underline{H}_2CH_2$, $CH_3C\underline{H}_2CH_2S$ and one of $CHCH_2C\underline{H}_2$), 1.45 (s, 9 H, $C(C\underline{H}_3)_3$), 1.30 – 1.26 (m, 9 H, $CH_2(C\underline{H}_2)_4CH_3$ and one of $CHCH_2C\underline{H}_2$), 0.97 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 0.87 (t, *J* = 7.0 Hz, 3 H, $CH(CH_2)_6C\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.3 ($\underline{C}{=}O$), 80.7 ($O\underline{C}(CH_3)_3$), 42.4 ($CH\underline{C}H_2C{=}O$), 42.0 ($C\underline{H}CH_2$), 35.2($CH\underline{C}H_2CH_2$), 32.8

($CH_2C\underline{H}_2S$), 31.9 ($CHCH_2\underline{C}H_2$), 29.6 ($CH(CH_2)_2\underline{C}H_2$), 29.3 ($CH(CH_2)_3\underline{C}H_2$), 28.2 ($C(\underline{C}H_3)_3$), 26.9 ($CH(CH_2)_4\underline{C}H_2$), 23.3 ($CH_3\underline{C}H_2CH_2S$), 22.8 ($CH(CH_2)_5\underline{C}H_2$), 14.2 ($CH(CH_2)_6\underline{C}H_3$), 13.7 ($\underline{C}H_3CH_2CH_2S$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{17}H_{34}O_2NaS$) requires *m/z* 325.2172, found *m/z* 325.2172; **IR** (film) ν_{max}/cm^{-1}: 2928, 2857, 1729 (C=O), 1368, 1147, 757.

6.3.3.22 Synthesis and characterisation of 2.108c

tert-butyl *(S)*-3-(propylthio)hept-6-enoate

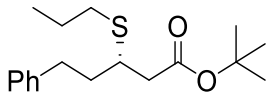


According to General Procedure L, to a solution *tert*-butyl (*E*)-hepta-2,6-dienoate **2.107c** (36.4 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 48 h. The product was purified by FCC (99:1 PE: Et_2O) to afford **2.108c** the title compound as a colourless oil in 84% yield (43.2 mg) and 90% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ = 230 nm, 1.0 mL/min, t (major) = 9.73 min, t (minor) = 11.36 min]. $\mathbf{[\alpha]_D^{23}}$ = -6.4 (*c 0.9*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1 H, $CH_2=C\underline{H}$), 5.03 (dt, H = 17.0, 1.5 Hz, 1 H, $C\underline{H_A}H_B=CH$), 4.96 (dt, *J* = 10.0, 2.0 Hz, 1 H, $CH_A\underline{H_B}=CH$), 2.99 (qd, *J* = 7.5, 5.5 Hz, 1 H, $C\underline{H}CH_2C=O$), 2.54 - 2.41 (m, 4 H, $C\underline{H}_2S$ and $CHC\underline{H}_2C=O$), 2.23 - 2.17 (m, 2 H, $CH_2=CHC\underline{H}_2$), 1.71 - 1.54 (m, 4 H, $C\underline{H}_2CH_2S$ and $CH_2=CHCH_2C\underline{H}_2$), 1.44 (s, 9 H, $C(C\underline{H}_3)_3$), 0.97 (t, *J* = 7.5 Hz, 3 H,

$C\underline{H}_3CH_2CH_2S$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.1 ($\underline{C}$=O), 138.1 (CH_2=$\underline{C}$H), 115.2 ($\underline{C}H_2$=CH), 80.8 (O$\underline{C}(CH_3)_3$), 42.5 (CH$\underline{C}H_2$C=O), 41.5 ($\underline{C}$HCH$_2$C=O), 34.3 (CH_2=CHCH$_2\underline{C}H_2$), 32.8 ($\underline{C}H_2$S), 31.1 (CH_2=CH$\underline{C}H_2$), 28.2 (C($\underline{C}H_3)_3$), 23.2 ($CH_3\underline{C}H_2CH_2S$), 13.7 ($\underline{C}H_3CH_2CH_2S$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{14}H_{26}O_2NaS$) requires *m/z* 281.1546, found *m/z* 281.1533. **IR** (film) ν_{max}/cm^{-1}: 2967, 2931, 1727 (C=O), 1367, 1250, 1144, 909 (C=C), 731.

6.3.3.23 Synthesis and characterisation of 2.108d

tert-butyl *(S)*-5-phenyl-3-(propylthio)pentanoate

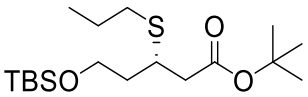


According to General Procedure L, to a solution *tert*-butyl (*E*)-5-phenylpent-2-enoate **2.107d** (46.4 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.108d** as a colourless oil in 88% yield (54.0 mg) and 88% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ = 210 nm, 1.0 mL/min, t (major) = 17.39 min, t (minor) = 20.08 min]. **$[\alpha]_D^{23}$** = -6.6 (*c 1.1*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.22 - 7.20 (m, 2 H, Ar$\underline{H}$), 7.13 - 7.09 (m, 3 H, Ar$\underline{H}$), 2.96 - 2.93 (qd, *J* = 7.5, 5.5 Hz, 1 H, C$\underline{H}$CH$_2$C=O), 2.76 - 2.62 (m, 2 H, PhC$\underline{H}_2$), 2.50 - 2.38 (m, 4 H, CHC$\underline{H}_2$C=O and C$\underline{H}_2$S), 1.85-1.74 (m, 2 H, PhCH$_2$C$\underline{H}_2$), 1.55 - 1.50 (m, 2 H, $CH_3C\underline{H}_2CH_2S$), 1.37 (s, 9 H, C(C$\underline{H}_3)_3$), 0.92 (t, *J*

= 7.5 Hz, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.0 (<u>C</u>=O), 141.9 (Ar<u>C</u>), 128.5 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 80.8 (O<u>C</u>(CH$_3$)$_3$), 42.5 (CH<u>C</u>H$_2$C=O), 41.6 (<u>C</u>HCH$_2$C=O), 36.8 (Ph<u>C</u>H$_2$), 33.1 (PhCH$_2$<u>C</u>H$_2$), 32.7 (CH$_3$CH$_2$<u>C</u>H$_2$S), 28.2 (C(<u>C</u>H$_3$)$_3$), 23.2 (CH$_3$<u>C</u>H$_2$CH$_2$S),13.7 (<u>C</u>H$_3$CH$_2$CH$_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{18}H_{28}O_2NaS$) requires *m/z* 331.1702, found *m/z* 331.1702. **IR** (film) ν_{max}/cm^{-1}: 2964, 1726 (C=O), 1454, 1141, 748, 693.

6.3.3.24 Synthesis and characterisation of 2.108e

<u>*tert*-butyl *(S)*-5-((tert-butyldimethylsilyl)oxy)-3-(propylthio)pentanoate</u>

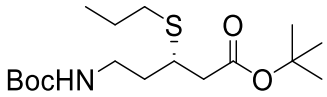


According to General Procedure L, to a solution of *tert*-butyl (*E*)-5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoate **2.107e** (57.2 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.108e** as a colourless oil in 97% yield (70.0 mg) and 87% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ = 230 nm, 1.0 mL/min, t (major) = 15.25 min, t (minor) = 17.40 min]. **$[\alpha]_D^{23}$** = -6.8 (*c 1.2*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.80 - 3.71 (m, 2 H, C<u>H</u>$_2$OTBS), 3.19 - 3.12 (m, 1 H, C<u>H</u>CH$_2$C=O), 2.56 - 2.49 (m, 4 H, CHC<u>H</u>$_2$C=O and C<u>H</u>$_2$S), 1.84 - 1.68 (m, 2 H, C<u>H</u>$_2$CH$_2$OTBS), 1.60 (sxt, *J* = 7.5 Hz, 2 H, C<u>H</u>$_2$CH$_2$S), 1.46 (s, 9 H, OC(C<u>H</u>$_3$)$_3$), 0.98 (t, *J* = 7.5 Hz, 3 H, CH$_2$C<u>H</u>$_3$), 0.89

(s, 9 H, SiC($C\underline{H}_3$)$_3$), 0 (s, 6 H, Si($C\underline{H}_3$)$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.0 ($\underline{C}$=O), 80.7 (O$\underline{C}$(CH_3)$_3$), 60.5 ($\underline{C}H_2$OTBS), 42.7 (CH$\underline{C}H_2$C=O), 38.8 ($\underline{C}$HCH$_2$C=O), 38.2 ($\underline{C}H_2CH_2$OTBS), 32.9 ($\underline{C}H_2$S), 28.2 (OC($\underline{C}H_3$)$_3$), 26.1 (SiC($\underline{C}H_3$)$_3$), 23.3 ($CH_3\underline{C}H_2CH_2$S), 18.4 (Si$\underline{C}$(CH_3)$_3$), 13.7 ($\underline{C}H_3CH_2CH_2$S), -5.2 (Si($\underline{C}H_3$)$_2$); **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{18}H_{39}O_3SSi$) requires *m/z* 363.2384, found *m/z* 363.2376. **IR** (film) ν_{max}/cm^{-1}: 2958, 2930, 2858, 1731 (C=O), 1255, 1147, 1100, 836, 776, 735.

6.3.3.25 Synthesis and characterisation of 2.108f

<u>*tert*-butyl *(S)*-5-((tert-butoxycarbonyl)amino)-3-(propylthio)pentanoate</u>

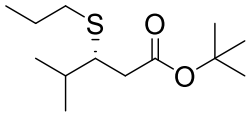


According to General Procedure L, to a solution of tert-butyl (*E*)-5-((tert-butoxycarbonyl)amino)pent-2-enoate **2.107f** (54.2 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.60 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.108f** as a colourless oil in 81% yield (56.0 mg) and 87% ee [determined by HPLC, chiralpak AD-H, hexane/isopropanol 99:1, λ = 210 nm, 1.0 mL/min, t (minor) = 17.56 min, t (major) = 18.79 min]. **$[\alpha]_D^{23}$** = -7.3 (*c 0.8*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 4.77 (br. s, 1 H, N$\underline{H}$), 3.26 - 3.23 (m, 2 H, $C\underline{H}_2$NHBoc), 3.02 - 2.98 (m, 1 H, C$\underline{H}CH_2$C=O), 2.55 - 2.43 (m, 4 H, CHC$\underline{H}_2$C=O and C$\underline{H}_2$S), 1.81 - 1.62 (m, 2 H, $\underline{C}H_2CH_2$NHBoc),

1.61 - 1.53 (m, 2 H, C$\underline{H}_2$CH$_2$S), 1.44 (s, 9 H, one of NHCOC(C$\underline{H}_3$)$_3$ and COOC(C$\underline{H}_3$)$_3$), 1.42 (s, 9 H, one of NHCOOC(C$\underline{H}_3$)$_3$ and COOC(C$\underline{H}_3$)$_3$), 0.96 (t, *J* = 7.5 Hz, 3 H, C$\underline{H}_3$CH$_2$CH$_2$S); **^{13}C NMR** (CDCl$_3$, 100 MHz) δ (ppm): 171.0 (CH$_2\underline{C}$=O), 156.0 (NH$\underline{C}$=O), 81.0 (CH$_2$COO$\underline{C}$(CH$_3$)$_3$), 79.3 (NHCOO$\underline{C}$(CH$_3$)$_3$), 42.4 (CH$\underline{C}$H$_2$C=O), 39.5 ($\underline{C}$HCH$_2$C=O), 38.5 ($\underline{C}$H$_2$NHBoc), 34.9 ($\underline{C}$H$_2$CH$_2$NHBoc), 32.6 ($\underline{C}$H$_2$S), 28.5 (one of NHCOOC($\underline{C}$H$_3$)$_3$ and COOC($\underline{C}$H$_3$)$_3$), 28.2 (one of NHCOOC($\underline{C}$H$_3$)$_3$ and COOC($\underline{C}$H$_3$)$_3$), 23.2 (CH$_3\underline{C}$H$_2$CH$_2$S), 13.7 ($\underline{C}$H$_3$CH$_2$CH$_2$S); **HRMS** (EI+) mass calculated for [M+Na]$^+$ (C$_{17}$H$_{33}$O$_4$NaS) requires *m/z* 370.2023, found *m/z* 370.2019; **IR** (film) ν_{max}/cm^{-1}: 3470 (NH), 2979, 2932, 1713 (C=O), 1504, 1366, 1249, 1144, 736.

6.3.3.26 Synthesis and Characterisation of 2.108g

tert-butyl *(R)*-4-methyl-3-(propylthio)pentanoate

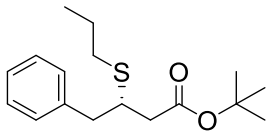


According to General Procedure L, to a solution of *tert*-butyl (*E*)-4-methylpent-2-enoate **2.107g** (36 mg, 0.1 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.2 mL Et$_2$O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE: Et$_2$O) to afford **2.108g** as a colourless oil in 92% yield (45.2 mg) and 74% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ = 220 nm, 1.0 mL/min, t (major) = 6.58 min, t (minor) = 7.30 min]. **$[\alpha]_D^{25}$** = +45.0 (*c 0.5*, CHCl$_3$); **^{1}H NMR**

($CDCl_3$, 400 MHz) δ (ppm): 2.96 - 2.91 (m, 1 H, C<u>H</u>CH_2), 2.53 (t, *J* = 7.5 Hz, 2 H, $CH_2C\underline{H_2}S$), 2.52 (dd, *J* = 15.0, 6.5 Hz, 1 H, $CHC\underline{H_A}H_BC{=}O$), 2.41 (dd, *J* = 15.5, 9.0 Hz, 1 H, $CHCH_A\underline{H_B}C{=}O$), 1.94 - 1.88 (m, 1 H, C<u>H</u>$(CH_3)_2$), 1.65 - 1.56 (m, 2 H, $CH_3C\underline{H_2}CH_2S$), 1.47 (s, 9 H, C($C\underline{H_3}$)$_3$), 1.01 - 0.94 (m, 9 H, $C\underline{H_3}CH_2CH_2S$ and CH($C\underline{H_3}$)$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.6 (<u>C</u>=O), 80.5 (O<u>C</u>$(CH_3)_3$), 49.3 (<u>C</u>HCH_2C=O), 40.1 (CH<u>C</u>H_2C=O), 34.6 ($CH_3CH_2C\underline{H_2}S$), 32.4 (<u>C</u>H$(CH_3)_2$), 28.1 (C(<u>C</u>$H_3$)$_3$), 23.2 ($CH_3\underline{C}H_2CH_2S$), 19.8 and 18.9 (<u>C</u>H_3CH<u>C</u>H_3), 13.6 (<u>C</u>$H_3CH_2CH_2S$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{13}H_{26}O_2NaS$) requires *m/z* 269.1546, found *m/z* 269.1546; **IR** (film) ν_{max}/cm^{-1}: 2963, 1730 (C=O), 1367, 1147, 909, 733.

6.3.3.27 Synthesis and characterisation of 2.108h

<u>*tert*-butyl *(S)*-4-phenyl-3-(propylthio)butanoate</u>

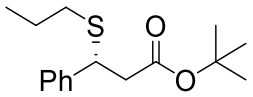


According to General Procedure L, to a solution *tert*-butyl *(E)*-5-phenylpent-2-enoate **2.107h** (43.6 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE: Et_2O) to afford **2.108h** as a colourless oil in 89% yield (52.2 mg) and 75% ee [determined by HPLC, chiralpak OD, hexane/isopropanol 100:0, λ = 220 nm, 1.0 mL/min, t

(major) = 28.04 min, t (minor) = 32.25 min]. **$[\alpha]_D^{25}$** = +6.7 (*c 1.4*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.24 - 7.13 (m, 5 H, Ar<u>H</u>), 3.17 (quin, *J* = 7.0 Hz, 1 H, C<u>H</u>CH_2C=O), 2.87 - 2.77 (m, 2 H, PhC<u>H_2</u>), 2.43 - 2.32 (m, 4 H, CHC<u>H_2</u>C=O and C<u>H_2</u>S), 1.52 - 1.43 (m, 2 H, C<u>H_2</u>CH_2S), 1.38 (s, 9 H, C(C<u>H_3</u>)$_3$), 0.86 (t, *J* = 7.5 Hz, 3 H, C<u>H_3</u>CH_2CH_2S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.9 (<u>C</u>=O), 139.0 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 126.5 (Ar<u>C</u>H), 80.8 (O<u>C</u>$(CH_3)_3$), 43.3 (<u>C</u>HCH_2C=O), 41.9 (Ph<u>C</u>H_2), 41.2 (CH<u>C</u>H_2C=O), 33.2 (<u>C</u>H_2S), 28.1 (C(<u>C</u>$H_3)_3$), 23.0 (CH_3<u>C</u>H_2CH_2S), 13.5 (<u>C</u>$H_3CH_2CH_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{17}H_{26}O_2NaS$) requires *m/z* 317.1546, found *m/z* 317.1546; **IR** (film) ν_{max}/cm^{-1}: 2965, 1726 (C=O), 1367, 1140, 1249, 733, 700.

6.3.3.28 Synthesis and characterisation of 2.108j

<u>*tert*-butyl *(R)*-3-phenyl-3-(propylthio)propanoate</u>

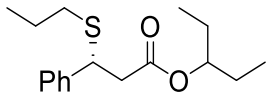


According to General Procedure L, to a solution of *tert*-butyl cinnamate **2.107j** (40.8 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.108j** as a colourless oil in 98% yield (55 mg) and 68% ee [determined by HPLC, chiralpak AD-H, hexane/isopropanol 95:5, λ 220 nm, 1.0 mL/min, t (minor) = 4.02 min, t (major) = 4.27 min]. **$[\alpha]_D^{25}$** = +60.2 (*c 1.7*, $CHCl_3$); **^{1}H NMR**

($CDCl_3$, 400 MHz) δ (ppm): 7.27 - 7.21 (m, 5 H, Ar<u>H</u>), 4.13 (t, *J* = 7.5 Hz, 1 H, C<u>H</u>CH_2), 2.73 (dd, *J* = 15.0, 7.5 Hz, 1 H, CHC<u>H_A</u>H_BC=O), 2.67 (dd, *J* = 15.0, 8.5 Hz, 1 H, CHCH_A<u>H_B</u>C=O), 2.28 - 2.17 (m, 2 H, C<u>H_2</u>S), 1.48 - 1.43 (m, 2 H, C<u>H_2</u>CH_2S), 1.24 (s, 9 H, OC(C<u>H_3</u>)$_3$), 0.83 (t, *J* = 7.5 Hz, 3 H, C<u>H_3</u>CH_2CH_2S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.0 (<u>C</u>=O), 141.6 (Ar<u>C</u>), 128.4 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 80.8 (O<u>C</u>$(CH_3)_3$), 45.5 (Ph<u>C</u>H), 42.7 (CH<u>C</u>H_2C=O), 33.2 (CH_2<u>C</u>H_2S), 27.9 (OC(<u>C</u>H_3)$_3$), 22.6 (<u>C</u>H_2CH_2S), 13.5 (<u>C</u>$H_3CH_2CH_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{16}H_{24}O_2NaS$) requires *m/z* 303.1389, found *m/z* 303.1389; **IR** (film) ν_{max}/cm^{-1}: 2966, 1728 (C=O), 1367, 1142, 699.

6.3.3.29 Synthesis and characterisation of 2.108k

<u>pentan-3-yl *(R)*-3-phenyl-3-(propylthio)propanoate</u>

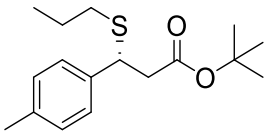


According to General Procedure L, to a solution of pentan-3-yl cinnamate **2.107k** (50.4 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.108k** as a colourless oil in 89% yield (52.3 mg) and 51% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 99:1, λ 230 nm, 1.0 mL/min, t (minor) = 5.11 min, t (major) = 5.48 min]. **$[\alpha]_D^{25}$** = +64.2 (*c 1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.41 - 7.20 (m, 5 H, Ar<u>H</u>), 4.70 (quin, *J* = 6.0

Hz, 1 H, C<u>H</u>CH_2CH_3), 4.28 (t, *J* = 8.0 Hz, 1 H, C<u>H</u>CH_2C=O), 2.89 (dd, *J* = 8.0, 1.5 Hz, 2 H, CHC<u>H</u>$_2$C=O), 2.27 - 2.18 (m, 2 H, C<u>H</u>$_2$S), 1.61 - 1.55 (m, 2 H, C<u>H</u>$_2$$CH_2$S), 1.47 - 1.29 (m, 4 H, C<u>H</u>$_2$CHC<u>H</u>$_2$), 0.91 (t, *J* = 7.5 Hz, 3 H, C<u>H</u>$_3$$CH_2$$CH_2$S), 0.82 (t, *J* = 7.5 Hz, 3 H, one of CH(CH_2C<u>H</u>$_3$)$_2$), 0.71 (t, *J* = 7.5 Hz, 3 H, one of CH(CH_2C<u>H</u>$_3$)$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.7 (<u>C</u>=O), 141.6 (Ar<u>C</u>), 128.5 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 127.3 (Ar<u>C</u>H), 76.8 (O<u>C</u>H), 45.3 (Ph<u>C</u>H), 41.8 (CH<u>C</u>H_2C=O), 33.2 (CH_2<u>C</u>H_2S), 26.6 and 26.3 (CH(<u>C</u>H_2CH_3)$_2$), 22.6 (<u>C</u>$H_2$$CH_2$S), 13.5 (<u>C</u>$H_3$$CH_2$$CH_2$S), 9.7 and 9.6 (CH($CH_2$<u>C</u>$H_3$)$_2$) ; **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{17}H_{26}O_2NaS$) requires *m/z* 317.1557, found *m/z* 317.1545; **IR** (film) ν_{max}/cm^{-1}: 2966, 1729 (C=O), 1254, 754, 699.

6.3.3.30 Synthesis and characterisation of 2.108l

<u>*tert*-butyl *(R)*-3-(propylthio)-3-(p-tolyl)propanoate</u>

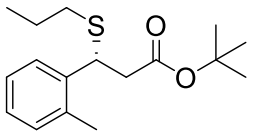


According to General Procedure L, to a solution of *tert*-butyl *(E)*-3-(p-tolyl)acrylate **2.107l** (43.6 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.108l** as a colourless oil in 97% yield (57.2 mg) and 65% ee [determined by HPLC, chiralpak AS-H, hexane/isopropanol 100:0, λ = 230 nm, 1.0

mL/min, t (major) = 18.71 min, t (minor) = 21.59 min]. **$[\alpha]_D^{25}$** = +65.5 (*c 1.3*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.14 - 7.02 (m, 4 H, ArH), 4.10 (t, *J* = 8.0 Hz, 1 H, CHCH$_2$C=O), 2.74 - 2.57 (m, 2 H, CHCH$_2$C=O), 2.24 (s, 3 H, ArCH$_3$), 2.30 (td, *J* = 7.5, 3.0 Hz, 2 H, CH$_2$S), 1.48 - 1.38 (m, 2 H, CH$_2$CH$_2$S), 1.26 (s, 9 H, C(CH$_3$)$_3$), 0.83 (t, *J* = 7.5 Hz, 3 H CH$_3$CH$_2$CH$_2$S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.1 (C=O), 138.6 (ArC), 136.8 (ArC), 129.1 (ArCH), 127.6 (ArCH), 80.8 (C(CH$_3$)$_3$), 45.2 (CHCH$_2$C=O), 42.8 (CHCH$_2$C=O), 33.2 (CH$_2$S), 27.9 (C(CH$_3$)$_3$), 22.6 (CH$_2$CH$_2$S), 21.1 (ArCH$_3$), 13.5 (CH$_3$CH$_2$CH$_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{17}H_{26}O_2NaS$) requires *m/z* 317.1746, found *m/z* 317.1745. **IR** (film) ν_{max}/cm^{-1}: 2978, 1708 (C=O), 1148, 907, 730.

6.3.3.31 Synthesis and characterisation of 2.108m

tert-butyl *(R)*-3-(propylthio)-3-(p-tolyl)propanoate

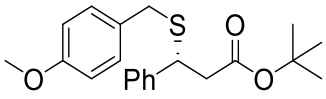


According to General Procedure L, to a solution of *tert*-butyl *(E)*-3-(o-tolyl)acrylate **2.107m** (43.6 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 96 h. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.108m** as a colourless oil in 80% yield (47 mg) and 13% ee [determined by HPLC, chiralpak AD-H, hexane/isopropanol 100:0, λ = 220 nm, 1.0

mL/min, t (major) = 7.96 min, t (minor) = 11.47 min]. **$[\alpha]_D^{25}$** = +21.0 (*c 2.4*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.29 - 7.27 (m, 1 H, ArH), 7.10 - 7.03 (m, 3 H, ArH), 4.42 (t, *J* = 8.0 Hz, 1 H, CHCH$_2$C=O), 2.81 - 2.71 (m, 2 H, CHCH$_2$C=O), 2.35 (s, 3 H, ArCH$_3$), 2.30 (td, *J* = 7.5, 3.0 Hz, 2 H, CH$_2$S), 1.49 - 1.43 (m, 2 H, CH$_2$CH$_2$S), 1.22 (s, 9 H, C(CH$_3$)$_3$), 0.85 (t, *J* = 7.5 Hz, 3 H, CH$_3$CH$_2$CH$_2$S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.3 (C=O), 139.4 (ArC), 135.8 (ArC), 130.4 (ArCH), 127.0 (ArCH), 126.8 (ArCH), 126.2 (ArCH), 80.8 (C(CH$_3$)$_3$), 42.4 (CHCH$_2$C=O), 41.0 (CHCH$_2$C=O), 33.1 (CH$_2$S), 27.9 (C(CH$_3$)$_3$), 22.9 (CH$_2$CH$_2$S), 19.5 (ArCH$_3$), 13.6 (CH$_3$CH$_2$CH$_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{17}H_{26}O_2NaS$) requires *m/z* 317.1746, found *m/z* 317.1745; **IR** (film) ν_{max}/cm^{-1}: 2969, 1727 (C=O), 1145, 907, 730.

6.3.3.32 Synthesis and characterisation of 2.109

tert-butyl *(R)*-3-((4-methoxybenzyl)thio)-3-phenylpropanoate

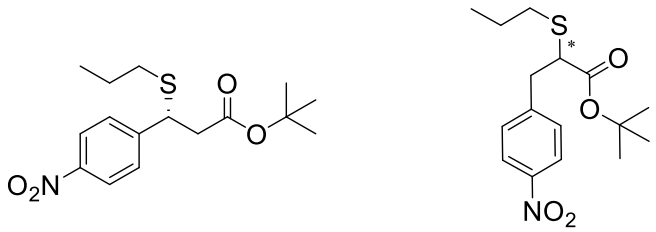


According to General Procedure L, to a solution of *tert*-butyl cinnamate (40.0 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 4-Methoxy-α-toluenethiol (84 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 72 h. The product was purified FCC (99:1 PE: Et_2O) to afford **2.109** as a colourless oil in 98% yield (70.0 mg) and 76% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ = 240 nm, 0.5 mL/min, t (major) = 12.18

min, t (minor) = 13.15 min]. **$[\alpha]_D^{23}$** = +89.0 (*c 1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.27 - 7.26 (m, 4 H, Ar<u>H</u>), 7.2 - 7.19 (m. 1 H, Ar<u>H</u>), 7.09 (d, *J* = 8.5 Hz, 2 H, Ar<u>H</u>), 6.77 (d, *J* = 8.5 Hz, 2 H, Ar<u>H</u>), 4.06 (dd, *J* = 8.5 Hz, 7.0 Hz, 1 H, C<u>H</u>CH_2C=O), 3.74 (s, 3 H, O<u>C</u>H_3), 3.48 - 3.36 (m, 2 H, C<u>H</u>$_2$S), 2.76 - 2.64 (m, 2 H, CHC<u>H</u>$_2$C=O), 1.24 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 169.9 (<u>C</u>=O), 158.7 (Ar<u>C</u>), 141.3 (Ar<u>C</u>), 130.1 (Ar<u>C</u>H), 129.9 (Ar<u>C</u>), 128.5 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 114.0 (Ar<u>C</u>H), 80.9 (<u>C</u>(CH$_3$)$_3$), 55.4 (O<u>C</u>H$_3$), 45.3 (<u>C</u>HCH$_2$C=O), 42.7 (CH<u>C</u>H$_2$C=O), 35.1 (<u>C</u>H$_2$S), 28.0 (C(<u>C</u>H$_3$)$_3$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{21}H_{26}O_3NaS$) requires *m/z* 381.1495, found *m/z* 381.1495; **IR** (film) ν_{max}/cm^{-1}: 2977, 1729 (C=O), 1511, 1249, 1140.

5.3.3.33 Synthesis and characterisation of 2.110a and 2.110b

<u>*tert*-butyl 3-(4-nitrophenyl)-3-(propylthio)propanoate and *tert-butyl 3-(4-nitrophenyl)-2-(propylthio)-2λ^3-propanoate*</u>



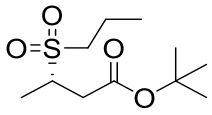
According to General Procedure L, to a solution of *tert*-butyl *(E)*-3-(4-nitrophenyl)acrylate **2.107n** (49.8 mg, 0.2 mmol, 1.0 eq) and BIMP catalyst (0.02 mmol, 0.1 eq) in 0.4 mL Et_2O was added 1-propanethiol (54.4 µL, 0.6 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C for 12 h. The product was purified by FCC

(99:1 PE: Et_2O) to afford **2.110a** and **2.110b** as an inseparable colourless oil in >99% yield (65 mg, 5:4 ratios, 71% ee for **2.110a** and 29% ee for **2.110b**)[xxiii] [determined by HPLC, chiralpak AD-H, hexane/isopropanol 100:0, λ = 230 nm, 1.0 mL/min, **2.110b**, t (minor) = 14.38 min, t (major) = 19.11 min, **2.110a**, t (minor) = 16.61 min, t (major) = 17.07 min]; **^{1}H NMR** of **2.110a** ($CDCl_3$, 400 MHz) δ (ppm): 8.22 - 8.13 (m, 2 H, Ar<u>H</u>), 7.42 (d, *J* = 9.0 Hz, 2 H, Ar<u>H</u>), 3.42 (dd, *J* = 9.0, 6.5 Hz, 1 H, C<u>H</u>CH_2), 3.27 (dd, *J* = 14.0, 9.0 Hz, 1 H, CHC<u>H_A</u>H_B), 3.03 (dd, *J* = 14.0, 6.5 Hz, 1 H, $CHCH_A$<u>H_B</u>), 2.70-2.57 (m, 2 H, C<u>H_2</u>S), 1.79-1.53 (m, 2 H, C<u>H_2</u>CH_2S), 1.42 (s, 9 H, C(C<u>H_3</u>)$_3$), 0.98 (t, *J* = 7.5 Hz, C<u>H_3</u>CH_2CH_2S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.8 (<u>C</u>=O), 152.3 (Ar<u>C</u>), 146.1 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 123.6 (Ar<u>C</u>H), 81.9 (<u>C</u>$(CH_3)_3$), 48.2 (<u>C</u>HCH_2C=O), 37.6 (CH<u>C</u>H_2C=O), 33.7 (<u>C</u>H_2S), 27.9 (C(<u>C</u>H_3)$_3$), 22.6 (<u>C</u>H_2CH_2S), 13.4 (<u>C</u>$H_3CH_2CH_2$S); Observable NMR signals of **2.110b**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.54 (d, *J* = 9.0 Hz, 2 H, Ar<u>H</u>), 4.30 (dd, *J* = 9.0, 6.5 Hz, 1 H, C<u>H</u>CH_2), 2.87 (dd, *J* = 15.5, 6.5 Hz, 1 H, CHC<u>H_A</u>H_B), 2.77 (dd, *J* = 15.5, 9.0 Hz, 1 H, $CHCH_A$<u>H_B</u>), 2.38 - 2.26 (m, 2 H, C<u>H_2</u>S), 1.35 (s, 9 H, C(C<u>H_3</u>)$_3$), 0.93 (t, *J* = 7.5 Hz, C<u>H_3</u>CH_2CH_2S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 169.3 (<u>C</u>=O), 151.7(Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 123.7 (Ar<u>C</u>H), 44.9 (<u>C</u>HCH_2), 36.5 (CH<u>C</u>H_2), 33.4 (<u>C</u>H_2S), 22.5 (<u>C</u>H_2CH_2S), 13.2 (<u>C</u>$H_3CH_2CH_2$S); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{16}H_{23}O_4NNaS$) requires *m/z* 348.1200, found *m/z* 348.1240; **IR** (film) ν_{max}/cm^{-1}: 2964, 1721 (C=O), 1520, 1345, 1142, 849, 748.

[xxiii] **$[\alpha]_D$** was not measured as it is a mixture of two compounds.

6.3.3.34 Synthesis and characterisation of 2.114

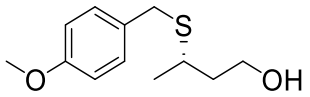
tert-butyl *(S)*-3-(propylsulfonyl)butanoate



To a solution of 3-chloroperbenzoic acid (86 mg, 0.5 mmol, 2.5 eq) in CH_2Cl_2 (1 mL) was added *tert*-butyl *(S)*-3-(propylthio)butanoate **2.77d** (43.6 mg, 0.2 mmol, 1.0 eq) in CH_2Cl_2 (1 mL) at 0 ˚C. The reaction was stirred at 0 ˚C for 2 h, and then quenched with $NaHCO_3$ (2 mL). The mixture was extracted with Et_2O (5 mL) three times and the organic layers combined, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The crude was purified by FCC to afford the title compound **2.114** as a colourless oil in 96% yield (48 mg) and 91% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 95:5, λ = 220 nm, 1.0 mL/min, t (minor) = 9.88 min, t (major) = 13.54 min]. **$[\alpha]_D^{23}$** = +4.6 (*c 1.1*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.50 - 3.41 (m, 1 H, C$\underline{H}$$CH_3$), 2.97 (dd, *J* = 16.5, 4.5 Hz, 1 H, CHC$\underline{H}_A$$H_B$), 2.92 (t, *J* = 8.0 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.39 (dd, *J* = 16.5, 9.5 Hz, 1 H, $CHCH_A\underline{H}_B$), 1.96 - 1.88 (m, 2 H, $CH_3C\underline{H}_2CH_2S$), 1.46 (s, 9 H, $OC(C\underline{H}_3)_3$), 1.41 (d, *J* = 7.0 Hz, 3 H, $CHC\underline{H}_3$), 1.08 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 169.6 ($\underline{C}$=O), 82.0 ($O\underline{C}(CH_3)_3$), 54.1 ($\underline{C}HCH_3$), 52.0 ($\underline{C}H_2S$), 35.3 ($CH\underline{C}H_2$), 28.2 ($C(\underline{C}H_3)_3$), 15.2 ($\underline{C}H_2CH_2S$), 14.0 ($\underline{C}H_3CH$), 13.4 ($\underline{C}H_3CH_2CH_2S$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{11}H_{22}O_4NaS$) requires *m/z* 273.1131, found *m/z* 273.1132; **IR** (film) ν_{max}/cm^{-1}: 2980, 2360, 1729 (C=O), 1155, 754.

6.3.3.35 Synthesis and characterisation of 2.115

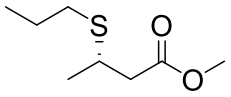
(S)-3-((4-methoxybenzyl)thio)butan-1-ol



To a solution of *tert*-butyl *(S)*-3-((4-methoxybenzyl)thio)butanoate **2.106h** (28mg, 0.095 mmol, 1.0 eq) in toluene (1 mL) at –60˚C was added DIBAL (1 M in toluene, 0.2 mL, 0.2 mmol, 2.2 eq) dropwise. The reaction was stirred at –60˚C for 2 h and then quenched with saturated NH_4Cl (aq), extracted three times with CH_2Cl_2 (5 mL). The organic phase was combined, dried (Na_2SO_4), filtered and concentrated *in vacuo.* The crude mixture was purified by FCC to afford the title compound **2.115** as colourless oil 93% yield (20 mg) and 87% ee [determined by HPLC, chiralpak ADH, hexane/isopropanol 97:3, λ = 220 nm, 1.0 mL/min, t (minor) = 37.72 min, t (major) = 39.48 min]. **$[\alpha]_D^{23}$** = - 0.2 (*c 1.0*, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.28 (d, *J* = 8.5 Hz, 2 H, Ar<u>H</u>), 6.87 (d, *J* = 8.5 Hz, 2 H, Ar<u>H</u>), 3.82 (s, 3 H, OC<u>H</u>$_3$), 3.75 (d, *J* = 3.0 Hz, 2 H, C<u>H</u>$_2$S), 3.78 - 3.66 (m, 2 H, C<u>H</u>$_2$OH), 2.84 (sxt, *J* = 7.0 Hz, 1 H, C<u>H</u>CH$_3$), 1.79 (q, *J* = 6.5 Hz, 2 H, C<u>H</u>$_2$CH$_2$OH), 1.34 (d, *J* = 7.0 Hz, 3 H, CHC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 158.6 (Ar<u>C</u>), 130.4 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 113.9 (Ar<u>C</u>H), 60.6 (<u>C</u>H$_2$OH), 55.3 (O<u>C</u>H$_3$), 39.0 (<u>C</u>H$_2$CH$_2$OH), 36.7 (<u>C</u>HCH$_3$), 34.3 (<u>C</u>H$_2$S), 21.7 (<u>C</u>H$_3$CH); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{12}H_{18}O_2NaS$) requires *m/z* 249.0920, found *m/z* 249.0921. **IR** (film) ν_{max}/cm^{-1}: 3390 (OH), 2957, 1510, 1236, 1032, 831, 734.

6.3.3.36 Synthesis and characterisation of 2.77a

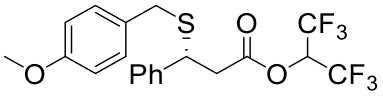
methyl *(S)*-3-(propylthio)butanoate



To a solution of *tert*-butyl *(S)*-3-(propylthio)butanoate **2.77d** (43.6 mg, 0.2 mmol, 1.0 eq) in 1.0 mL Et_2O was added trifluoroacetic acid (0.1 mL) at 0 °C dropwise. The reaction mixture was warmed to rt and stirred for 4 h, and the volatiles removed by N_2 stream. 5mL of saturated $NaHCO_3$ (aq) was added into the mixture and the organic phase was extracted using Et_2O (2 x 5 mL), washed with brine (5 mL), dried ($NaSO_4$), filtered, and concentrated *in vacuo* to afford the crude mixture, which was used in the next step without purification. The carboxylic acid intermediate was dissolve in MeOH (5 mL). To the solution was added $SOCl_2$ (0.12 mL, 0.44 mmol, 2.2 eq) at 0˚C. The reaction was warmed up to rt and stirred overnight. The reaction mixture was then quenched with saturated $NaHCO_3$ (aq) and then extracted three times with CH_2Cl_2 (5 mL). The organic phase was combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by FCC (99:1 PE:Et_2O) to afford the title compound **2.77a** as a colourless oil in 78 % yield (27.5 mg) and 89% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ = 220 nm, 1.0 mL/min, t (major) = 19.96 min, t (minor) = 23.58 min]; $\mathbf{[\alpha]_D^{25}}$ = + 9.8 (c *0.9*, $CHCl_3$). Other data are the same as those reported in section 6.3.3.2.

6.3.3.37 Synthesis and characterisation of 2.116

1,1,1,3,3,3-hexafluoropropan-2-yl *(R)*-3-((4-methoxybenzyl)thio)-3-phenylpropanoate

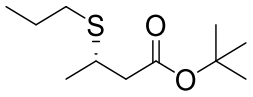


To a solution of *tert*-butyl *(R)*-3-((4-methoxybenzyl)thio)-3-phenylpropanoate **2.109** (68.0 mg, 0.19 mmol, 1.0 eq) in 1.0 mL Et_2O was added trifluoroacetic acid (0.1 mL) at 0 °C dropwise. The reaction mixture was warmed to rt and stirred for 4 h, and the volatiles removed by N_2 stream. The crude mixture was dissolved in CH_2Cl_2 (5 mL). To the solution was added 4-dimethylaminopyridine (5 mg, 0.04 mmol, 0.2 eq) and N,N'-dicyclohexylcarbodiimide (49.4 mg, 0.24 mmol, 1.2 eq) and 1,1,1,3,3,3-Hexafluoro-2-propanol (0.025 mL, 0.24 mmol, 1.2 eq) at 0˚C. The reaction was warmed up to rt and stirred overnight. The reaction mixture was then filtered and then extracted with CH_2Cl_2 (5 mL× 3). The organic phase was combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by FCC (99:1 PE:Et_2O) to afford title compound **2.116** as a colourless oil in 82 % yield (70.0 mg) and 80% ee [determined by HPLC, chiralpak AS-H, hexane/isopropanol 99:1, λ = 230 nm, 1.0 mL/min, t (major) = 6.68 min, t (minor) = 11.64 min]. $\mathbf{[\alpha]_D^{23}}$ = +102.2 (*c 0.9*, $CHCl_3$), lit. -65.9 (c 0.41, CDCl3) for (S)-**2.115**;[35] **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.27 - 7.18 (m, 5 H, ArH), 7.05 (d, *J* = 8.5 Hz, 2 H, ArH), 6.75 (d, *J* = 8.5 Hz, 2 H, ArH), 5.57 (dt, *J* = 12.0, 6.0 Hz, 1 H,

C<u>H</u>(CF_3)$_2$), 4.06 (t, *J* = 8.0 Hz, 1 H, C<u>H</u>CH_2), 3.72 (s, 3 H, OC<u>H</u>$_3$), 3.48 - 3.37 (m, 2 H, CHC<u>H</u>$_2$), 2.96 (d, *J* = 8.0 Hz, 2 H, C<u>H</u>$_2$S); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 167.4 (<u>C</u>=O), 158.7 (Ar<u>C</u>), 139.8 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 129.2 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 120.2 (q, *J* = 282.0 Hz, <u>C</u>F_3), 113.9 (Ar<u>C</u>H), 66.3 (hept, *J* = 34.6 Hz, <u>C</u>H(CF_3)$_2$), 55.2 (O<u>C</u>H_3), 44.3 (<u>C</u>HCH_2C=O), 40.4 (CH<u>C</u>H_2C=O), 35.1 (<u>C</u>H_2S); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -73.3; Data consistent with reported in literature.[35]

6.3.3.38 Synthesis and Characterisation of 2.77d (Preparative Scale)

<u>*tert*-Butyl (*S*)-3-(propylsulfanyl)butanoate</u>

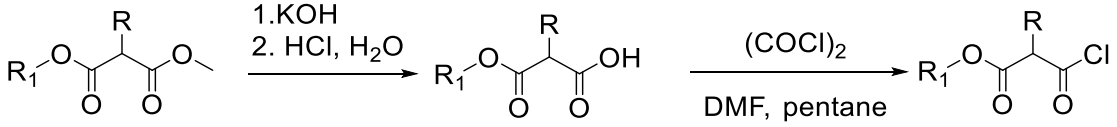


According to General Procedure L, to a solution of *tert*-butyl crotonate (1.12 mL, 7.0 mmol, 1.0 eq) and BIMP catalyst (0.07 mmol, 0.01 eq) in 1.4 mL Et_2O was added 1-propanolthiol (1.89 µL, 21.0 mmol, 3.0 eq) at 0 °C, and then stirred at 0 °C. The product was purified by FCC (99:1 PE: Et_2O) to afford the title compound **2.77d** as a colourless oil in 97% yield (1.48 g) and 88% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 100:0, λ 220 nm, 1.0 mL/min, t (major) = 9.36 min, t (minor) = 10.58 min]. All the data are consistent with those reported in section 5.3.3.4.

6.4 Enantioselective Dearomatisation

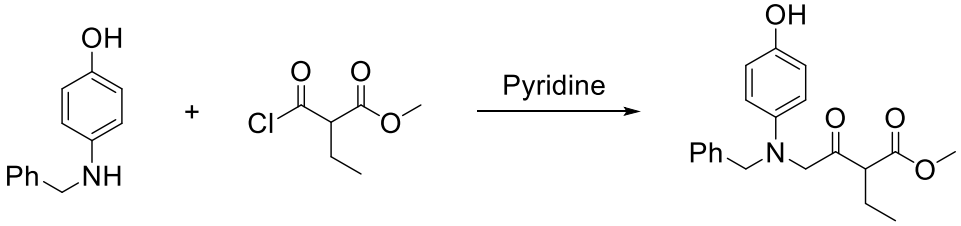
6.4.1 General Procedures

6.4.1.1 General Procedure M: Ester Hydrolysis and Synthesis of Acid Chlorides



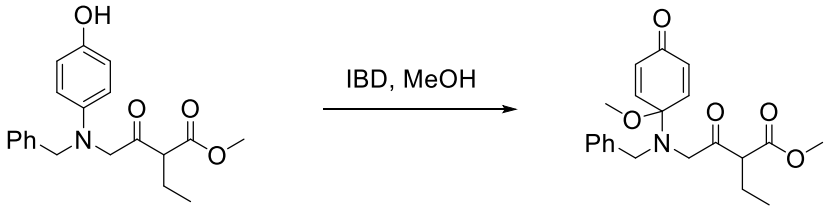
According to a literature procedure[36], a solution of KOH (1.2 eq) in MeOH (1.0 M) was added to a stirred solution of malonate (1.0 eq) in MeOH (1.0 M). The reaction mixture was stirred at rt for 21 h and then diluted with H_2O (5 mL/mmol) and extracted with Et_2O (3 x 2 mL/mmol). The organic extracts were discarded and the aqueous layer was concentrated under reduced pressure to provide the crude product, which was dissolved in 0.5M HCl (aq.) and extracted six times with CH_2Cl_2, dried ($MgSO_4$), and concentrated under reduced pressure to yield the crude acid. This crude was then directly suspended in pentane (80 mL) and anhydrous DMF (0.1 eq) and oxalyl chloride (2.4 eq) were added to the suspension. The reaction mixture was stirred at rt for 2 h. The pentane layer was separated and concentrated under reduced pressure to provide the acid chloride, which was immediately used in the next step without purification.

6.4.1.2 General Procedure N: Synthesis of malonamide



To a solution of secondary amine (1.0 eq) in CH_2Cl_2 (5 mL/mmol) and pyridine (5.0 eq) at 0 °C, ethyl methyl 2-(chlorocarbonyl)butanoate (or its derivatives, 1.05 eq) in CH_2Cl_2 (1 mL/mmol) was added dropwise over a period of 30 minutes. The resulting mixture was then stirred at room temperature for 2 - 3 hours. The reaction mixture was then treated with 2N HCl (1 mL/mmol) for 10 minutes and the aqueous phase was separated and the organic phase was washed with water (2 × 2 mL/mmol). After dried over anhydrous sodium sulfate and filtration, the solvent was removed under reduced pressure and the residue was purified by FCC (petroleum ether : EtOAc = 5: 1-2:1) to afford the amides.[37]

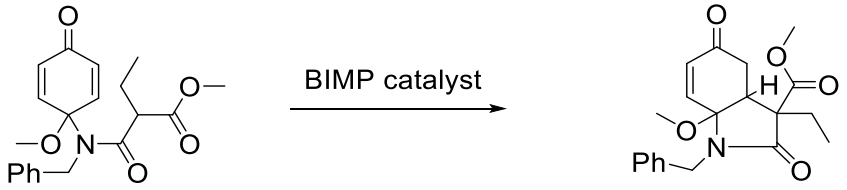
6.4.1.3 General Procedure O: Dearomatisation of Substrate Using $PhI(OAc)_2$



According to a modified literature procedure[38], IBD (iodobenzene diacetate, 1.2 eq) was added in one portion to a solution of amide (1.0 eq) in methanol (0.1 M) at 0 ºC. After stirring at 0 ºC for 1 - 2 hours, the reaction mixture was quenched with saturated $NaHCO_3$ (aq), extracted with Et_2O (3 × 2mL/mmol). The organic

layers were dried over Na_2SO_4, concentrated *in vacuo*. The crude products were purified by FCC (CH_2Cl_2:MeOH 98:2) to provide the pure product.

6.4.1.4 General Procedure P: Cyclisation

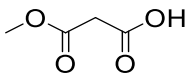


BIMP catalyst (0.01 mmol, 0.1 eq) was added into the dienone substrate (0.1 mmol, 1.0 eq) in solvent (0.5 M) at specified temperature. The reaction was followed by tlc and quenched with acetic acid in CH_2Cl_2 (0.1 M, 0.1 mL). The volatiles were removed under a stream of N_2 and the residue was purified by FCC to provide the final product.

6.4.2 Synthesis of Substrates

6.4.2.1 Synthesis and Characterisation of 3.39

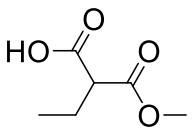
3-methoxy-3-oxopropanoic acid



According to General Procedure M, dimethyl malonate (10 mL, 88 mmol, 1.0 eq) was reacted with KOH (1.0 M, 120 mL) solution to give the title compound **3.39** as an colourless oil in 98% yield (10.2 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.81 (s, 3 H, $OC\underline{H}_3$), 3.48 (s, 2 H, $C\underline{H}_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 52.9 ($O\underline{C}H_3$), 40.5 ($\underline{C}H_2$). All data is consistent with those reported in literature.[39]

6.4.2.2 Synthesis and Characterisation of 3.40

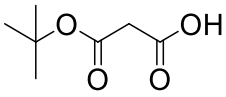
2-(methoxycarbonyl)butanoic acid



According to General Procedure M, dimethyl 2-ethylmalonate (3.2 g, 20 mmol, 1.0 eq) was reacted with KOH (24 mmol, 0.5 M in 48 mL H_2O) to give the title compound **3.40** as a colourless oil in 89% yield (2.6 g). **^{1}H NMR** ($CDCl_3$, 400 MHz): 8.51 (br. s, 1 H, O<u>H</u>), 3.76 (s, 3 H, OC<u>H</u>$_3$), 3.31 (t, *J* = 7.5 Hz, 1 H, C<u>H</u>CH_2CH_3), 1.94 (quin, *J* = 7.5 Hz, 2 H, CHC<u>H</u>$_2$CH_3), 0.97 (t, *J* = 7.5 Hz, 3 H, CHCH_2C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) 174.7 (<u>C</u>=O), 160.6 (<u>C</u>=O), 53.7 (<u>C</u>HCH_2CH_3), 52.5 (O<u>C</u>H_3), 22.6 (CH<u>C</u>H_2CH_3), 11.8 (CHCH_2<u>C</u>H_3). All data consistent with those reported in literature.[40]

6.4.2.3 Synthesis and Characterisation of 3.41

3-(*tert*-butoxy)-3-oxopropanoic acid

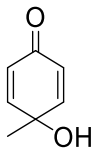


According to General Procedure J, to a solution of malonic acid (2.12 g, 20 mmol, 1.0eq) and *tert*-butyl alcohol (1.56 g, 20 mmol, 2.0 eq) in acetonitrile (60 mL) was added a solution of DCC (4.53 g, 22 mmol, 1.1 eq) in acetonitrile (22 mL). The reaction mixture was stirred for 20 min, filtered, and evaporated. The residue was

dissolved in ether (50 mL), and the ether layer was extracted with saturated $NaHCO_3$ solution (2 × 20 mL). The water solution was acidified to pH 1 by 10% HCl solution and extracted with ethyl acetate (2 × 35 mL). The ethyl acetate solution was dried and evaporated to give the title compound **3.41** as a colourless oil in 64% yield (2.05 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.37 (s, 2 H, C$\underline{H}_2$), 1.51 (s, 9 H, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.1 ($\underline{C}$=O), 166.9 ($\underline{C}$=O), 83.3 (O$\underline{C}$(CH$_3$)$_3$), 41.5 ($\underline{C}$H$_2$), 27.9 (OC($\underline{C}$H$_3$)$_3$); All data is consistent with those reported in literature.[41]

6.4.2.4 Synthesis and Characterisation of 3.11

4-hydroxy-4-methylcyclohexa-2,5-dien-1-one

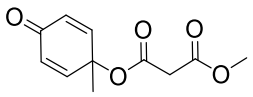


According to a modified General Procedure O, a solution of *p*-cresol (2.08 mL, 20 mmol, 1.0 eq) in H_2O (50 mL) and MeCN (150 mL) was cooled to 0 ºC and treated with $PhI(OAc)_2$ (7.08 g, 22 mmol, 1.1 eq). The reaction mixture was stirred until consumption of the starting material, then diluted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound **3.11** as a red oil in 92% yield (2.29 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 6.82 (d, *J* = 10.0 Hz, 2 H, C$\underline{H}$C(OH)C$\underline{H}$), 6.02 (d, *J* = 10.0 Hz, 2 H, C$\underline{H}$(C=O)C$\underline{H}$), 3.14 (br. s, 1 H, O$\underline{H}$), 1.40 (s, 3 H, CC$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 185.8 ($\underline{C}$=O), 152.7 ($\underline{C}$HC(OH)$\underline{C}$H), 126.9

(CH(C=O)CH), 67.1 (COH), 26.7 (CCH_3); All data is consistent with those reported in literature.[42]

6.4.2.5 Synthesis and Characterisation of 3.45

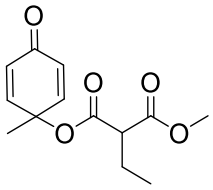
methyl (1-methyl-4-oxocyclohexa-2,5-dien-1-yl) malonate



According to modified General Procedure J, a solution of dienone (1.43 g, 10 mmol, 1.0 eq) in MeCN (10 mL) was treated with DMAP (122 mg, 1.0 mmol, 0.1 eq) and mono-methyl malonic acid (2.36 g, 20 mmol, 2.0 eq). A solution of DCC (6.18 g, 30 mmol, 3.0 eq) in MeCN (5 mL) was added. The crude mixture was purified by FCC to give the title compound **3.45** a yellow oil in 81% yield (1.81 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 6.91 (d, *J* = 10.0 Hz, 2 H, CHC(CH_3)CH), 6.25 (d, *J* = 10.0 Hz, 2 H, CHC=OCH), 3.76 (s, 3 H, OCH_3), 3.39 (s, 2 H, CH_2), 1.58 (s, 3 H, CCH_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 184.8 (CHC=O), 166.7 (OC=O), 164.9 (OC=O), 148.3 (CHC(CH_3)CH), 128.5 (CHC=OCH), 73.4 (CCH_3), 52.7 (OCH_3), 41.5 (CH_2), 26.2 (CCH_3); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{11}H_{12}O_5Na$) requires *m/z* 247.0577, found *m/z* 247.0578; **IR** (film) ν_{max}/cm^{-1}: 2935, 1736 (C=O), 1667 (C=O), 1148, 1053, 856, 730.

6.4.2.6 Synthesis and Characterisation of 3.46

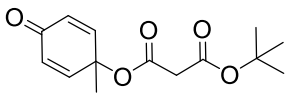
1-methyl 3-(1-methyl-4-oxocyclohexa-2,5-dien-1-yl) 2-ethylmalonate



According to modified General Procedure J, dienone (1.24 g, 10 mmol, 1.0 eq) was reacted with DCC (6.18 g, 30 mmol, 3.0 eq), DMAP (122 mg, 1.0 mmol, 0.1 eq) and 2-(methoxycarbonyl)butanoic acid (2.78 g, 19 mmol, 1.9 eq). The crude mixture was purified by FCC to afford the title compound **3.46** in 60% yield (1.5 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 6.90 - 6.87 (m, 2 H, C<u>H</u>C(CH_3)C<u>H</u>), 6.25 (d, *J* = 10.0 Hz, 2 H, C<u>H</u>C=OC<u>H</u>), 3.76 (s, 3 H, OC<u>H</u>$_3$), 3.29 (t, *J* = 7.5, 1 H, C<u>H</u>CH_2CH_3), 1.92 (quin, *J* = 7.5 Hz, 2 H, CHC<u>H</u>$_2$CH_3), 1.57 (s, 3 H, CC<u>H</u>$_3$), 0.98 (t, *J* = 7.5 Hz, 3 H, CHCH_2C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 184.8 (CH<u>C</u>=O), 169.6 (O<u>C</u>=O), 167.9 (O<u>C</u>=O), 148.4 (<u>C</u>H=CHC=O), 148.3 (<u>C</u>H=CHC=O), 128.5 (<u>C</u>HC=O), 128.4 (<u>C</u>HC=O), 75.1 (<u>C</u>CH_3), 53.4 (<u>C</u>HCH_2), 52.5 (O<u>C</u>H_3), 26.2 (C<u>C</u>H_3), 22.2 (<u>C</u>H_2CH_3), 11.8 (CH_2<u>C</u>H_3); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{13}H_{16}O_5^{Na}$) requires *m/z* 275.0890, found *m/z* 275.0887; **IR** (film) ν_{max}/cm^{-1}: 2936, 1735 (C=O), 1667 (C=O), 1610 (C=O), 1155, 1052, 857.

6.4.2.7 Synthesis and Characterisation of 3.47

<u>*tert*-butyl (1-methyl-4-oxocyclohexa-2,5-dien-1-yl) malonate</u>

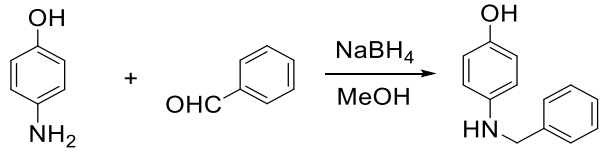


According to General Procedure J, a solution of dienone (620 mg, 5 mmol, 1.0 eq)

in MeCN (10 mL) was treated with DMAP (61 mg, 0.5 mmol, 0.1 eq) and mono-methyl malonic acid (880 mg, 5.5 mmol, 1.1 eq). A solution of DCC (3.09 g, 15 mmol, 3.0 eq) in MeCN (5 mL) was added. The crude mixture was purified by FCC to give the title compound **3.47** as a yellow oil in 72% yield (957 mg). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 6.92 (d, *J* = 10.0 Hz, 2 H, C<u>H</u>C(CH_3)C<u>H</u>), 6.25 (d, *J* = 10.0 Hz, 2 H, C<u>H</u>C=OC<u>H</u>), 3.29 (s, 2 H, C<u>H</u>$_2$), 1.58 (s, 3 H, CC<u>H</u>$_3$), 1.48 (s, 9 H, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 184.9 (CH<u>C</u>=O), 165.4 (O<u>C</u>=O and C=O), 148.5 (<u>C</u>HC(OH)<u>C</u>H), 128.4 (<u>C</u>HC=O<u>C</u>H), 82.5 (<u>C</u>(CH_3)$_3$), 75.1 (<u>C</u>CH_3), 43.1 (<u>C</u>H_2), 27.9 (C(<u>C</u>H$_3$)$_3$), 26.2 (C<u>C</u>H$_3$); Data consistent with those reported in the literature.[42]

6.4.2.8 Synthesis and Characterisation of 3.52

<u>4-(benzylamino)phenol</u>

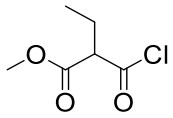


Benzaldehyde (2.12 g, 20 mmol, 1.0 eq) was added to a solution of 4-aminophenol (2.18 g, 20 mmol, 1.0 eq) in MeOH (50 mL). The reaction mixture was refluxed for 3 hours before adding $NaBH_4$ (740 mg, 20 mmol, 1.0 eq) at 0 °C slowly. The mixture was then stirred for another 2 h, quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to afford the title compound **3.52** in quantitative yield (3.98 g). **^{1}H NMR** ($CDCl_3$,

400 MHz) δ (ppm): 7.42 - 7.29 (m, 5 H, ArH), 6.73 (d, *J* = 9.0 Hz, 2 H, ArH), 6.60 (d, *J* = 9.0 Hz, 2 H, ArH), 4.31 (s, 2 H, $NHCH_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 147.8 (ArC), 142.3 (ArC), 139.5 (ArC), 128.6 (ArCH), 127.6 (ArCH), 127.2 (ArCH), 116.2 (ArCH), 114.4 (ArCH), 49.3 ($NHCH_2$); Data is consistent with those reported in literature.[43]

6.4.2.9 Synthesis and Characterisation of 3.43

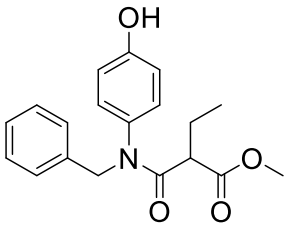
methyl 2-(chlorocarbonyl)butanoate



According to General Procedure M, 2-(methoxycarbonyl) butanoic acid (730 mg, 5.0 mmol) was used for the preparation of the corresponding acid chloride. The crude mixture was obtained and used directly in the next step.

6.4.2.10 Synthesis and Characterisation of 3.53

methyl 4-(benzyl(4-hydroxyphenyl)amino)-2-ethyl-3-oxobutanoate

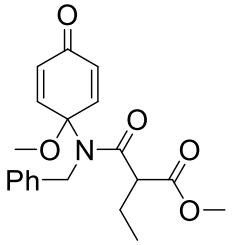


According to General Procedure N, **3.52** (952 mg, 4.76 mmol, 1.0 eq) was reacted with **3.43** (820 mg, 5.0 mmol, 1.05 eq) and pyridine (1.88 g, 23.8 mmol, 5.0 eq). Purification by FCC afforded the title compound **3.53** as a colourless solid in 83%

yield (1.29 g). **m.p.** = 122 - 124 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.28 - 7.19 (m, 5 H, Ar<u>H</u>), 6.85 - 6.74 (m, 4 H, Ar<u>H</u>), 6.17 (s, 1 H, O<u>H</u>), 4.89 (s, 2 H, NC<u>H</u>$_2$), 3.65 (s, 3 H, OC<u>H</u>$_3$), 3.28 (dd, *J* = 8.5, 6.5 Hz, 1 H, C<u>H</u>CH$_2$CH$_3$), 2.06 - 1.81 (m, 2 H, CHC<u>H</u>$_2$CH$_3$), 0.86 (t, *J* = 7.5 Hz, CHCH$_2$C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.7 (<u>C</u>=O), 169.8 (<u>C</u>=O), 156.1 (Ar<u>C</u>), 137.1 (Ar<u>C</u>), 133.9 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 116.3 (Ar<u>C</u>H), 53.5 (N<u>C</u>H$_2$), 52.3 (O<u>C</u>H$_3$), 50.7 (<u>C</u>HCH$_2$ CH$_3$), 22.8 (CH<u>C</u>H$_2$CH$_3$), 12.0 (CHCH$_2$<u>C</u>H$_3$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{19}H_{21}NO_4^{Na}$) requires *m/z* 350.1363, found *m/z* 350.1360; **IR** (film) ν_{max}/cm^{-1}: 2958, 1726 (C=O), 1511 (C=O), 1249, 1146, 1036, 733.

6.4.2.11 Synthesis and Characterisation of 3.54

<u>methyl-4-(benzyl(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)amino)-2-ethyl-3-oxobutanoate</u>

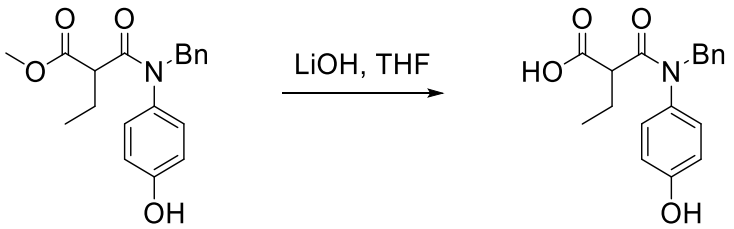


According to General Procedure O, **3.53** (164 mg, 0.5 mmol) was reacted with IBD (193 mg, 0.6 mmol). The crude mixture was purified by FCC to give title compound **3.54** as a red oil in 75% yield (133 mg). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.32 - 7.18 (m, 5 H, Ar<u>H</u>), 6.60 - 6.56 (m, 2 H, C<u>H</u>C(N)C<u>H</u>), 6.32 - 6.27 (m, 2 H,

C<u>H</u>C(O)C<u>H</u>), 4.83 (d, *J* = 18.0 Hz, NC<u>H</u>$_A$H$_B$), 4.68 (d, *J* = 18.0 Hz, 1 H, NCH$_A$<u>H</u>$_B$), 3.62 (s, 3 H, COOC<u>H</u>$_3$), 3.69 - 3.58 (m, 1 H, C<u>H</u>CH$_2$CH$_3$), 3.13 (s, 3 H, COC<u>H</u>$_3$), 1.82 - 1.78 (quin, *J* = 7.0 Hz, 2 H, CHC<u>H</u>$_2$CH$_3$), 0.68 (t, *J* = 7.0 Hz, CHCH$_2$C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 170.3 (<u>C</u>=O), 170.1 (<u>C</u>=O), 144.7 and 142.3 (<u>C</u>HC(N)<u>C</u>H), 138.2 (Ar<u>C</u>), 130.6 and 129.7 (<u>C</u>HC(O)<u>C</u>H), 128.8 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 53.5 (COO<u>C</u>H$_3$), 52.5 (<u>C</u>HCH$_2$), 51.0 (CO<u>C</u>H$_3$), 46.9 (N<u>C</u>H$_2$), 23.0 (<u>C</u>H$_2$CH$_3$), 12.1 (CH$_2$<u>C</u>H$_3$); **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{20}H_{24}O_5N$) requires *m/z* 358.1649, found *m/z* 358.1650; **IR** (film) ν_{max}/cm^{-1}: 3326, 2955, 1740 (C=O), 1662 (C=O), 1076, 908, 729.

6.4.2.12 Synthesis and Characterisation of 3.76

<u>2-(benzyl(4-hydroxyphenyl)carbamoyl)butanoic acid</u>

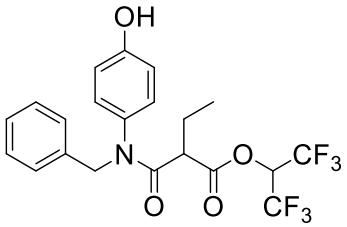


3.53 (654 mg, 2.0 mmol, 1.0 eq) was dissolved in THF (20 mL) and stirred at 0 °C. LiOH (144 mg, 6.0 mmol, 3.0 eq) was added in one portion. The reaction mixture was monitored by TLC and quenched with water (10 mL) and Et_2O (10mL). The aqueous layer was acidified to pH 3 and extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **3.76** as a colourless solid in 83% yield (518 mg). **m.p.** = 150 - 152 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.31 - 7.28 (m, 3 H, Ar<u>H</u>), 7.20 - 7.18 (m, 2 H,

ArH), 6.82 - 6.77 (m, 4 H, ArH), 4.91 (d, *J* = 17.5 Hz, 1 H, NCH_AH_B), 4.98 (d, *J* = 17.5 Hz, 1 H, NCH_AH_B), 3.28 (t, *J* = 7.0 Hz, 1 H, $CHCH_2CH_3$), 1.91 - 1.88 (m, 2 H, $CHCH_2CH_3$), 0.91 (t, *J* = 7.0 Hz, 3 H, $CHCH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 172.7 (C=O), 172.5 (C=O), 156.6 (ArC), 136.2 (ArC), 132.4 (ArC), 129.4 (ArCH), 129.0 (ArCH), 128.6 (ArCH), 127.9 (ArCH), 116.6 (ArCH), 53.5 (NCH_2), 49.1 ($CHCH_2CH_3$), 25.6 ($CHCH_2CH_3$), 11.5 ($CHCH_2CH_3$); **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{18}H_{20}NO_4$) requires *m/z* 314.1387, found *m/z* 314.1387; **IR** (film) ν_{max}/cm^{-1}: 3332 (COOH), 2970, 1378, 1128, 950, 816.

6.4.2.13 Synthesis and Characterisation of 3.77

1,1,1,3,3,3-hexafluoropropan-2-yl 2-(benzyl(4-hydroxyphenyl)carbamoyl)butanoate

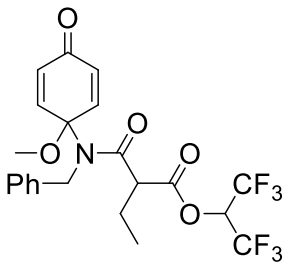


According to modified General Procedure J, DCC (865 mg, 4.2 mmol, 1.2 eq) was added into a solution of **3.76** (1.1 g, 3.5 mmol, 1.0 eq), 1,1,1,3,3,3-hexafluoro-2-propanol (0.73 mL, 7.0 mmol, 2.0 eq) and DMAP (85.4 mg, 0.7 mmol, 0.2 eq). Purification by FCC afforded the title compound **3.77** as a colourless solid in 81% yield (1.31 g). **m.p.** = 189 - 191 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.18 - 7.10 (m, 5 H, ArH), 6.72 (m, 4 H, ArH), 5.66 (dt, *J* = 12.0, 6.0 Hz, 1 H, $CH(CF_3)_2$),

5.03 (d, *J* = 14.0 Hz, 1 H, NC$\underline{H_A}H_B$), 4.59 (d, *J* = 14.0 Hz, 1 H, NCH$_A\underline{H_B}$), 3.39 (dd, *J* = 9.0, 6.0 Hz, 1 H, C$\underline{H}CH_2CH_3$), 1.99-1.77 (m, 2 H, CHC$\underline{H_2}CH_3$), 0.81 (t, *J* = 7.5 Hz, 3 H, CHCH$_2$C$\underline{H_3}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 168.1 ($\underline{C}$=O), 166.9 ($\underline{C}$=O), 156.5 (Ar$\underline{C}$), 136.5 (Ar$\underline{C}$), 133.2 (Ar$\underline{C}$), 129.7 (Ar$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 128.5 (Ar$\underline{C}$H), 127.7 (Ar$\underline{C}$H), 120.3 (CH($\underline{C}F_3$)$_2$, q, *J* = 282.1 Hz), 116.5 (Ar$\underline{C}$H), 66.7 (O$\underline{C}$H(CF$_3$)$_2$, quint, *J* = 34.7 Hz), 53.6 (N$\underline{C}$H$_2$), 49.7 ($\underline{C}$HCH$_2$), 22.7 ($\underline{C}$H$_2$CH$_3$), 11.6 (CH$_2\underline{C}$H$_3$); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -73.4; **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{21}H_{20}O_4NF_6$) requires *m/z* 464.1291, found *m/z* 464.1289; **IR** (film) ν_{max}/cm^{-1}: 2972, 1789 (C=O), 1635 (C=O), 1514, 1231, 1203, 1112, 908, 732.

6.4.2.14 Synthesis and Characterisation of 3.78

1,1,1,3,3,3-hexafluoropropan-2-yl 2-(benzyl(1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)carbamoyl)butanoate

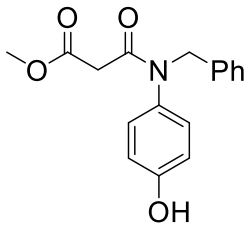


According to General Procedure O, **3.77** (1.31 g, 2.8 mmol, 1.0 eq) was reacted with IBD (1.05 g, 3.36 mmol, 1.2 eq). The crude mixture was purified by FCC to give the title compound **3.78** as a red oil in 43% yield (600 mg). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.31 - 7.11 (m, 5 H, Ar$\underline{H}$), 6.56 (dd, *J* = 10.0, 3.0 Hz, 1 H,

C$\underline{H}_A$C(N)CH$_B$), 6.56 (dd, *J* = 10.0, 3.0 Hz, 1 H, CH$_A$C(N)C$\underline{H}_B$), 6.31 - 6.28 (m, 2 H, C$\underline{H}$C(O)C$\underline{H}$), 5.73 - 5.63 (m, 1 H, C$\underline{H}$(CF$_3$)$_2$), 4.78 - 4.64 (m, 2 H, NC$\underline{H}_2$), 3.63 - 3.58 (m, 1 H, C$\underline{H}$CH$_2$CH$_3$), 3.13 (s, 3 H, OC$\underline{H}_3$), 1.90 - 1.80 (m, 2 H, CHC$\underline{H}_2$CH$_3$), 0.79 - 0.71 (m, 3 H, CHCH$_2$C$\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 168.3 ($\underline{C}$=O), 167.6 ($\underline{C}$=O), 166.5 ($\underline{C}$=O), 144.0 and 142.9 ($\underline{C}$HC(N)$\underline{C}$H), 137.7 (Ar$\underline{C}$), 130.6 and 130.2 ($\underline{C}$HC(O)$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 127.6 (Ar$\underline{C}$H), 126.5 (Ar$\underline{C}$H), 120.3 (CH($\underline{C}$F$_3$)$_2$, q, *J* = 282.1 Hz), 66.8 (O$\underline{C}$H(CF$_3$)$_2$, quint, *J* = 34.7 Hz), 51.0 (O$\underline{C}$H$_3$), 50.6 ($\underline{C}$HCH$_2$), 46.9 (N$\underline{C}$H$_2$), 22.8 ($\underline{C}$H$_2$CH$_3$), 11.7 (CH$_2$$\underline{C}H_3$); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -73.6; **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{22}H_{22}O_5NF_6$) requires *m/z* 494.1397, found *m/z* 494.1395; **IR** (film) ν_{max}/cm^{-1}: 2970, 1789 (C=O), 1669 (C=O), 1386, 1229, 1199, 1108, 1074.

6.4.2.15 Synthesis and Characterisation of 3.82

<u>methyl 3-(benzyl(4-hydroxyphenyl)amino)-3-oxopropanoate</u>

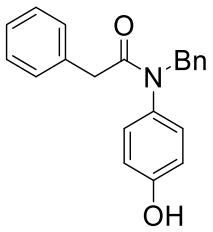


According to General Procedure N, **3.52** (1.99 g, 10.0 mmol, 1.0 eq) was reacted with **3.81** (1.43 g, 10.5 mmol, 1.05 eq) and pyridine (3.95 g, 50 mmol, 5.0 eq). Purification by FCC afforded the title compound **3.82** as a colourless solid in 88% yield (2.64 g). **m.p.** = 118 - 120 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.28 -

7.21 (m, 5 H, Ar<u>H</u>), 6.84 - 6.79 (m, 4 H, Ar<u>H</u>), 4.88 (s, 2 H, NC<u>H</u>$_2$), 3.66 (s, 3 H, OC<u>H</u>$_3$), 3.27 (s, 2 H, C<u>H</u>$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.5 (<u>C</u>=O), 168.3 (<u>C</u>=O), 156.7 (Ar<u>C</u>), 136.7 (Ar<u>C</u>), 133.5 (Ar<u>C</u>), 129.3 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 116.5 (Ar<u>C</u>H), 53.4 (N<u>C</u>H$_2$), 52.4 (O<u>C</u>H$_3$), 41.5 (<u>C</u>H$_2$); **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{17}H_{18}O_4N$) requires *m/z* 300.1230, found *m/z* 300.1231; **IR** (film) ν_{max}/cm^{-1}: 3242, 2978, 1750 (C=O), 1626 (C=O), 1514, 1154, 704.

6.4.2.16 Synthesis and Characterisation of 3.86

<u>N-benzyl-N-(4-hydroxyphenyl)-2-phenylacetamide</u>

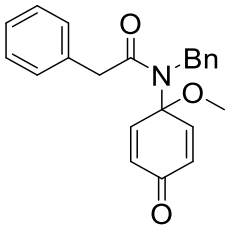


According to General Procedure N, **3.52** (960 mg, 4.8 mmol, 1.0 eq) was reacted with **3.85** (816 mg, 5.3 mmol, 1.1 eq) and Et_3N (1.0 mL, 7.2 mmol, 1.5 eq). Purification by FCC afforded the title compound **3.86** as a colourless solid in 59% yield (900 mg). **m.p.** = 148 - 150 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.28 - 7.19 (m, 8 H, Ar<u>H</u>), 7。01 – 6.99 (m, 2 H, Ar<u>H</u>), 6.74 - 6.71 (m, 4 H, Ar<u>H</u>), 4.86 (s, 2 H, NC<u>H</u>$_2$), 3.50 (s, 2 H, C<u>H</u>$_2$C=O); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.6 (<u>C</u>=O), 155.7 (Ar<u>C</u>), 137.4 (Ar<u>C</u>), 135.4 (Ar<u>C</u>), 134.6 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H),

116.1 (Ar<u>C</u>H), 53.4 (N<u>C</u>H$_2$), 41.2 (CO<u>C</u>H$_2$); **HRMS** (EI+) mass calculated for [M+H]$^+$ ($C_{21}H_{20}O_2N$) requires *m/z* 318.1489, found *m/z* 318.1490; **IR** (film) ν_{max}/cm^{-1}: 3233, 3030, 1625 (C=O), 1513, 1270, 729, 699.

6.4.2.17 Synthesis and Characterisation of 3.87

<u>N-benzyl-N-(4-oxocyclohexa-2,5-dien-1-yl)-2-phenylacetamide</u>

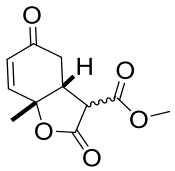


According to General Procedure O, **3.86** (634 mg, 2.0 mmol, 1.0 eq) was reacted with IBD (760 mg, 2.4 mmol, 1.2 eq). Purification by FCC afforded the title compound **3.87** as a yellow oil in 53% yield (370 mg). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.31 - 7.04 (m, 10 H, Ar<u>H</u>), 6.55 (d, *J* = 10.0 Hz, 2 H, C<u>H</u>C(O)C<u>H</u>), 6.25 (d, *J* = 10.0 Hz, 2 H, C<u>H</u>C(N)C<u>H</u>), 4.68 (s, 2 H, NC<u>H</u>$_2$), 3.54 (s, 2 H, C<u>H</u>$_2$C=O), 3.08 (s, 3 H, OC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 172.1 (<u>C</u>=O), 144.3 (<u>C</u>HC(N)<u>C</u>H), 138.5 (Ar<u>C</u>), 134.3 (Ar<u>C</u>), 129.8 (Ar<u>C</u>H), 129.3 (<u>C</u>HC(O)<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 83.5 (<u>C</u>OCH$_3$), 50.9 (O<u>C</u>H$_3$), 47.0 (N<u>C</u>H$_2$), 42.5 (<u>C</u>H$_2$C=O); **HRMS** (EI+) mass calculated for [M+H]$^+$ ($C_{22}H_{22}O_3N$) requires *m/z* 348.1594, found *m/z* 348.1596; **IR** (film) ν_{max}/cm^{-1}: 1660 (C=O), 1076, 907, 725, 699.

6.4.3 Asymmetric Cyclisation

6.4.3.1 Synthesis and Characterisation of 3.48a and 3.48b

methyl (3aR,7aR)-7a-methyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate



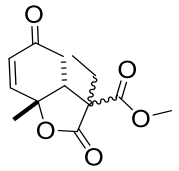
According to General Procedure P, BIMP catalysts (0.01 mmol, 0.1 eq) was reacted with **3.45** (0.1 mmol, 1.0 eq). The crude mixture was purified by FCC to give a 2:3 mixture of diastereomers (**3.48a**:**3.48b**) as a yellow oil in >99% yield (22 mg).[xxiv] **^{1}H NMR** ($CDCl_3$, 400 MHz, minor diastereomer marked with *) δ (ppm): 6.69 (dd, *J* = 10.0, 1.0 Hz, 1 H, C<u>H</u>CHCCH$_3$ and C<u>H*</u>CHCCH$_3$), 6.10 (dd, *J* = 10.5, 2.0 Hz,1 H, CHC<u>H</u>CCH$_3$ and CHC<u>H*</u>CCH$_3$), 3.84 (s, 3 H, OC<u>H</u>$_3$ and OC<u>H</u>$_3$*), 3.49 (s, 1 H, C<u>H*</u>CO$_2$Me), 3.46 (s, 1 H, C<u>H</u>CO$_2$Me), 3.38 (dt, *J* = 5.5, 2.0 Hz, 1 H, C<u>H</u>CH$_2$), 3.33 (dt, *J* = 5.5, 2.0 Hz, 1 H, C<u>H*</u>CH$_2$), 2.78 - 2.63 (m, 2 H, CHC<u>H</u>$_2$ and CHC<u>H</u>$_2$*), 1.74 (s, 3 H, CC<u>H</u>$_3$ and CC<u>H</u>$_3$*); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 194.0 (<u>C</u>=O and <u>C*</u>=O), 168.6 (<u>C</u>=O and <u>C*</u>=O), 166.7 (<u>C</u>=O and <u>C*</u>=O), 146.6 (<u>C</u>HCHCCH$_3$ and <u>C</u>H*CHCCH$_3$), 129.5 (CH<u>C</u>HCCH$_3$ and CH<u>C</u>H*CCH$_3$), 80.6 (<u>C</u>CH$_3$ and <u>C*</u>CH$_3$), 53.4 (O<u>C</u>H$_3$ and O<u>C</u>H$_3$*), 51.3 (<u>C</u>H*CO$_2$Me and <u>C</u>H*CO$_2$Me), 44.6 (<u>C</u>HCH$_2$ and <u>C</u>H*CH$_2$), 35.8 (CH<u>C</u>H$_2$ and CH<u>C</u>H$_2$*), 23.9 (C<u>C</u>H$_3$ and C<u>C</u>H$_3$*); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{11}H_{12}O_5Na$) requires *m/z* 247.0577,

[xxiv] **$[\alpha]_D$** was not measured as it is a mixture of two diastereomers.

found *m/z* 247.0578; **IR** (film) ν_{max}/cm^{-1}: 2924, 1784 (C=O), 1737 (C=O), 1684 (C=O), 1297, 1164, 1094, 751.

6.4.3.2 Synthesis and Characterisation of 3.49a and 3.49b

methyl 3-ethyl-7a-methyl-2,5-dioxo-2,3,5,7a-tetrahydro-4H-3al3-benzofuran-3-carboxylate



According to General Procedure P, BIMP catalysts (0.01 mmol, 0.1 eq) was reacted with **3.46** (0.1 mmol, 1.0 eq). The crude mixture was purified by FCC to give a 2:3 mixture of diastereomers (**3.49a**:**3.49b**) as a yellow oil in >99% yield (25.2 mg).[xxv] **^{1}H NMR** ($CDCl_3$, 400 MHz, minor diastereomer marked with *) δ (ppm): 6.76 (d, *J* = 10.5 Hz, 1 H, C$\underline{H}$*CHC=O), 6.71 (d, *J* = 10.5 Hz, 1 H, C$\underline{H}$CHC=O), 6.09 (d, *J* = 10.5 Hz, 1 H, CHC$\underline{H}$C=O), 5.95 (d, *J* = 10.5 Hz, 1 H, CHC$\underline{H}$*C=O), 3.81 (s, 3 H, OC$\underline{H_3}$*), 3.58 (s, 3 H, OC$\underline{H_3}$), 3.24 (d, *J* = 7.0 Hz, 1 H, C$\underline{H}$*CH_2), 2.97 - 2.93 (m, 1 H, CHC$\underline{H_A}H_B$), 2.85 (d, *J* = 7.0 Hz, 1 H, C$\underline{H}CH_2$), 2.82 - 2.78 (m, 1 H, CHC$\underline{H_A}$*H_B), 2.70 (t, *J* = 6.0 Hz, 1 H, CHC$H_A\underline{H_B}$), 2.66 (t, *J* = 6.0 Hz, 1 H, CHC$H_A\underline{H_B}$*), 2.06 - 1.77 (m, 2 H, CC$\underline{H_2}$ and CC$\underline{H_2}$*), 1.68 (s, 3 H, CC$\underline{H_3}$ and CC$\underline{H_3}$*), 1.06 (t, *J* = 7.5 Hz, 3 H, $CH_2C\underline{H_3}$), 1.00 (t, *J* = 7.5 Hz, 3 H, $CH_2C\underline{H_3}$*); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 194.7 (C=O and C*=O), 171.6 (C=O and

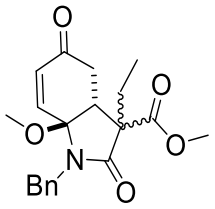
[xxv] **$[\alpha]_D$** was not measured as it is a mixture of two diastereomers.

C*=O), 170.0 (C=O and C*=O), 147.8 (C*HCHC=O), 147.5 (CHCHC=O), 129.4 (C*HC=O), 128.5 (CHC=O), 79.1 (C*CH_3), 78.7 (CCH_3), 58.3 (CCH_2), 57.9 (C*CH_2), 53.1 (OCH_3), 52.5 (OC*H_3), 48.6 (CHCH_2), 48.5(C*HCH_2), 34.1 (CHCH_2), 34.5 (CHC*H_2), 27.4 (CCH_2), 26.6 (CCH_3), 25.7 (CCH_3*), 23.5 (CCH_2), 8.9 (CH_2CH_3), 8.5 (CH_2C*H_3); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{13}H_{16}O_5^{Na}$) requires *m/z* 275.0890, found *m/z* 275.0887; **IR** (film) ν_{max}/cm^{-1}: 2955, 2923, 1780 (C=O), 1736 (C=O), 1684 (C=O), 1241, 1085.

6.4.3.3 Synthesis and Characterisation of 3.55a and 3.55b

methyl 1-benzyl-3-ethyl-7a-methoxy-2,5-dioxo

-1,2,3,4,5,7a-hexahydro-3al3-indole-3-carboxylate



According to General Procedure P, BIMP catalyst (0.01 mmol, 0.1 eq) was reacted with **3.54** (0.1 mmol, 1.0 eq). The crude mixture was purified by FCC to give a 2:3 mixture of diastereomers (**3.55a**:**3.55b**) as a red oil in >99% yield (35.5 mg), with 27% ee for **3.55a** and 29% ee for **3.55b**.[xxvi] [determined by HPLC, chiralpak AD, hexane/isopropanol 90:10, λ 220 nm, 1.0 mL/min, **3.55a**, t (minor) = 19.17 min, t (major) = 28.30 min, **3.55b**, t (major) = 25.34 min, t (minor) = 33.67 min]; Diastereomer **3.55a**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.39 - 7.23 (m, 5 H, ArH),

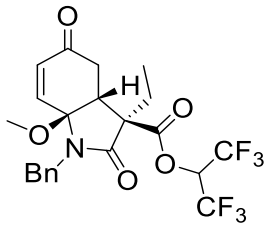
[xxvi] **$[\alpha]_D$** was not measured as it is a mixture of two diastereomers.

6.30 (dd, *J* = 10.5, 1.5 Hz, 1 H, C<u>H</u>CHC=O), 5.89 (d, *J* = 10.5 Hz, 1 H, CHC<u>H</u>C=O), 4.97 (d, *J* = 15.5 Hz, 1 H, NC<u>H</u>$_A$H$_B$), 4.26 (d, *J* = 15.5 Hz, 1 H, NCH$_A$<u>H</u>$_B$), 3.56 (s, 3 H, C(O)OC<u>H</u>$_3$), 3.27 (s, 3 H, COC<u>H</u>$_3$), 3.07 - 3.01 (m, 1 H, C<u>H</u>CH$_2$), 2.71 - 2.68 (m, 2 H, CHC<u>H</u>$_2$), 2.12 (dq, *J* = 14.5, 7.5 Hz, 1 H, CC<u>H</u>$_A$H$_B$), 2.06 - 2.02 (m, 1 H, CCH$_A$<u>H</u>$_B$), 1.08 (t, *J* = 7.5 Hz, 3 H, CCH$_2$C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 196.2 (CH<u>C</u>=O), 172.4 (<u>C</u>=O), 170.8 (<u>C</u>=O), 143.5 (<u>C</u>HCHCO), 137.7 (Ar<u>C</u>), 132.4 (<u>C</u>HCO), 128.6 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 89.2 (<u>C</u>OCH$_3$), 58.7 (<u>C</u>CH$_2$CH$_3$), 51.9 (C(O)O<u>C</u>H$_3$), 49.7 (CO<u>C</u>H$_3$), 42.7 (N<u>C</u>H$_2$), 40.2 (<u>C</u>HCH$_2$), 34.7 (CH<u>C</u>H$_2$), 26.4 (C<u>C</u>H$_2$CH$_3$), 9.2 (CCH$_2$<u>C</u>H$_3$); Diastereomer **3.55b**: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.39 - 7.23 (m, 5 H, Ar<u>H</u>), 6.54 (d, *J* = 10.5, 1.5 Hz, 1 H, C<u>H</u>CHC=O), 5.99 (d, *J* = 10.5 Hz, 1 H, C<u>H</u>C=O), 4.93 (d, *J* = 15.5 Hz, 1 H, NC<u>H</u>$_A$H$_B$), 4.23 (d, *J* = 15.5 Hz, 1 H, NCH$_A$<u>H</u>$_B$), 3.79 (s, 3 H, C(O)OC<u>H</u>$_3$), 3.50 (dd, *J* = 11.5, 5.5 Hz, 1 H, C<u>H</u>CH$_2$), 3.17 (s, 3 H, COC<u>H</u>$_3$), 2.60 (dd, *J* = 16.0, 6.0 Hz, 1 H, CHC<u>H</u>$_A$H$_B$), 2.25 (dd, *J* = 16.0, 11.5 Hz, 1 H, CHCH$_A$<u>H</u>$_B$), 2.04 - 1.97 (m, 1 H, CC<u>H</u>$_A$H$_B$), 1.73 (dq, *J* = 14.5, 7.5 Hz, 1 H, CCH$_A$<u>H</u>$_B$), 1.04 (t, *J* = 7.5 Hz, 3 H, CCH$_2$C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 194.2 (CH<u>C</u>=O), 171.3 (<u>C</u>=O), 170.1 (<u>C</u>=O), 141.7 (<u>C</u>HCHCO), 137.5 (Ar<u>C</u>), 129.1 (<u>C</u>HCO), 128.6 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 88.1 (<u>C</u>OCH$_3$), 57.7 (<u>C</u>CH$_2$CH$_3$), 52.8 (C(O)O<u>C</u>H$_3$), 51.0 (CO<u>C</u>H$_3$), 43.5 (N<u>C</u>H$_2$), 41.2 (<u>C</u>HCH$_2$), 36.6 (CH<u>C</u>H$_2$), 23.3 (C<u>C</u>H$_2$CH$_3$), 8.9 (CCH$_2$<u>C</u>H$_3$); **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{20}H_{24}O_5N$) requires *m/z* 358.1649, found *m/z* 358.1650; **IR** (film) ν_{max}/cm^{-1}: 2969, 1738 (C=O), 1666 (C=O),

1388, 1210, 1074,1065.

6.4.3.4 Synthesis and Characterisation of 3.80a and 3.80b

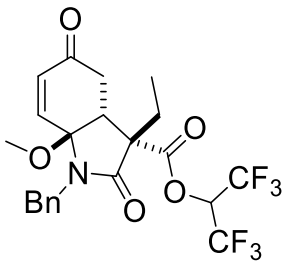
1,1,1,3,3,3-hexafluoropropan-2-yl (3R,3aR,7aS)-1-benzyl-3-ethyl-7a-methoxy-2,5-dioxo-2,3,3a,4,5,7a-hexahydro-1H-indole-3-carboxylate



According to General Procedure P, BIMP catalyst (0.01 mmol, 0.1 eq) was reacted with **3.79** (0.1 mmol, 1.0 eq). The crude mixture was purified by FCC to give a 1:1 mixture of diastereomers (**3.80a**:**3.80b**) in 96% yield (47.5 mg). Diastereomer **3.80a** was isolated as a colourless oil in 48% yield (24 mg) and 59% ee. [determined by HPLC, chiralpak ADH, hexane/isopropanol 95:5, λ 220 nm, 1.0 mL/min, t (minor) = 10.57 min, t (major) = 11.45 min]; $\mathbf{[\alpha]_D^{25}}$ = +5.7 (*c 0.3,* $CHCl_3$); **^{1}H NMR** (acetone-d_6, 500 MHz) δ (ppm): 7.37 - 7.36 (m, 2 H, Ar<u>H</u>), 7.31 - 7.24 (m, 3 H, Ar<u>H</u>), 6.56 (ddd, *J* = 10.5, 3.5, 1.5 Hz, C<u>H</u>CHC=O), 6.44 - 6.39 (m, 1 H, C<u>H</u>$(CF_3)_2$), 5.90 (dd, *J* = 10.5, 1.5 Hz, C<u>H</u>C=O), 4.90 (d, *J* = 15.5 Hz, 1 H, NC<u>H_A</u>H_B), 4.34 (d, *J* = 15.5 Hz, 1 H, NCH_A<u>H_B</u>), 3.37 - 3.35 (m, 1 H, C<u>H</u>CH_2), 3.31 (s, 3 H, OC<u>H_3</u>), 2.69 (dd, *J* = 17.5, 7.5 Hz, 1 H, CHC<u>H_A</u>H_B), 2.54 (dd, *J* = 17.5, 5.5 Hz, 1 H, CHCH_A<u>H_B</u>), 2.24 - 2.13 (m, 2 H, CC<u>H_2</u>CH_3), 1.08 (t, *J* = 7.5 Hz, 3 H, CCH_2C<u>H_3</u>); **^{13}C NMR** (acetone-d_6, 125 MHz) δ (ppm): 194.2 (CH<u>C</u>=O), 170.5 (<u>C</u>=O), 168.6

(C=O), 142.6 (CHCHC=O), 139.1 (ArC), 131.6 (CHC=O), 129.4 (ArCH), 128.6 (ArCH), 128.3 (ArCH), 121.6 ($CH(CF_3)_2$, q, *J* = 279.4 Hz), 89.4 ($COCH_3$), 67.8 ($CH(CF_3)_2$, quint, *J* = 34.3 Hz), 59.8 (CCH_2CH_3), 51.0 (OCH_3), 43.5 (NCH_2), 42.3 ($CHCH_2$), 32.7 ($CHCH_2$), 23.4 (CCH_2CH_3), 9.3 (CCH_2CH_3); **^{19}F NMR** (acetone-d_6, 376 MHz) δ (ppm): -73.5; **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{22}H_{22}O_5NF_6$) requires *m/z* 494.1397, found *m/z* 494.1395; **IR** (film) ν_{max}/cm^{-1}: 2972, 1769 (C=O), 1719 (C=O), 1693 (C=O), 1386, 1287, 1223, 1201, 1110.

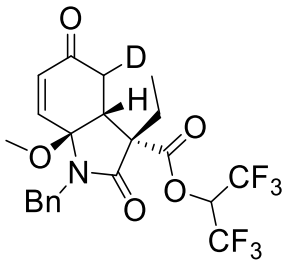
1,1,1,3,3,3-hexafluoropropan-2-yl (3S,3aR,7aS)-1-benzyl-3-ethyl-7a-methoxy-2,5-dioxo-2,3,3a,4,5,7a-hexahydro-1H-indole-3-carboxylate



Diastereomer **3.80b** was isolated as a colourless oil in 48% yield (23.5 mg) and 24% ee. [determined by HPLC, chiralpak ADH, hexane/isopropanol 95:5, λ 220 nm, 1.0 mL/min, t (major) = 18.10 min, t (minor) = 19.85 min]. **$[\alpha]_D^{25}$** = +62 (*c 0.1,* $CHCl_3$);); **^{1}H NMR** (MeOD-d_4, 500 MHz) δ (ppm): 7.29 - 7.22 (m, 5 H, ArH), 6.85 (d, *J* = 10.5 Hz, CHCHC=O), 6.44 (quin, *J* = 6.0 Hz, 1 H, $CH(CF_3)_2$), 6.04 (d, *J* = 10.5 Hz, CHC=O), 4.73 (d, *J* = 15.5 Hz, 1 H, NCH_AH_B), 4.43 (d, *J* = 15.5 Hz, 1 H, NCH_AH_B), 3.60 (d, *J* = 11.5 Hz, 1 H, $CHCH_2$), 3.11 (s, 3 H, OCH_3), 2.63 (ddd, J = 16.0, 5.5, 1.0 Hz, 1 H, $CHCH_AH_B$), 2.28 (d, *J* = 16.0, 11.5 Hz, 1 H, $CHCH_AH_B$), 2.04

(dq, *J* = 15.0, 7.5 Hz, 1 H, CC$\underline{H_A}H_B$), 1.85 (dq, *J* = 14.5, 7.5 Hz, 1 H, CCH$_A\underline{H_B}$), 1.03 (t, *J* = 7.5 Hz, 3 H, $CCH_2C\underline{H_3}$);

1,1,1,3,3,3-hexafluoropropan-2-yl (3S,3aR,7aS)-1-benzyl-3-ethyl-7a-methoxy-2,5-dioxo-2,3,3a,4,5,7a-hexahydro-1H-indole-3-carboxylate-4-d[xxvii]



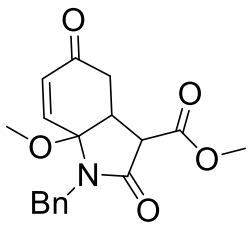
^{1}H NMR (MeOD-d$_4$, 500 MHz) δ (ppm): 7.29 - 7.22 (m, 5 H, Ar$\underline{H}$), 6.85 (d, *J* = 10.5 Hz, C$\underline{H}$CHC=O), 6.44 (quin, *J* = 6.0 Hz, 1 H, C$\underline{H}(CF_3)_2$), 6.04 (d, *J* = 10.5 Hz, C$\underline{H}$C=O), 4.73 (d, *J* = 15.5 Hz, 1 H, NC$\underline{H_A}H_B$), 4.43 (d, *J* = 15.5 Hz, 1 H, NCH$_A\underline{H_B}$), 3.60 (d, *J* = 11.5 Hz, 1 H, C$\underline{H}$CHD), 3.11 (s, 3 H, OC$\underline{H_3}$), 2.28 (d, *J* = 11.5 Hz, 1 H, CHC$\underline{H}$D), 2.04 (dd, *J* = 15.0, 7.5 Hz, 1 H, CC$\underline{H_A}H_B$), 1.85 (dd, *J* = 15.0, 7.5 Hz, 1 H, CCH$_A\underline{H_B}$), 1.03 (t, *J* = 7.5 Hz, 3 H, $CCH_2C\underline{H_3}$); **^{13}C NMR** (MeOD-d$_4$, 125 MHz) δ (ppm): 197.6 (CH$\underline{C}$=O), 173.0 ($\underline{C}$=O), 169.0 ($\underline{C}$=O), 144.7 ($\underline{C}$HCHC=O), 139.1 (Ar$\underline{C}$), 134.1 ($\underline{C}$HC=O), 129.7 (Ar$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 122.1 (CH($\underline{C}F_3)_2$, q, *J* = 275.1 Hz), 91.1 ($\underline{C}OCH_3$), 68.5 ($\underline{C}H(CF_3)_2$, quint, *J* = 34.3 Hz), 59.2 ($\underline{C}CH_2CH_3$), 51.6 (O$\underline{C}H_3$), 44.8 (N$\underline{C}H_2$), 43.2 ($\underline{C}$HCHD), 30.1 ($\underline{C}$HD, sextet, *J* = 20.0 Hz), 24.3 (C$\underline{C}H_2CH_3$), 9.2 ($CCH_2\underline{C}H_3$); **^{19}F NMR** (MeOD-d$_4$, 376 MHz) δ

[xxvii] The α-proton of **3.80b** was deuterated after storing in MeOD-d$_4$ for over two weeks.

(ppm): -73.5; **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{22}H_{20}DO_5NF_6^{Na}$) requires *m/z* 517.1279, found *m/z* 517.1270; **IR** (film) ν_{max}/cm^{-1}: 2980, 1768 (C=O), 1711 (C=O), 1698 (C=O), 1387, 1288, 1236, 1202, 1111.

6.4.3.5 Synthesis and Characterisation of 3.83

methyl 1-benzyl-7a-methoxy-2,5-dioxo-2,3,3a,4,5,7a-hexahydro-1H-indole-3-carboxylate

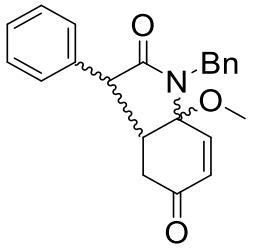


According to General Procedure P, to a solution of **3.82** (66 mg, 0.2 mmol, 1.0 eq) in MeOH (2 mL) was added IBD (77 mg, 0.24 mmol, 1.2 eq) at 0 °C. The crude mixture was purified by FCC to afford the title compound **3.83** as a yellow oil in 80% yield (52.6 mg). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.25 - 7.20 (m, 5 H, Ar<u>H</u>), 6.27 (dd, *J* = 10.5, 2.0 Hz, 1 H, C<u>H</u>CHC=O), 5.87 (dd, *J* = 10.5, 1.0 Hz, 1 H, CHC<u>H</u>C=O), 4.70 (d, *J* = 15.0 Hz, 1 H, NC<u>H_A</u>H_B), 4.20 (d, *J* = 15.0 Hz, 1 H, NCH_A<u>H_B</u>), 3.78 (s, 3 H, C(O)OC<u>H_3</u>), 3.18 (s, 3 H, COC<u>H_3</u>), 3.44 - 3.39 (m, 1 H, C<u>H</u>CH_2), 3.13 (d, *J* = 10.0 Hz, 1 H, C<u>H</u>C(O)OCH_3), 2.70 (dd, *J* = 17.0, 6.0 Hz, 1 H, CHC<u>H_A</u>H_B), 2.42 (ddd, *J* = 17.0, 2.5, 1.0 Hz, 1 H, CHCH_A<u>H_B</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 195.2 (<u>C</u>=O), 168.4 (<u>C</u>=O), 167.7 (<u>C</u>=O), 141.7 (<u>C</u>HCHC=O), 137.2 (Ar<u>C</u>), 129.5 (CH<u>C</u>HC=O), 128.8 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 88.9

($\underline{C}OCH_3$), 53.1 (C(O)O$\underline{C}H_3$), 52.7 ($\underline{C}HC(O)OCH_3$), 50.6 ($CO\underline{C}H_3$), 43.2 ($N\underline{C}H_2$), 36.9 ($CH\underline{C}H_2$), 36.8 ($\underline{C}HCH_2$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{18}H_{19}O_5NNa$) requires *m/z* 352.1155, found *m/z* 352.1153; **IR** (film) ν_{max}/cm^{-1}: 2954, 1742 (C=O), 1703 (C=O), 1078, 702.

6.4.3.6 Synthesis and Characterisation of 3.88

1-benzyl-7a-methoxy-3-phenyl-1,3a,4,7a-tetrahydro-2H-indole-2,5(3H)-dione



According to General Procedure P, to a solution of **3.87** (34.7 mg, 0.1 mmol, 1.0 eq) in Et_2O (0.2 mL) was added BIMP catalyst (0.01 mmol, 0.1 eq). The crude mixture was purified by FCC to afford the title compound **3.88** as a yellow oil in 84% yield (29 mg). Major diastereomer: **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.43 - 7.13 (m, 10 H, Ar$\underline{H}$), 6.27 (dd, *J* = 10.5, 2.0 Hz, 1 H, C$\underline{H}$CHC=O), 5.87 (dd, *J* = 10.5, 1.0 Hz, 1 H, C$\underline{H}$C=O), 4.74 (d, *J* = 15.0 Hz, 1 H, NC$\underline{H_A}H_B$), 4.35 (d, *J* = 15.0 Hz, 1 H, NC$H_A\underline{H_B}$), 3.18 (s, 3 H, COC$\underline{H_3}$), 3.23 (d, *J* = 11.0 Hz, 1 H, C$\underline{H}$C=O), 2.91 - 2.86 (m, 1 H, C$\underline{H}CH_2$), 2.61 (dd, *J* = 17.0, 6.0 Hz, 1 H, CHC$\underline{H_A}H_B$), 2.42 (ddd, *J* = 17.0, 1.5, 0.5 Hz, 1 H, CHC$H_A\underline{H_B}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 196.0 ($\underline{C}$=O), 172.7 ($\underline{C}$=O), 141.4 ($\underline{C}$HCHC=O), 137.9 (Ar$\underline{C}$), 136.0 (Ar$\underline{C}$), 129.3 (Ar$\underline{C}$H), 129.2 ($\underline{C}$HC=O), 128.8 (Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 127.9 (Ar$\underline{C}$H), 127.8

(Ar<u>C</u>H), 88.6 (<u>C</u>OCH$_3$), 53.3 (<u>C</u>HC=O), 51.0 (CO<u>C</u>H$_3$), 43.0 (N<u>C</u>H$_2$), 42.8 (<u>C</u>HCH$_2$), 36.1 (CH<u>C</u>H$_2$), **HRMS** (EI+) mass calculated for $[M+H]^+$ ($C_{22}H_{22}O_3N$) requires *m/z* 348.1594, found *m/z* 348.1596; **IR** (film) ν_{max}/cm^{-1}: 1659 (C=O), 1075, 731.

6.5 Michael Addition of Malonate to Crotonate and Acrylate Derivatives

6.5.1 General Procedures

6.5.1.1 General Procedure Q for the Catalytic Reaction

To a solution of crotonate (0.12 mmol, 1.2 eq) in Et_2O was added catalyst (0.01 mmol, 0.1 eq) and malonate (0.1 mmol, 1.0 eq) in Et_2O (0.2 mL) under a N_2 atmosphere. The reaction mixture was monitored by TLC and quenched with 1.0 M AcOH (in CH_2Cl_2, 0.1 mL). The volatiles were removed under a stream of N_2 and the reaction mixture was purified by FCC to afford the product.

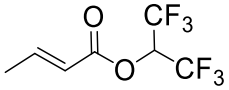
6.5.1.2 General Procedure R for the Catalytic Reaction

To a solution of acrylate derivative (0.1 mmol, 1.0 eq) in Et_2O was added catalyst (0.01 mmol, 0.1 eq) and malonate (0.2 mmol, 2.0 eq) in Et_2O (0.2 mL) under a N_2 atmosphere. The reaction mixture was monitored by TLC and quenched with 1.0 M AcOH (in CH_2Cl_2, 0.1 mL). The volatiles were removed under a stream of N_2 and the reaction mixture was purified by FCC to afford the product.

6.5.2 Substrate Synthesis

6.5.2.1 Synthesis and Characterisation of 4.17

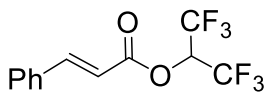
1,1,1,3,3,3-hexafluoropropan-2-yl *(E)*-but-2-enoate



According to General Procedure J, crotonic acid (1,72 g, 20 mmol, 1.0 eq) and 1,1,1,3,3,3-hexafluoropropan-2-ol (1.54 mL, 24 mmol, 1.2 eq) were added into a solution of 4-dimethylaminopyridine (488 mg, 4.0 mmol, 0.2 eq) in CH_2Cl_2 (50 mL). DCC (4.94 g, 24 mmol, 1.2 eq) was then added into the mixture. The crude mixture was then purified by FCC (PE/Et_2O, 99/1) to afford the title compound **4.17** as a colourless oil in 83% yield (3.92 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 7.31 - 7.22 (m, 1 H, C<u>H</u>=CHC=O), 6.00 (dq, *J* = 15.5, 1.5, 1.5 Hz, 1 H, C<u>H</u>C=O), 5.85 (spt, *J* = 6.0 Hz, 1 H, C<u>H</u>(CF_3)$_2$), 0.90 (t, *J* = 7.0 Hz, 3 H, CHC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 162.6 (<u>C</u>=O), 150.3 (<u>C</u>H=CHC=O), 120.6 (CH(<u>C</u>F_3)$_2$, q, *J* = 282.1 Hz), 119.5 (<u>C</u>HC=O), 66.3 (O<u>C</u>H(CF_3)$_2$, quint, *J* = 34.7 Hz), 22.3 (CH<u>C</u>H$_3$); **^{19}F NMR** ($CDCl_3$, 133 MHz) δ (ppm): -73.5; Molecule couldn't be detected on either EI or ESI; **IR** (film) ν_{max}/cm^{-1}: 1754 (C=O), 1194, 1103, 965, 693.

6.5.2.2 Synthesis and Characterisation of 4.20

1,1,1,3,3,3-hexafluoropropan-2-yl cinnamate



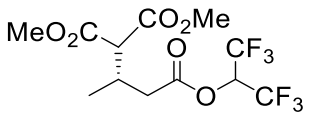
According to General Procedure J, cinnamic acid (1,48 g, 10 mmol, 1.0 eq) and

1,1,1,3,3,3-hexafluoropropan-2-ol (0.77, 12 mmol, 1.0 eq) were added into a solution of 4-dimethylaminopyridine (244 mg, 2.0 mmol, 0.2 eq) in CH_2Cl_2 (25 mL). DCC (2.47 g, 10 mmol, 1.0 eq) was then added into the mixture. The crude mixture was then purified by FCC (PE/Et_2O, 99/1) to afford the title compound **4.20** as a colourless oil in 97% yield (2.89 g). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 7.90 (d, *J* = 16.0 Hz, 1 H, C<u>H</u>=CHC=O), 7.61 - 7.58 (m, 2 H, Ar<u>H</u>), 7.47 - 7.42 (m, 3 H, Ar<u>H</u>), 6.54 (d, *J* = 16.0 Hz, 1 H, C<u>H</u>C=O), 5.92 (spt, *J* = 6.0 Hz, 1 H, C<u>H</u>(CF_3)$_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 163.4 (<u>C</u>=O), 149.4 (<u>C</u>H=CHC=O), 133.5 (Ar<u>C</u>), 131.5 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 120.6 (<u>C</u>F_3, q, *J* = 285.4 Hz), 114.2 (<u>C</u>HC=O), 66.3 (O<u>C</u>H(CF_3)$_2$, spt, *J* = 34.5 Hz); **^{13}F NMR** ($CDCl_3$, 133 MHz) δ (ppm): -76.5; All data consistent with those reported in literature.[44]

6.5.3 Michael Addition

6.5.3.1 Synthesis and Characterisation of 4.19

<u>3-(1,1,1,3,3,3-hexafluoropropan-2-yl) 1,1-dimethyl *(S)*-2-methylpropane-1,1,3-tricarboxylate</u>

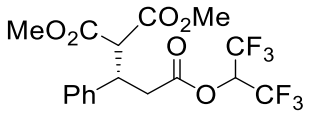


According to General Procedure Q, to a solution of **4.17** (28 mg, 0.12 mmol, 1.2 eq) in 0.2 mL Et_2O was added BIMP catalyst (0.01 mmol, 0.1 eq) and dimethyl malonate (11.4 µL, 0.1 mmol, 1.0 eq). The product was purified by FCC (9:1 petrol: Et_2O) to afford **4.19** as a colourless oil in 95% yield (35 mg) and 20% ee

[determined by HPLC, chiralpak OD-H, hexane/isopropanol 99:1, λ 220 nm, 1.0 mL/min, t (minor) = 13.66 min, t (major) = 16.66 min]. **$[\alpha]_D^{25}$** = +2.2 (*c 1.4,* $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 5.78 (quint, *J* = 6.0 Hz, 1 H, C<u>H</u>$(CF_3)_2$), 3.76 (s, 6 H, OC<u>H</u>$_3$ and OC<u>H</u>$_3$), 3.46 (d, *J* = 7.0 Hz, C<u>H</u>CO_2Me), 2.83 - 2.78 (m, 2 H, C<u>H</u>CH_2 and CHC<u>H</u>$_A$H$_B$), 2.60 - 2.53 (m, 1 H, CHCH_A<u>H</u>$_B$), 1.10 (d, *J* = 7.0 Hz, 3 H, CHC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 169.0 (<u>C</u>=O), 168.5 (<u>C</u>=O), 168.5 (<u>C</u>=O), 66.2 (quint, *J* = 34.7 Hz, <u>C</u>H$(CF_3)_2$), 55.5 (<u>C</u>HCO_2Me), 52.6 (O<u>C</u>H$_3$), 37.4 (CH<u>C</u>H$_2$), 29.9 (<u>C</u>HCH_2), 17.3 (CH<u>C</u>H$_3$); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -73.3; **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{12}H_{14}O_6F_6Na$) requires *m/z* 391.0587, found *m/z* 391.0586. **IR** (film) ν_{max}/cm^{-1}: 3288, 2965, 2101, 1640 (C=O), 1536 (C=O), 1217, 755.

6.5.3.2 Synthesis and Characterisation of 4.21

<u>3-(1,1,1,3,3,3-hexafluoropropan-2-yl) 1,1-dimethyl (S)-2-phenylpropane-1,1,3-tricarboxylate</u>

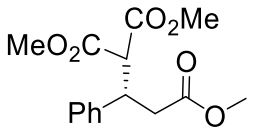


According to General Procedure Q, to a solution of **4.20** (36 mg, 0.12 mmol, 1.2 eq) in 0.2 mL Et_2O was added BIMP catalyst (0.01 mmol, 0.1 eq) and dimethyl malonate (11.4 µL, 0.1 mmol, 1.0 eq). The product was purified by FCC (9:1 petrol: Et_2O) to afford **4.21** as a colourless oil in 91% yield (39.1 mg) and 63% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 95:5, λ 220 nm, 1.0

mL/min, t (minor) = 7.73 min, t (major) = 10.11 min]. **$[\alpha]_D^{25}$** = +17.2 (*c 0.7* $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.23 - 7.13 (m, 5 H, Ar<u>H</u>), 5.51 (spt, *J* = 6.0 Hz, 1 H, C<u>H</u>$(CF_3)_2$), 3.88 (td, *J* = 10.0, 5.0 Hz, 1 H, C<u>H</u>CH_2), 3.69 (d, *J* = 8.0 Hz, 1 H, C<u>H</u>CO_2Me), 3.68 (s, 3 H, OC<u>H</u>$_3$), 3.45 (s, 3 H, OC<u>H</u>$_3$), 3.08 (dd, *J* = 16.0, 5.0 Hz, 1 H, C<u>H</u>$_A$H$_B$C=O), 2.96 (dd, *J* = 16.0, 10.0 Hz, 1 H, CH$_A$<u>H</u>$_B$C=O); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 168.2 (<u>C</u>=O), 168.1 (<u>C</u>=O), 167.6 (<u>C</u>=O), 138.4 (Ar<u>C</u>), 128.7 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 66.4 (quint, *J* = 34.6 Hz, <u>C</u>H$(CF_3)_2$), 56.9 (<u>C</u>HCO_2Me), 52.8 (O<u>C</u>H$_3$), 52.6 (O<u>C</u>H$_3$), 41.8 (<u>C</u>HCH_2), 37.1 (CH<u>C</u>H$_2$); **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm): -73.3; **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{17}H_{16}O_6F_6Na$) requires *m/z* 453.0743, found *m/z* 453.0739; **IR** (film) ν_{max}/cm^{-1}: 2959, 1781 (C=O), 1736 (C=O), 1232, 1199, 1110, 907, 733, 700.

6.5.3.3 Synthesis and Characterisation of 4.43

<u>trimethyl *(S)*-2-phenylpropane-1,1,3-tricarboxylate</u>

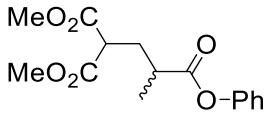


According to a literature Procedure[44], a mixture of methanol (0.5 mL, 0.2 M in the ester) and triethylamine (50 µL, 0.35 mmol, 3.5 eq) was stirred at room temperature for approximately five minutes. At this time, the ester **4.21** (43 mg, 0.1 mmol, 1.0 eq) was added. The reaction mixture was stirred at room temperature overnight. Once complete, the volatiles were removed under a

stream of N_2. The crude mixture was purified by FCC to afford the title compound **4.43** in 99% yield (29 mg) as a colorless oil and 64% ee [determined by HPLC, chiralpak IA, hexane/isopropanol 95:5, λ 220 nm, 1.0 mL/min, t (minor) = 18.37 min, t (major) = 22.55 min]. $\mathbf{[\alpha]_D^{25}}$ = +9.8 (*c 2.2,* $CHCl_3$), lit. +13.5 (*c* 0.8, $CHCl_3$)[45]; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.23 - 7.14 (m, 5 H, Ar<u>H</u>), 3.86 (td, *J* = 10.0, 5.0 Hz, 1 H, C<u>H</u>Ph), 3.69 (d, *J* = 8.0 Hz, 1 H, C<u>H</u>CO_2Me), 3.67 (s, 3 H, OC<u>H_3</u>), 3.46 (s, 3 H, OC<u>H_3</u>), 3.41 (s, 3 H, OC<u>H_3</u>), 2.77 (dd, *J* = 15.5, 5.0 Hz, 1 H, C<u>H_A</u>H_BC=O), 2.96 (dd, *J* = 15.5, 10.0 Hz, 1 H, CH_A<u>H_B</u>C=O); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 171.6 (<u>C</u>=O), 168.4 (<u>C</u>=O), 167.9 (<u>C</u>=O), 139.8 (Ar<u>C</u>), 128.5 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.4 (Ar<u>C</u>H), 57.0 (<u>C</u>HCO_2Me), 52.7 (O<u>C</u>H_3), 52.4 (O<u>C</u>H_3), 51.6 (O<u>C</u>H_3), 41.4 (<u>C</u>HCH_2), 38.3 (CH<u>C</u>H_2); All data consistent with those reported in literature.[46]

6.5.3.4 Synthesis and Characterisation of 4.45a

<u>1,1-dimethyl 3-phenyl butane-1,1,3-tricarboxylate</u>

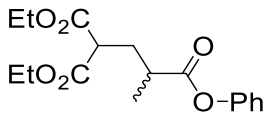


According to General Procedure R, to a solution of phenyl methacrylate (16.2 mg, 0.1 mmol, 1.0 eq) in 0.2 mL Et_2O was added BIMP catalyst (0.01 mmol, 0.1 eq) and dimethyl malonate (22.8 µL, 0.2 mmol, 2.0 eq). The product was purified by FCC (9:1 petrol: Et_2O) to afford **4.45a** as a colourless oil in >99% yield (29.5 mg) and 57% ee [determined by HPLC, chiralpak OD, hexane/isopropanol 99:1, λ 220

nm, 1.0 mL/min, t (minor) = 19.58 min, t (major) = 26.56 min]. **$[\alpha]_D^{25}$** = +10.0 (*c 0.9,* $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.42 - 7.38 (m, 2 H, Ar<u>H</u>), 7.28 - 7.23 (m, 1 H, Ar<u>H</u>), 7.12 - 7.09 (m, 2 H, Ar<u>H</u>), 3.79 (s, 3 H, OC<u>H</u>$_3$), 3.77 (s, 3 H, OC<u>H</u>$_3$), 3.63 (dd, *J* = 9.0, 6.5 Hz, 1 H, C<u>H</u>($CO_2Me)_2$), 2.81 - 2.75 (m, 1 H, C<u>H</u>CH_3), 2.42 (ddd, *J* =14.0, 9.0, 6.5 Hz, 1 H, C<u>H</u>$_A$H$_B$$CHCH_3$), 2.19 (ddd, *J* = 14.0, 8.5, 5.5 Hz, 1 H, CH_A<u>H</u>$_B$$CHCH_3$), 1.39 (d, *J* = 7.5 Hz, 3 H, CHC<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 174.0 (<u>C</u>OOPh), 169.5 (<u>C</u>OOMe), 169.3 (<u>C</u>OOMe), 150.6 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 121.4 (Ar<u>C</u>H), 52.7 (O<u>C</u>H$_3$), 52.7 (O<u>C</u>H$_3$), 49.5 (<u>C</u>H($CO_2Me)_2$), 37.5 (<u>C</u>HCH_3), 32.2 (CH<u>C</u>H$_2$), 17.5 (CHC<u>H</u>$_3$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{15}H_{18}O_6Na$) requires *m/z* 317.0996, found *m/z* 317.0994; **IR** (film) ν_{max}/cm^{-1}: 2980, 2955, 1753 (C=O), 1735 (C=O), 1194, 1162.

6.5.3.5 Synthesis and Characterisation of 4.45b

<u>1,1-diethyl 3-phenyl butane-1,1,3-tricarboxylate</u>

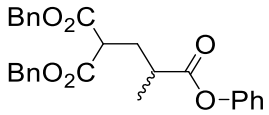


According to General Procedure R, to a solution of phenyl methacrylate (16.2 mg, 0.1 mmol, 1.0 eq) in 0.2 mL Et_2O was added BIMP catalyst (0.01 mmol, 0.1 eq) and diethyl malonate (30 µL, 0.2 mmol, 2.0 eq). The product was purified by FCC (9:1 petrol: Et_2O) to afford the title compound **4.45b** as a colourless oil in 86% yield (27.7 mg) and 64% ee [determined by HPLC, chiralpak AS-H, hexane/isopropanol 99:1, λ 220 nm, 1.0 mL/min, t (major) = 26.73 min, t (minor) = 30.69 min]. **$[\alpha]_D^{25}$** =

+ 21.0 (*c 2.4,* $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.33 - 7.28 (m, 2 H, Ar<u>H</u>), 7.19-7.14 (m, 1 H, Ar<u>H</u>), 7.03 - 7.00 (m, 2 H, Ar<u>H</u>), 4.19 - 4.10 (m, 4 H, $CH(CO_2C\underline{H}_2CH_3)_2$), 3.48 (dd, *J* = 9.0, 6.5 Hz, 1 H, $C\underline{H}(CO_2Et)_2$), 2.70 (ddd, *J* = 9.0, 7.0, 5.5 Hz, 1 H, $C\underline{H}CH_3$), 2.31 (ddd, *J* = 14.0, 9.0, 6.5 Hz, 1 H, $C\underline{H}_AH_BCHCH_3$), 2.19 (ddd, *J* = 14.0, 8.5, 5.5 Hz, 1 H, $CH_A\underline{H}_BCHCH_3$), 1.29 (d, *J* = 7.0 Hz, 3 H, $CHC\underline{H}_3$), 1.21 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.20 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 174.1 (<u>C</u>OOPh), 169.1 (<u>C</u>OOMe), 169.0 (<u>C</u>OOMe), 150.7 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 121.5 (Ar<u>C</u>H), 61.6 and 61.5 ($O\underline{C}H_2CH_3$), 49.9 ($\underline{C}H(CO_2Et)_2$), 37.5 ($\underline{C}HCH_3$), 32.1 ($CH\underline{C}H_2$), 17.5 ($CHC\underline{H}_3$), 14.1 and 14.1 ($OCH_2\underline{C}H_3$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{17}H_{22}O_6Na$) requires *m/z* 345.1309, found *m/z* 345.1306. **IR** (film) ν_{max}/cm^{-1}: 2981, 1751 (C=O), 1731 (C=O), 1192, 1162, 1149, 730.

6.5.3.6 Synthesis and Characterisation of 4.45c

<u>1,1-dibenzyl 3-phenyl butane-1,1,3-tricarboxylate</u>

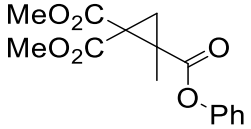


According to General Procedure R, to a solution of phenyl methacrylate (16.2 mg, 0.1 mmol, 1.0 eq) in 0.4 mL Et_2O was added BIMP catalyst (0.01 mmol, 0.1 eq) and dibenzyl malonate (50 µL, 0.2 mmol, 2.0 eq). The product was purified by FCC (9:1 petrol: Et_2O) to afford **4.45c** as a colourless oil in >99% yield (44.8 mg) and 62% ee [determined by HPLC, chiralpak AS-H, hexane/isopropanol 95:5, λ

220 nm, 1.0 mL/min, t (minor) = 13.98 min, t (major) = 14.94 min]. **$[\alpha]_D^{25}$** = +12.5 (*c 3.7,* $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.30 - 7.11 (m, 13 H, Ar<u>H</u>), 6.96 - 6.94 (m, 2 H, Ar<u>H</u>), 5.09 - 5.06 (m, 4 H, $COO(C\underline{H}_2Ph)_2$), 3.60 (dd, *J* = 9.0, 6.5 Hz, 1 H, $C\underline{H}(CO_2Bn)_2$), 2.66 (ddd, *J* = 9.0, 7.0, 5.5 Hz, 1 H, $C\underline{H}CH_3$), 2.35 (ddd, *J* =14.0, 9.0, 6.5 Hz, 1 H, $C\underline{H}_AH_BCHCH_3$), 2.19 (ddd, *J* = 14.0, 8.5, 5.5 Hz, 1 H, $CH_A\underline{H}_BCHCH_3$), 1.25 (d, *J* = 7.0 Hz, 3 H, $CHC\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 174.0 (<u>C</u>OOPh), 168.8 (<u>C</u>OOBn), 168.7 (<u>C</u>OOBn), 150.6 (Ar<u>C</u>), 135.2 (Ar<u>C</u>), 135.2 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 121.5 (Ar<u>C</u>H), 67.4 and 67.3 ($O\underline{C}H_2Ph$), 49.9 ($\underline{C}H(CO_2Bn)_2$), 37.4 ($\underline{C}HCH_3$), 32.1 ($CH\underline{C}H_2$), 17.5 ($CHC\underline{H}_3$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{27}H_{26}O_6Na$) requires *m/z* 469.1622, found *m/z* 469.1620; **IR** (film) ν_{max}/cm^{-1}: 2980, 1751 (C=O), 1732 (C=O), 1191, 1162, 1146, 733, 696.

6.5.3.7 Synthesis and Characterisation of 4.48

<u>1,1-dimethyl 2-phenyl 2-methylcyclopropane-1,1,2-tricarboxylate</u>



According to modified General Procedure R, to a solution of phenyl methacrylate (81 mg, 0.5 mmol, 1.0 eq) in 2.5 mL Et_2O was added BEMP (15 µL, 0.05 mmol, 0.1 eq) and dimethyl 2-chloromalonate (0.2 mL, 1.0 mmol, 2.0 eq). The product

was purified by FCC (9:1 petrol: Et_2O) to afford **4.48** as a colourless oil in 8% yield (12 mg). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 7.42 - 7.38 (m, 2 H, Ar<u>H</u>), 7.28 - 7.23 (m, 1 H, Ar<u>H</u>), 7.15 - 7.12 (m, 2 H, Ar<u>H</u>), 3.84 (s, 3 H, OC<u>H</u>$_3$), 3.76 (s, 3 H, OC<u>H</u>$_3$), 2.26 (d, *J* = 5.0 Hz, 1 H, C<u>H</u>$_A$H$_B$), 1.80 (d, *J* = 5.0 Hz, 1 H, CH$_A$<u>H</u>$_B$), 1.62 (s, 3 H, C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 169.7 (<u>C</u>=O), 167.6 (<u>C</u>=O), 167.2 (<u>C</u>=O), 150.8 (Ar<u>C</u>), 129.4 (Ar<u>C</u>H), 126.0 (Ar<u>C</u>H), 121.3 (Ar<u>C</u>H), 53.2 (O<u>C</u>H$_3$), 53.1 (O<u>C</u>H$_3$), 41.2 (<u>C</u>(CO$_2$Me)$_2$), 33.4 (<u>C</u>CO$_2$Ph), 24.7 (<u>C</u>H$_2$), 15.3 (CC<u>H</u>$_3$); **HRMS** (EI+) mass calculated for $[M+Na]^+$ ($C_{15}H_{16}O_6Na$) requires *m/z* 315.0947, found *m/z* 315.0946; **IR** (film) ν_{max}/cm^{-1}: 2955, 1736 (C=O), 1246, 1193.

6.6 Reference

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