Development and Application of a New Class of Potent Bifunctional Organocatalysts

A thesis submitted in partial fulfilment of the requirement for the degree of

Doctor of Philosophy (D. Phil.)

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Trinity Term 2015

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Abstract

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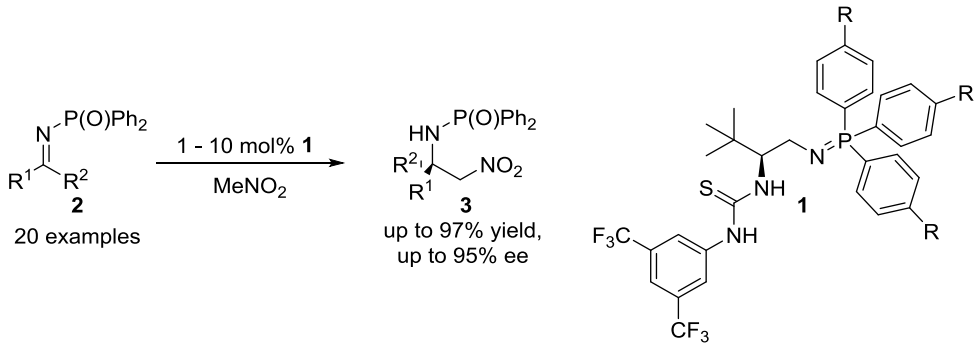
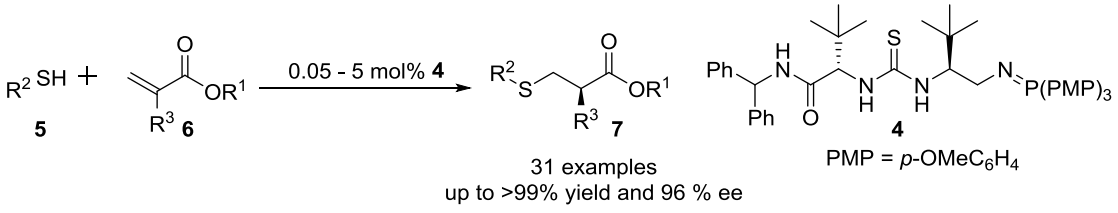
This thesis describes the development and application of a new class of bifunctional organocatalysts, incorporating the novel triaryliminophosphorane organosuperbases, for asymmetric synthesis. This thesis seeks to address some of the limitations of organocatalysis, namely long reaction times, high catalyst loadings and poor atom economy was sought. Chapter 2 outlines the design and synthesis of the bifunctional iminophosphorane (BIMP) catalysts such as **1** which were synthesised on gram scale.

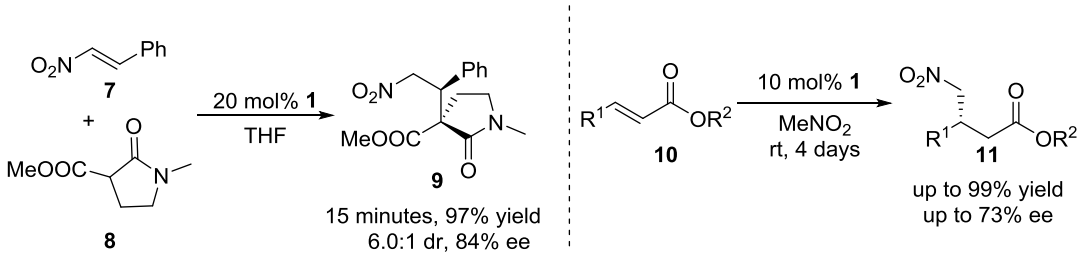


Chapter 3 describes the application of the BIMP catalysts to the first general organocatalytic enantioselective ketimine nitro-Mannich reaction. Twenty ketimines **2** were investigated and the β-nitroamine products **3** were formed in up to 97% yield and 95% ee. The reaction was demonstrated on a 10 gram preparative scale with 1 mol% catalyst.



Chapter 4 describes the first organocatalytic enantioselective sulfa-Michael addition of alkyl and benzylic thiols **5** to simple α-substituted α,β-unsaturated esters **6**. The reaction required the development of BIMP catalysts such as **4** that incorporated an amide thiourea H-bond donor group. 31 examples were investigated with quantitative yields and up to 96% ee obtained in the formation of β-mercaptoesters **7**. Catalyst loadings as low as 0.05 mol% were achieved on a 100 mmol scale.

Chapter 5 describes some structure and stability properties of the BIMP catalysts. The work disclosed in chapter 6 demonstrates the rate enhancements of the BIMP catalysts relative to tertiary amine bifunctional organocatalysts in the key steps of Dixon's total syntheses of nakadomarin A. Rate enhancements of up to 1300 times were observed in related reactions such as the Michael addition of β-amido ester **8** to nitrostyrene **7**.



Chapter 7 describes a miscellany of reactions catalysed by the BIMP catalysts to demonstrate the efficacy of the new catalysts. The organocatalytic enantioselective addition of nitromethane to β-substituted α,β-unsaturated esters **10** such as methyl crotonate is disclosed with quantitative yields and enantiomeric excesses up to 73% achieved.

Declarations and Copyright

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 2011 and as a candidate for the degree of Doctor of Philosophy in October 2012; the higher study for which this is a record was carried out in the University of Oxford between 2011 and 2015.

Alistair J. M. Farley

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Acknowledgements

First and foremost, I would like to thank Darren for taking me on first as a Part II and then as a DPhil student. Thank you for the opportunity to work on such an exciting project and for your drive and enthusiasm throughout the course of the DPhil.

Secondly, I must thank Dr Marta G. Núñez for the discovery of the catalyst system and continuing the initial catalyst development with me during my first year. We made a pretty good team even if you don't admit it. I know it wasn't always easy but we got there with the paper in the end!

I am also greatly indebted to Dr Pavol Jakubec, strictly colleague (but also briefly flatmate), for all his help and supervision right from the start of my Part II. Thank you for teaching me the correct way of doing things in the lab and I'm sorry for not being able to keep my fumehood and desk space anything like yours. You must have despaired about the state of G6 but we tried. Thank you also for your unwavering patience answering all the questions I threw at you, proofreading and general help on anything chemistry related. And latterly, for joining team BIMP and putting us all to shame.

Special thanks to Chris for all your hard work and dedication to the project during and after your time here. It really was a pleasure to have the opportunity to work with you during your Part II. Thank you to all the group members who worked on and contributed to the BIMP catalyst project: Marta, Pavol, Chris, Anna, Jinchao, Jessie and Gerard.

Thank you to all members of the Dixon group past and present for making the lab such an interesting and for the most part an enjoyable place to work especially Alex, Dave, Adam, Matt. Thank you Vaibhav for being obscenely up to date with the literature and for all the helpful chemistry discussions we had. Thanks to all those who played football for team Brian over the last few years and won the Catalyst cup.

Thank you to all those who read excerpts of the thesis: Adam, Matt, Allegra, Jinchao, Gerard and lastly but not least Darren for battling through it.

Thank you to all the NMR staff but especially to Dr Barbara Odell for all the NMR experiments that she ran for me at short notice. Your help was very much appreciated!

Cheers to the Marsh Lane boys for providing a welcome distraction from the lab – I did try with the medic chat. Finally on to you Michelle, thank you for all your help, support and companionship over the latter part of the DPhil studies. Finishing our DPhils has been eventful and stressful but made easier being with you. Thank you for your help not only with the thesis but with everything else – I do much appreciate and value our relationship.

Lastly, a big thank you to the whole family for all your love and support over the years and to those of you who piqued my enthusiasm for science from a young age. Mum, Dad, Nick and Isabelle, none of all this would have been possible without you and although I don't show it enough I am extremely grateful for all your tireless support.

Abbreviations

18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
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
BOX	Bisoxazoline
BTMG	2-*tert*-Butyl-*N*,*N*,*N*′,*N*′-Tetramethylguanidine
Bu	Butyl
Cbz	Carboxybenzyl
conc.	Concentrated
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBP	3,5-Di-*tert*-butylphenyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAN	*N*,*N*,*N*′,*N*′-Tetramethyl-1,8-naphthalenediamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DOSY	Diffusion Ordered Spectroscopy
dr	Diastereomeric ratio
EDC•HCl	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
EPR	Electron Paramagnetic Resonance
eq	Equivalents

Et	Ethyl
EWG	Electron Withdrawing Group
EXSY	Exchange Spectroscopy
GABA	γ-Aminobutyric acids
GC	Gas Chromatography
HOBt	1-Hydroxybenzotriazole
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Im	Imidazole
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
KIE	Kinetic Isotope Effect
LiHMDS	Lithium bis(trimethylsilyl)amide
LRMS	Low Resolution Mass Spectrometry
LUMO	Lowest Unoccupied Molecular Orbital
Me	Methyl
Mes	Mesityl
MS	Molecular sieves
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
n. d.	Not determined
N-DPP	*N*-diphenylphosphoryl
NMM	*N*-Methylmorpholine
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Np	Naphthyl
NSAID	Nonsteroidal anti-inflammatory drug
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PG	Protecting group
Ph	phenyl
Piv	Pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl

Pr	Propyl
PS-BEMP	Polystyryl 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
RCM	Ring Closing Metathesis
RDS	Rate Determining Step
rt	Room temperature
SMA	Sulfa-Michael Addition
TADDOL	α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBME	*tert*-Butyl methyl ether
TBS	*tert*-Butyldimethylsilyl
*t*Bu	*tert*-Butyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMG	*N*,*N*,*N*′,*N*′-Tetramethylguanidine
TMS	Trimethylsilyl
TOF	Turnover frequency
TON	Turnover number
TS	Transition state
Ts	Tosylate
VT NMR	Variable Temperature NMR
ZPE	Zero Point Energy

1 Introduction

1.1 Introduction to Organocatalysis

Chemistry has transformed our way of life over the last hundred and fifty years through advances in materials and life sciences. To fuel technological growth, chemists continue to synthesise new and more complex chemical entities. In the pharmaceutical, agrochemical and fine chemical industries, many final molecules contain one or more stereogenic centres and methods to generate single enantiomers are central to the synthesis of new target molecules and the efficiency of individual reactions and processes. Asymmetric synthesis is regarded as the most valuable method for the preferential formation of a stereoisomer in a reaction sequence.

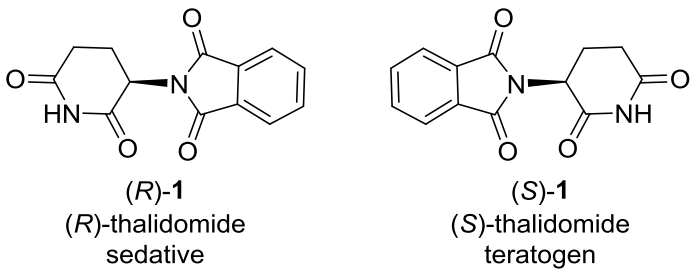


Figure 1 Example of the differing properties of enantiomers.

Up until the 1960s, and owing in large part to the use of thalidomide **1** to alleviate the onset of morning sickness in pregnant women, very little consideration was made for the differing effects of enantiomers in a biological organism (Figure 1). Unbeknownst at the time, only the (*R*)-enantiomer was effective to this end and tragically (*S*)-thalidomide was teratogenic, resulting in appalling deformities in the new-born babies.[1] Whilst not all enantiomeric pairs of drug molecules display such dichotomous properties *in vivo*, a detailed understanding of the biological properties of the various stereoisomers is nevertheless required to obtain FDA approval.

Methods to synthesise drug molecules in an enantiopure form are thus paramount.[2,3] Historically, this has been accomplished by chiral resolution or chromatographic

separation of the racemic mixtures;[4,5] however, these techniques necessarily suffer from a detrimental 50% loss of material associated with the undesired enantiomer. Alternatively, the development of chiral auxiliaries, where a chiral molecule is covalently bound to a substrate to induce asymmetry and subsequently cleaved to afford the highly enantiomerically enriched product, greatly contributed to the growth of asymmetric synthesis.[6,7] Although a highly effective method for the installation of chirality in a molecule, additional steps in a reaction sequence are required for the installation and removal of the auxiliary. Moreover, the auxiliary must be used in stoichiometric quantities and the atom economy of the sequence is poor.

Asymmetric catalysis, where only catalytic quantities of chiral molecules are required to induce asymmetry in a product, is on the other hand a much more efficient strategy for the synthesis of enantioenriched molecules. Enzymes – 'Nature's catalysts' – have been exploited on industrial scale for their ability to impart extraordinary levels of enantiocontrol during a reaction.[8-10] The high specificity of enzymes to catalyse a particular reaction under diffusion control can conversely be an inherent limitation as the scope of an individual enzyme is generally narrow. Alternatively, the use of transition metals, in conjunction with a suitable chiral organic ligand framework, is another branch of asymmetric catalysis that has received tremendous interest from the organic chemistry community.[11] In 2001, Knowles, Noyori and Sharpless were jointly awarded the Chemistry Nobel Prize for their seminal work on catalytic asymmetric hydrogenation and oxidation reactions. The high catalytic activity of many transition metals have enabled reactions to be performed with exceptionally low catalyst loadings (0.01 mol% typical) on multi-ton scale in the synthesis drug molecules.[12] However, the use of transition metal catalysts often requires stringent reaction conditions and can present problems pertaining to the removal and disposal of trace toxic metal contaminants.

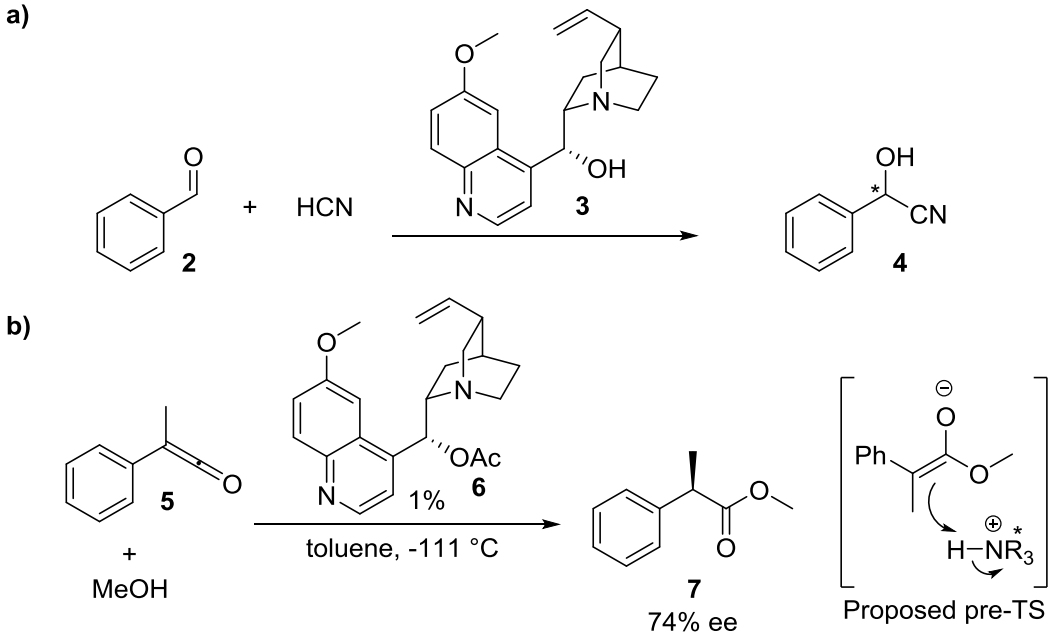
The start of the 21st century has seen asymmetric organocatalysis – the use of small organic molecules as catalysts – emerge as a new and complimentary area to enzymatic and metal approaches. Since MacMillan's conceptualisation of the field in 2000 by coining the term 'organocatalysis', research activity into this fundamental area has increased exponentially. Organocatalysts are generally readily synthesised in just a few steps from commercially available chiral building blocks and furthermore organocatalytic reactions can be performed under mild conditions without the exclusion of moisture and atmospheric oxygen. These advantages, as well as the development of various different classes of organocatalysts to perform numerous distinct reaction types have resulted in the synthetic community's widespread interest in these molecules and their applications.

As early as 1949, Langebeck used 'organic catalysts' to describe catalysts that did not contain metal centres[13] and intermittent illustrations of metal-free asymmetric catalysts have appeared in the literature over the course of the last century. With the benefit of hindsight, these examples can now be viewed as frontrunners to the field of organocatalysis. This introduction seeks to provide a brief historical overview in approximately chronological order of metal-free catalysis and organocatalysis, highlighting seminal and arguably the most notable advances whilst contextualising the work disclosed in this thesis.

1.2 Forerunners to Organocatalysis and Founding Examples

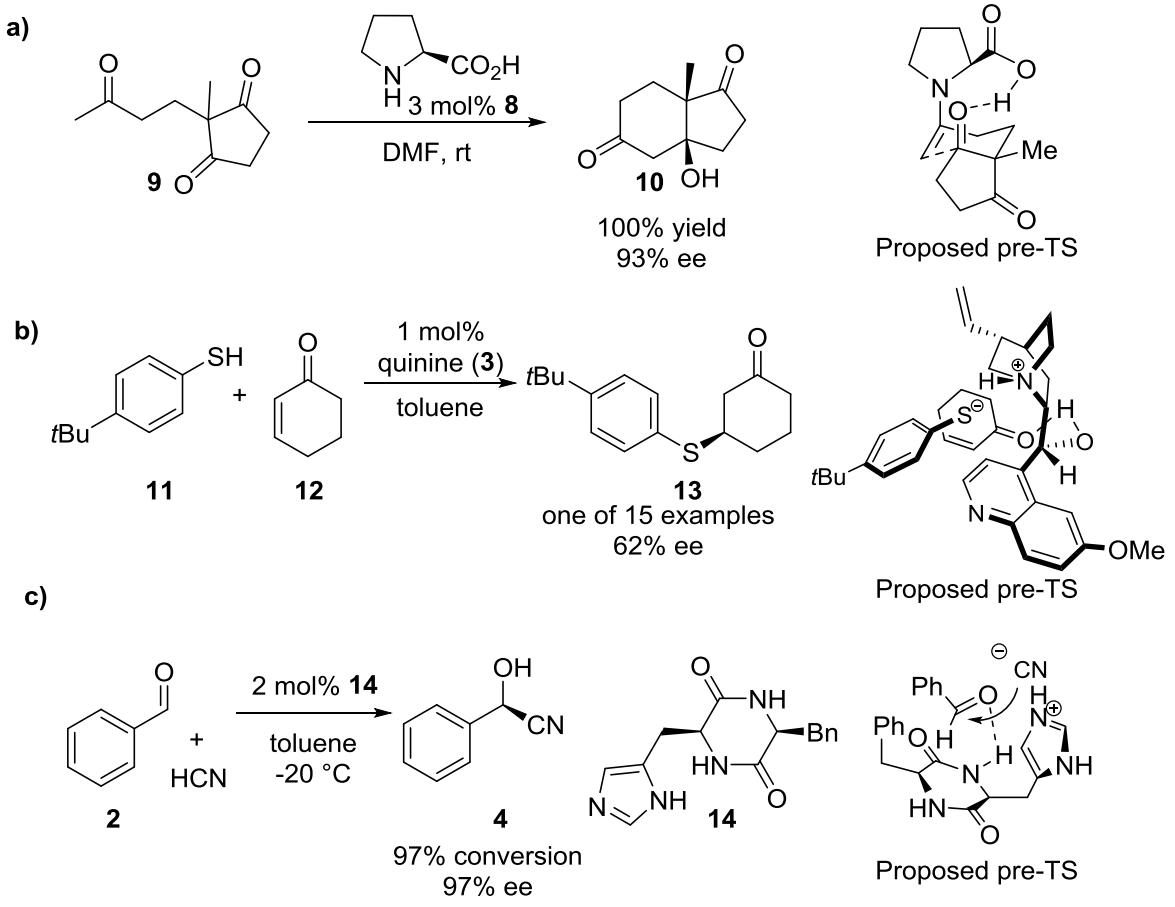
The very first example of a metal-free enantioselective carbon-carbon forming reaction was reported in 1913 by Georg Bredig (Scheme 1a).[14] Quinine **3**, extracted from the bark of cinchona trees, was demonstrated to impart some levels of asymmetric induction in the product in the addition of hydrogen cyanide to benzaldehyde **2**. Nearly half a century later, Pracejus described an early example of a metal free catalyst affording significant levels of

enantiocontrol in a reaction. Phenyl(methyl)ketene **5** was treated at low temperature with methanol in the presence of 1 mol% acylated quinine catalyst **6** to afford the ester **7** in up to 74% ee (Scheme 1b).[15] The enantioselectivity of the product was believed to arise from preferential protonation of the transient enolate, which was formed by the addition of MeOH to **5**, by the chiral protonated tertiary amine of the catalyst.



Scheme 1 a) Bredig's hydrocyanation reaction of benzaldehyde; b) Pracejus' synthesis of 7 **catalysed by quinine.**

(*S*)-Proline **8**, another small naturally occurring chiral molecule, was highly effective in catalysing an enantioselective intramolecular aldol reaction of prochiral trione **9** (Scheme 2a). The bicyclic product **10** was formed in a highly impressive 93% ee and was an extremely useful intermediate in the synthesis of various steroid molecules. The reaction is believed to occur *via* attack of the intermediate enamine to one of the prochiral ketones. Discrimination of the two ketones was facilitated by H-bonding between the carboxylic acid proton with one of the carbonyls to afford the highly enantioenriched bicycle **10** in quantitative yield.[16] This transformation and the related condensation reaction would later be known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction in recognition of the contributions of the principal scientists at Hoffmann-La Roche[17] and Schering AG.[18]

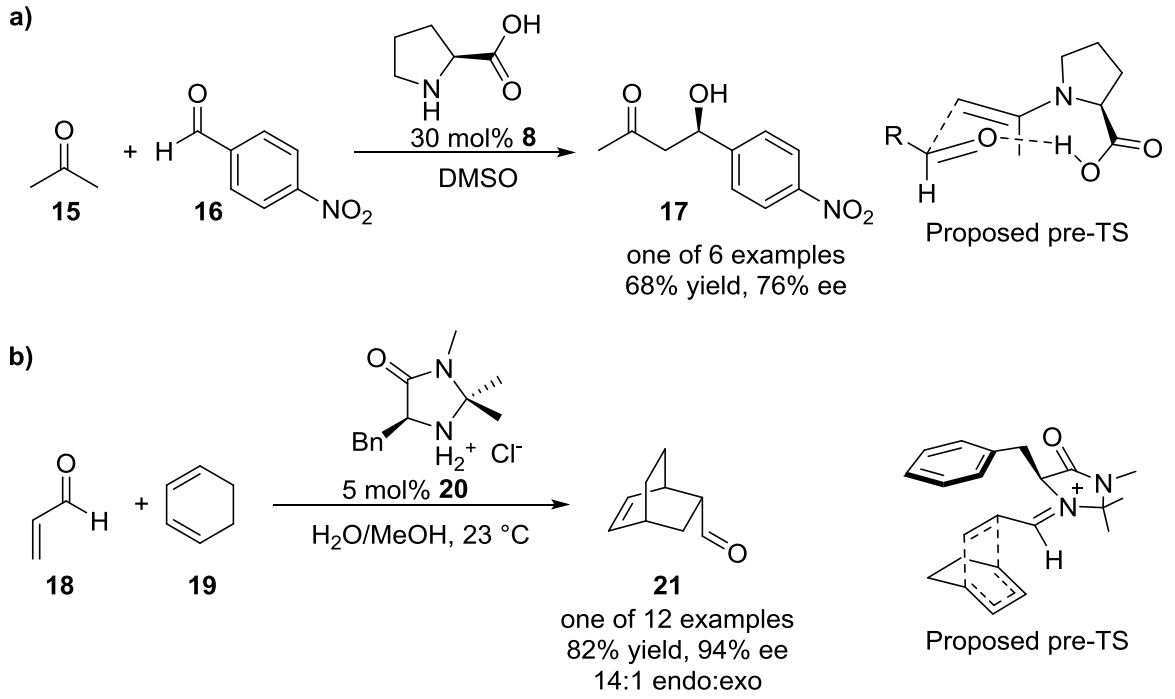


Scheme 2 a) The Hajos-Parrish-Eder-Sauer-Wiechert reaction catalysed by proline; b) Hiemstra and Wynberg's quinine catalysed conjugate addition of thiols to cyclohexenone; c) Inoue's cyclic peptide catalysed hydrocyanation reaction to benzaldehyde.

In 1981, Hiemstra and Wynberg published a comprehensive study on the conjugate addition of aromatic thiols such as **11** to cyclic enones with moderate to good levels of enantiocontrol using cinchona alkaloids as catalysts (Scheme 2b).[19] The authors demonstrated, for the first time, that the presence of the free hydroxyl moiety was critical for the enantioselectivity. Furthermore, when the diastereomer of **1**, 9-epiquinine, was used as the catalyst the enantioselectivity was reduced to 18%. The author's proposed transition state showed the deprotonated thiol aligned by the tertiary ammonium salt with the hydroxyl group activating the enone. They postulated that π-π stacking between the aromatic thiol moiety and the quinoline heterocycle also contributed to the enantiocontrol in the formation of **13**.

In an early example of a metal-free asymmetric catalyst that was designed, Inoue and co-workers, discovered that the cyclic dipeptide **14** – synthesised by the condensation of L-phenylalanine and L-histidine – was an effective catalyst in the hydrocyanation of benzaldehyde (Scheme 2c).[20,21] A series of dipeptide catalysts containing the Brønsted basic imidazole moiety from L-histidine were evaluated in the reaction and the authors were able to achieve the formation of cyanohydrin **4** in 97% ee with 97% conversion with just 2 mol% of catalyst. In a working model to explain the observed enantioselectivity, benzaldehyde interacted through H-bonding interactions with the conformationally rigid keto piperazine with the sterically bulkier phenyl group pointing away from the concave face of the catalyst. The nucleophile could then preferentially attack one face of the aldehyde to afford the enantioenriched product **4**.[22]

It was not until the year 2000 however, that the potential of organic molecules as asymmetric catalysts was realised and that the field of organocatalysis was born. Two landmark papers set the foundations of enamine and iminium organocatalysis. List and co-workers demonstrated the generality of enamine catalysis when they performed a proline catalysed cross-aldol reaction between ketones and aldehydes (Scheme 3a).[23] The authors proposed that the secondary amine catalyst condensed with the carbonyl of **15** to yield the enamine which then reacted with a non-enolisable aldehyde **16** to afford the α-hydroxy ketone **17**. Furthermore, they proposed that the key carbon-carbon bond forming step proceeded *via* a Zimmerman-Traxler-like transition state and the carboxylic acid of the proline activated the aldehyde, with the bulky substituent sitting in the equatorial position of the chair transition state.



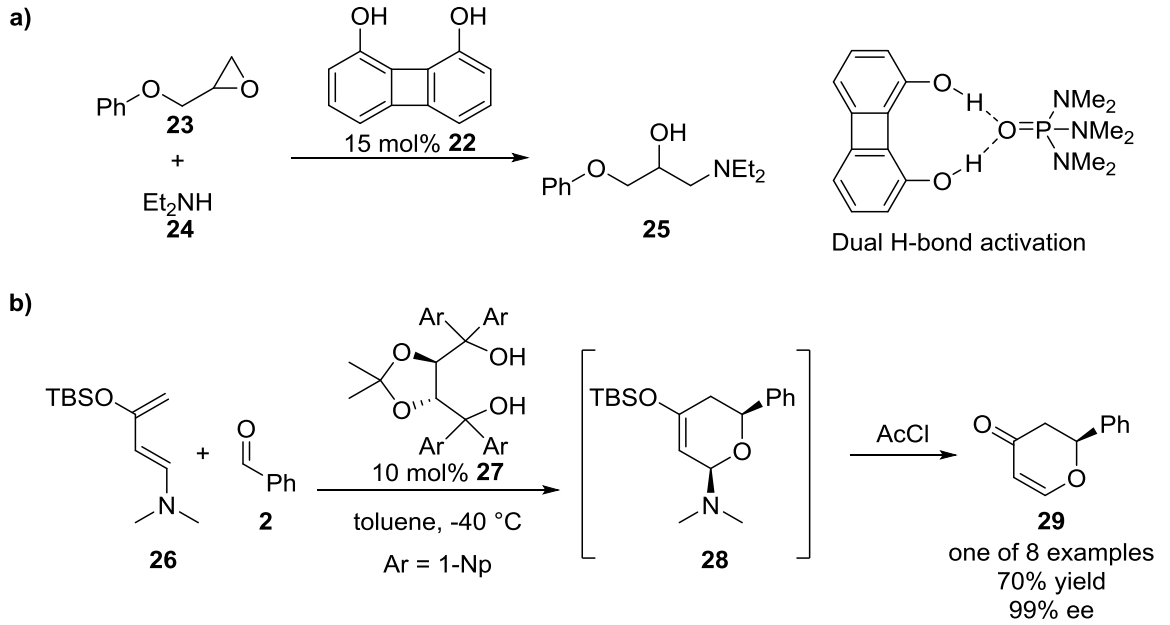
Scheme 3 a) List's intermolecular aldol reaction catalysed by (*S*)-proline; b) MacMillan's asymmetric Diels-Alder reaction catalysed by an imidazoline catalyst.

In the same year, MacMillan *et al.* showed the generality of iminium catalysis as a complementary use of chiral amines (Scheme 3b).[24] The authors reported that the Diels-Alder cycloaddition between α,β-unsaturated enals such as **18** and cyclohexadiene could be catalysed with just 5 mol% of imidazoline **20**. Condensation of the amine with the enal afforded the more reactive iminium ion which then readily underwent a cycloaddition reaction with cyclohexadiene. The authors proposed that the presence of the benzyl group on the catalyst blocked the *Si* face of the iminium to attack and allowed the formation of the product **21** with excellent enantioselectivities and *endo* selectivity.

These two seminal papers, examples of covalent catalysis, propelled organocatalysis to the forefront of asymmetric synthesis. The HOMO raising properties of enamine catalysis and LUMO lowering effects of iminium catalysis have enabled reactions between a plethora of electrophile/pro-nucleophile combinations where at least one of the reagents is capable of condensation with the amine catalyst. These include enolisable aldehydes and ketones as pro-nucleophiles and α,β-unsaturated enals and enones as electrophiles.[25,26]

1.3 Non-Covalent Organocatalysis

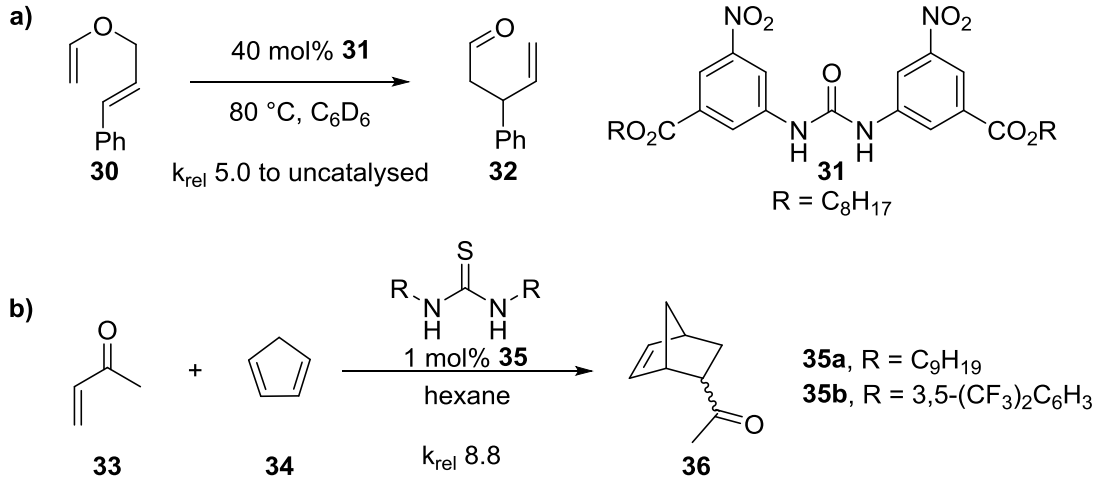
Non-covalent organocatalysis, primarily achieved through hydrogen bonding, is another area of research that has greatly contributed to the recent surge of interest in organocatalysis.[27-30] In 1985, early work on H-bond donor catalysis by Hine and co-workers showed that biphenylenediol **22** catalysed the epoxide ring opening of **23** (Scheme 4a). The authors demonstrated that the diol had the ability to form dual H-bonds with carbonyl moieties and other Lewis bases in both the solid and solution state.[31,32] The first catalytic enantioselective reaction using chiral diols was not reported until 2003 by Rawal *et al.* who used a TADDOL derivative **27** in the hetero-Diels-Alder reaction between **26** and **2** with excellent levels of enantiocontrol (Scheme 4b).[33] Further catalyst development led to a range of alternative bis-hydroxyl containing chiral catalysts for a variety of organocatalytic transformations.[27]



Scheme 4 a) Biphenylenediol catalysed ring opening of aziridines and evidence for dual H-bonding; b) Rawal's TADDOL catalysed hetero-Diels-Alder reaction.

In 1995, Curran and co-workers demonstrated that a *N*,*N*'-diphenyl urea **31**, an alternative dual H-bond donor group, could catalyse a Claisen rearrangement of **30** in an early example of urea catalysis (Scheme 5a).[34] Evidence of a urea's ability to form dual H-bonds

with carbonyls had been shown several years earlier by Etter's crystallographic studies.[35] In 2003, Schreiner, a stalwart of thiourea organocatalysis, published a comprehensive study on the rate enhancements of the Diels-Alder reaction between methyl vinyl ketone **33** and cyclopentadiene by a series of thioureas (Scheme 5b).[36] The use of the symmetrical electron deficient 3,5-$(CF_3)_2C_6H_3$ thiourea **35b** enhanced the rate of reaction by a factor of 9 relative to an aliphatic thiourea **35a**.



Scheme 5 a) Curran's urea catalysed Claisen rearrangement; b) Schreiner's thiourea catalysed Diels-Alder reaction.

The 3,5-$(CF_3)_2C_6H_3$ thiourea moiety would later emerge as a 'privileged' H-bond donor group in organocatalysis (*vide infra*).[37-40] The inductively electron withdrawing trifluoromethyl groups at the *meta* position of the aromatic ring increases the acidity of the protons of the thiourea. Furthermore, hydrogen bonding interactions between the sulfur thiourea and the proton at the *ortho* position increases the rigidity of the system (Figure 2).[41] The preorganisation of the thiourea reduces the activation barrier for complexation of Lewis bases through H-bonding as there are fewer conformational degrees of freedom of the free thiourea. The thiourea moiety can readily be incorporated into a catalyst by treating an amine with the commercially available 3,5-$(CF_3)_2C_6H_3$ isothiocyanate.

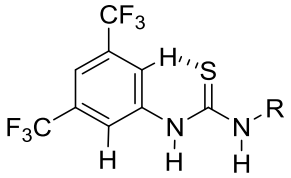
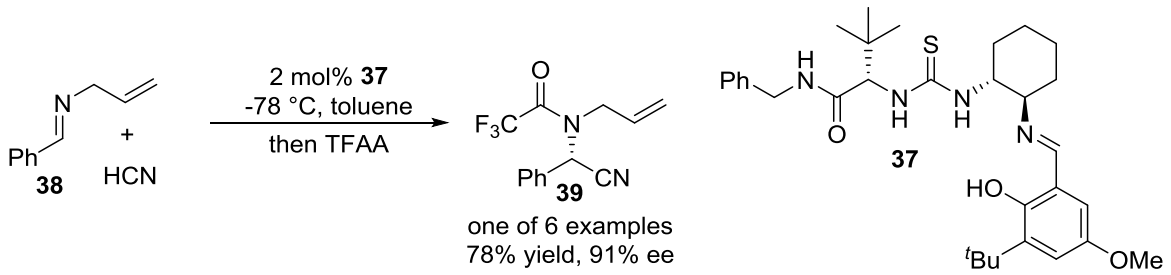


Figure 2 General representation of the 3,5-$(CF_3)_2C_6H_3$ thiourea moiety showing the rigidifying H-bond interaction between the *ortho* proton and the sulfur of the thiourea. R represents chiral and achiral structural motifs of organocatalysts that incorporate the 3,5-$(CF_3)_2C_6H_3$ thiourea moiety.

In 1998, when investigating chiral Schiff bases bearing a thiourea as ligands such as **37**, Jacobsen *et al.* made the unexpected discovery that these were themselves highly efficacious as catalysts in the asymmetric Strecker reaction to *N*-allylimine **38** (Scheme 6).[42] Subsequent investigations expanded the scope of the reaction to include other imines such as *N*-benzyl imines and ketimines with slight modifications to the catalyst structure.[43-46]



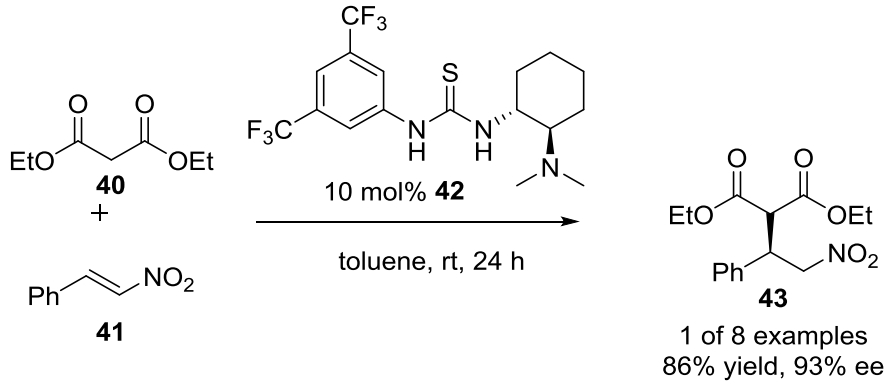
Scheme 6 Jacobsen's initial Schiff base thiourea catalysed hydrocyanation of *N*-allyl imines.

A range of catalysts, all containing the amide-thiourea moiety were found to catalyse the addition of a range of pro-nucleophiles to imines such as phosphites,[47] silyl-ketene acetals[48] and nitroalkanes.[49] The reactions are believed to all occur *via* H-bond activation of the imine by the thiourea moiety and recently related catalysts were shown to be effective in the acyl-Pictet-Spengler,[50] acyl-Mannich[51] and Cope-type hydroamination reactions.[52]

1.4 Tertiary Amine Brønsted Base H-Bond Donor Bifunctional Organocatalysis

The aforementioned catalysts are efficacious in reactions where activation of the electrophile through hydrogen bonding interactions is sufficient to allow product formation *via* a 'pull'-type mechanism. There are reactions, however, that also require activation of

the pro-nucleophile, for example by deprotonation.[53] To address some of the reactivity issues, Takemoto *et al.* reported the first example of an explicitly designed bifunctional thiourea catalyst **42** bearing a tertiary amine and the 3,5-$(CF_3)_2C_6H_3$ thiourea moiety in the addition of diethylmalonate **40** to nitro-olefins such as nitrostyrene **41** (Scheme 7).[54]



Scheme 7 Takemoto's conjugate malonate Michael addition to nitro-olefins catalysed by bifunctional catalyst 42**.**

The catalysts act by simultaneously activating the electrophile by H-bonding interactions and the pro-nucleophile by deprotonation; control experiments demonstrated that the presence of both functional groups was critical to achieve enantioselective catalysis. The authors postulated that the nitro-olefin is bound to the thiourea in the transition state, thus activating it towards nucleophilic attack. The tertiary amine deprotonates the pro-nucleophile to afford the enolate which can then preferentially attack one face of the electrophile (Figure 3a). In later computational studies, Soós and Pápai proposed an alternative mechanism whereby the enol is bound to the thiourea by hydrogen bonds and the tertiary ammonium salt activates the nitro-olefin (Figure 3b).[55] The calculations revealed that in both models, the rate determining step was the formation of the carbon-carbon bond and that transition state b) was 2.7 kcal/mol lower than that proposed by Takemoto.

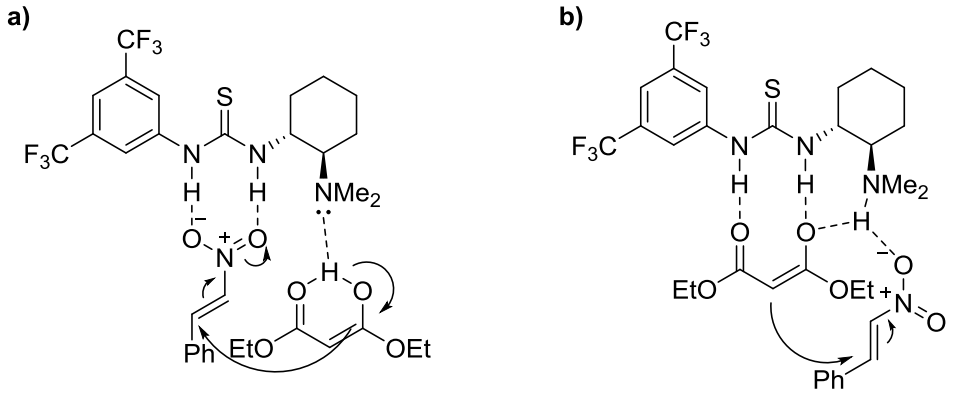
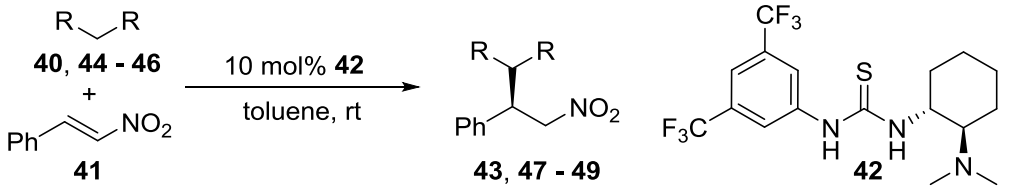


Figure 3 a) Takemoto's postulated pre-transition state; b) alternative transition state according to Soós and Pápai.

In Takemoto's seminal papers on the conjugate addition reactions to nitro-olefins with catalyst **42** a range of different acidity 1,3 dicarbonyl pro-nucleophiles were added to nitrostyrene (Table 1).[54,56] Interestingly, a clear correlation between the acidity of the pro-nucleophile and the rate of reaction was observed. The Michael addition of malononitrile (pK_a in DMSO 11.1) to nitrostyrene catalysed by 10 mol% was complete in 15 minutes at room temperature whereas the analogous reaction using acetyl acetone (pK_a in DMSO 13.3) as the pro-nucleophile required 1 hour to reach completion (Table 1, entries 1 and 2). The Michael addition reactions using dimethyl and diethyl malonate, pro-nucleophiles with pK_a values of 15.9 and 16.4 in DMSO respectively, required reaction times of 9 and 24 h to afford the 1,4 addition products under otherwise identical conditions. Qualitatively, there appears to be a link between the thermodynamic pK_a values and the rate of the conjugate addition as a more acidic pro-nucleophile will be more extensively deprotonated by the tertiary amine base and hence the rate of reaction will be increased.



Entry	Pro-Nucleophile	R =	pK_a (DMSO)	Product	Time / h	Yield / %	ee %
1	**44**	CN	11.1[57]	**47**	0.25	85[56]	25
2	**45**	C(O)Me	13.3[58]	**48**	1	80[56]	89
3	**46**	C(O)OMe	15.9[59]	**49**	9	89[56]	86
4	**40**	C(O)OEt	16.4[58]	**43**	24	86[54]	93

Table 1 Effect of the acidity of the pro-nucleophile on the rate of the conjugate addition to nitrostyrene catalysed by 42**.**

Following Takemoto's seminal report, various groups have designed alternative tertiary amine bifunctional catalysts; those derived from cinchona alkaloids are particularly prominent (Figure 4).[54,60-68] In 2004, Deng and co-workers developed a quinidine derived catalyst **51** where the methoxy group of the quinoline heterocycle was substituted with the free hydroxyl moiety.[60] The authors initially applied the catalyst system to the conjugate addition of malonate esters to aromatic nitro-olefins. The presence of the free hydroxyl group, which was proposed by the authors to activate the electrophile, was critical for the formation of the addition product with high levels of enantiocontrol.

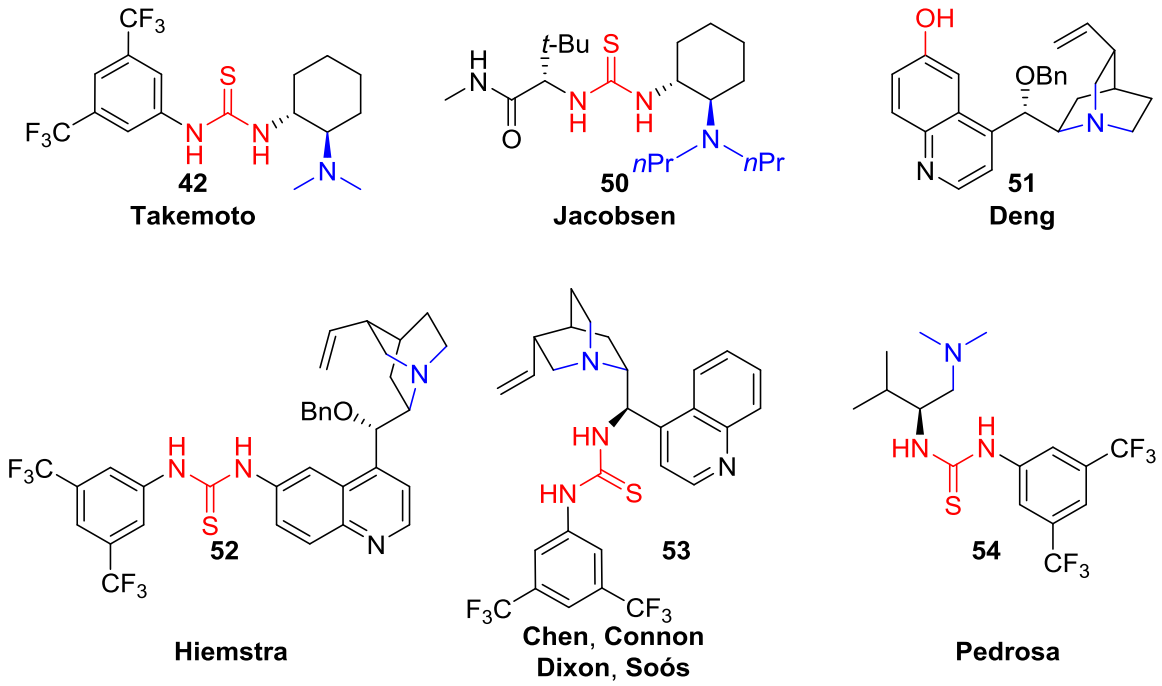


Figure 4 Representative tertiary amine Brønsted base/H-bond donor bifunctional organocatalysts.

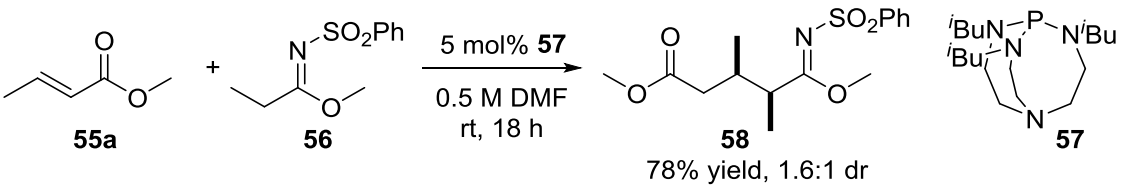
In 2005, four research groups independently developed the cinchona derived bifunctional thiourea organocatalysts such as **53**. Soós and co-workers reported the application of the bifunctional organocatalysts to the Michael addition of nitromethane to chalcone derivatives with up to 98% ee.[61] Meanwhile, Chen *et al.* applied the catalysts to the enantioselective conjugate addition of thiophenol to α,β-unsaturated enones and imides.[62] The groups of Connon[63] and Dixon[64] both reported that this class of catalyst was highly efficacious in the conjugate addition of malonates to nitro-olefins. Analogously to Takemoto's work using the cyclohexyl diamine derived bifunctional organocatalyst **42**, the presence of both the Brønsted base and the H-bond donor group was critical for the formation of enantioenriched product. The relative stereochemistry of the catalyst was found to be imperative for the synergistic activation of both the pro-nucleophile and the electrophile; when the epimer at the C-9 position of **53** was trialled both the enantioselectivity and reactivity were significantly reduced in the conjugate addition of malonate to nitrostyrene.[63]

In 2006, Hiemstra *et al.* disclosed that the cinchona derived thiourea catalyst **52** was highly effective in the enantioselective Henry reaction of nitromethane to aromatic aldehydes.[65] Two years later, Pedrosa and co-workers reported that the conjugate addition of malonate esters to nitro-olefins could also be effectively catalysed by an alternative tertiary amine bifunctional thiourea organocatalyst **54** derived from α-amino acids.[68]

Since the development of these tertiary amine bifunctional thiourea organocatalysts, the authors and many other research groups have exploited the bifunctional nature of the catalysts to catalyse numerous asymmetric reactions that include Michael and hetero-Michael addition reactions,[69] 1,2-additions[70,71] and desymmetrisations[72] amongst others. Comprehensive reviews on the development of tertiary amine bifunctional organocatalysts can be found in the literature[73] and only illustrative examples have been mentioned here.

1.5 Organocatalysts Incorporating Superbases

Tertiary amine Brønsted base bifunctional H-bond donor organocatalysts have found tremendous application in expanding the scope of pro-nucleophiles and electrophiles amenable to asymmetric union. There are however, instances in the literature of catalytic reactions that use alternative and stronger achiral Brønsted bases than tertiary amines (pK_{BH+} of triethylamine is 9.0 in DMSO). For example, Kobayashi and co-workers recently disclosed the conjugate addition of sulfonyl imidate **56** to methyl crotonate **55a** using 5 mol% of the organosuperbase, proazaphosphatrane **57** (Scheme 8).[74]



Scheme 8 Kobayashi's conjugate addition of sulfonyl imidate 56 **to methyl crotonate in an example of a reaction that required the use of an organosuperbase to proceed.**

1.5.1 Organosuperbases

The use of the term 'superbase' is equivocal with several interpretations; in the textbook, *Superbases for Organic Synthesis,*[75] editor Ishikawa and his co-authors adopt the term superbase to include compounds with basicities greater than that of proton-sponge® **60** (DMAN). In an earlier report, Caubère attempted to impose a definition:[76]

The term "superbases" should only be applied to bases resulting from a mixing of two (or more) bases leading to new basic species possessing inherent new properties. The term "superbase" does not mean a base is thermodynamically and/or kinetically stronger than another, instead it means that a basic reagent is created by combining the characteristics of several different bases.

An illustration of this is the enhanced basicity of DMAN **60** relative to *N*,*N*-dimethylaniline **59** (18.6 vs 11.4 in MeCN, Figure 5).[77] Due to unfavourable steric interactions of the methyl groups the *N*-lone pairs cannot conjugate as effectively in the aromatic system and the basicity is also increased due to the cooperative chelating effect of the two amine bases in close proximity. However, the former definition is of greater practical use when describing relative basicity strengths.

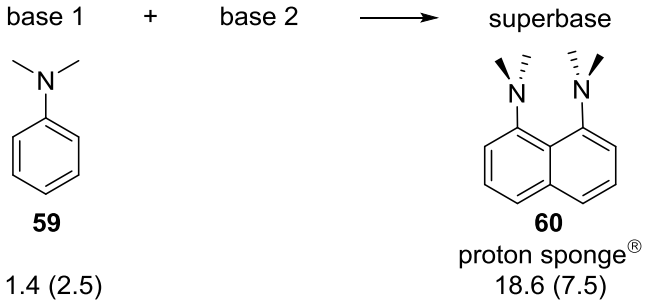
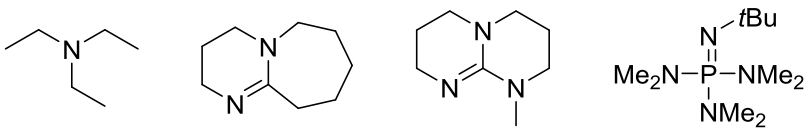


Figure 5 Definition of a superbase according to Caubère and enhanced basicity of DMAN relative to *N*,*N*-dimethylaniline; pK_{BH+} units are given in acetonitrile (and in DMSO).

Amidines and guanidines are the most commonly employed superbases and have been found in a variety of natural products.[78] Their exact basicity varies according to the substituents they possess but a representative example of each is given in Figure 6 (**62** and **63** respectively). The enhanced basicity with respect to tertiary amines is due to increased resonance stabilisation of the protonated amidinium or guanidinium cation from the additional nitrogen lone pairs.



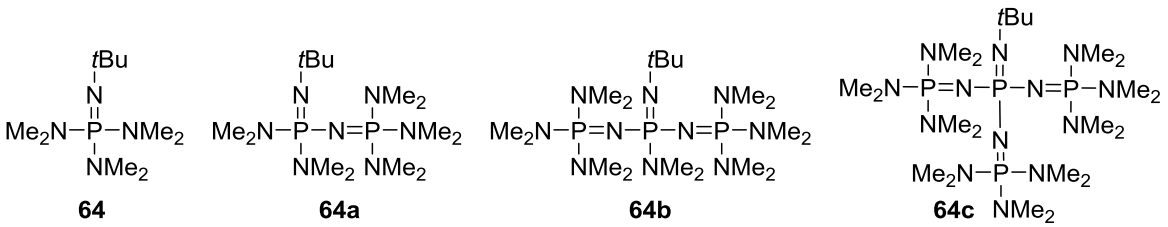
61 **62** **63** **64**

DBU MTBD P_1-*t*Bu

18.82 24.34 25.49 26.98

Figure 6 Representative examples of common organosuperbases with pK_{BH+} values in MeCN. Triethylamine is included for comparison.

An example of a P1-phosphazene **64** is also given in Figure 6 which was introduced in the 1970s and subsequently expanded in the 1980s by Schwesinger.[79] Phosphazenes are inherently more basic than amidines and guanidines and their basicities can be increased further by the addition of other phosphazene units (Figure 7).[80] The basicity increases significantly as the number of N atoms increases in the molecule.



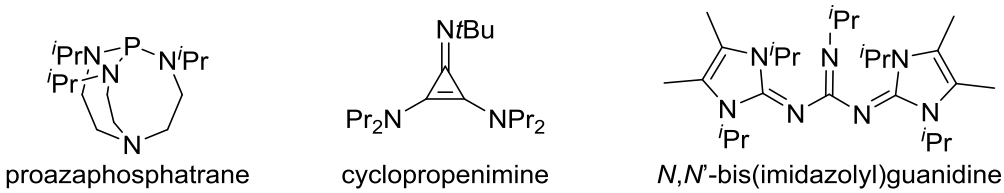
64 **64a** **64b** **64c**

P1 P2 P3 P4

26.98 33.49 38.6 42.7

Figure 7 Higher order phosphazenes with pK_{BH+} values given in acetonitrile.

As a result of phosphazenes being non-nucleophilic and hydrolytically stable strong bases, they have found use in a wide range of reactions.[81] Much attention has been devoted to the design and synthesis of novel superbases including proazaphosphatrane (Verkade) bases **65**,[82,83] cyclopropenimine[84] **66** and *N*,*N*'-bis(imidazolyl)guanidine (BIG) **67** bases (Figure 8).[85]



proazaphosphatrane cyclopropenimine *N*,*N*'-bis(imidazolyl)guanidine

65 **66** **67**

29.0 26.9 29.2 (THF)

Figure 8 Miscellaneous organosuperbases with pK_{BH+} values given in MeCN (or THF).

1.5.2 Asymmetric Organocatalysis with Organosuperbases

Recognising the importance of superbases, several research groups successfully incorporated an organosuperbase into a chiral scaffold to afford effective asymmetric organocatalysts (Figure 9). The most prevalent superbase incorporated into organocatalysts are guanidines.[86] In 1999, Corey described bicyclic guanidine **68** as an effective catalyst in the asymmetric Strecker reaction.[87] The guanidinium salt, formed by deprotonation of the pro-nucleophile, is postulated to act as an effective H-bond donor group.[88] Tan *et al.* demonstrated that a similar *C*2 symmetric guanidine **69** acted as a bifunctional catalyst in the conjugate addition of α-fluoro-β-ketoesters to *N*-alkyl maleimides.[89]

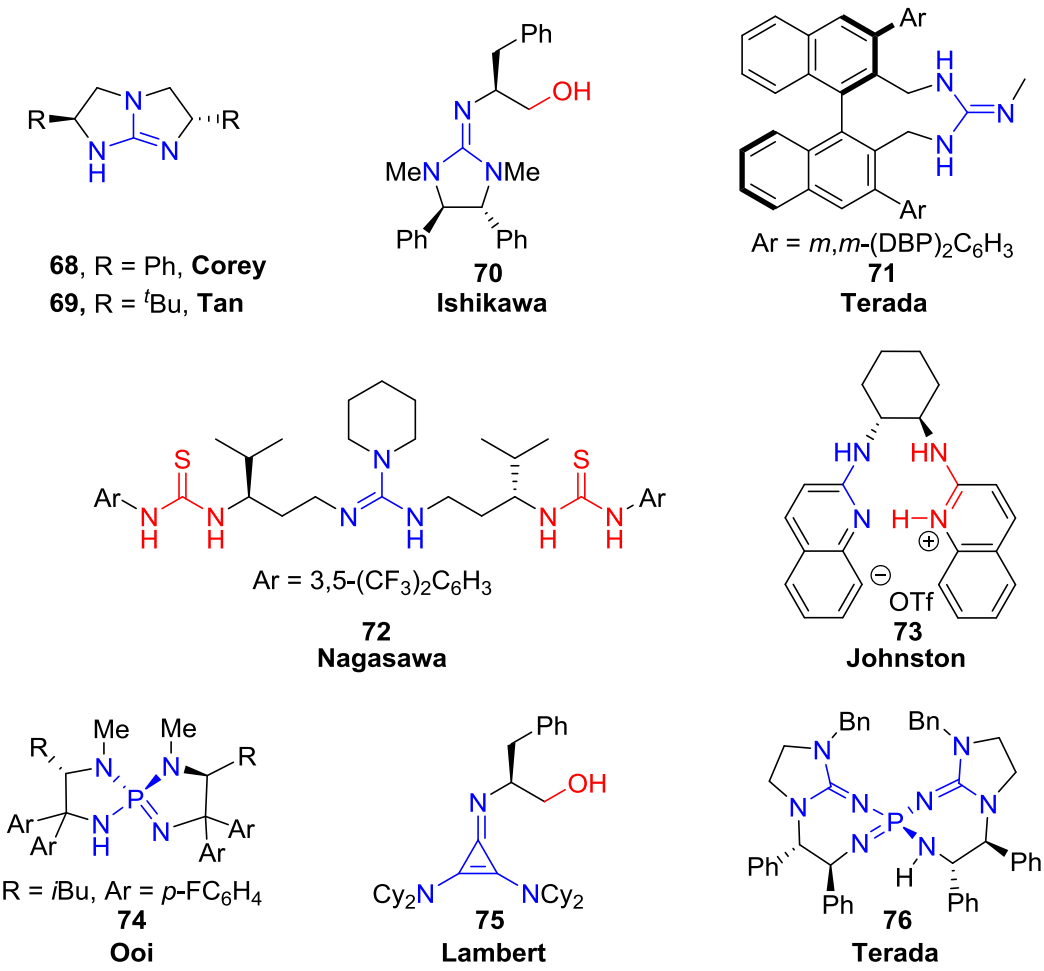


Figure 9 Representative chiral superbase organocatalysts.

Ishikawa, an early proponent of chiral superbases, developed a bifunctional chiral guanidine **70** with a hydroxyl group as the key H-bond donor group in the addition of

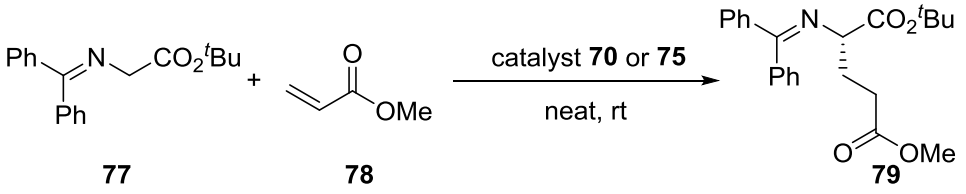
glycine imine to acrylic esters.[90,91] Terada *et al.* designed an axially chiral guanidine **71** as an effective catalyst in the conjugate addition of malonates to nitro-olefins.[92] The authors were able to demonstrate the applicability of their catalyst in a range of other transformations such as the asymmetric Henry reaction with benzaldehydes,[93] the aldol reaction between furanones and aldehydes[94] and α-amination of α-ketoesters.[95]

Nagasawa and co-workers disclosed that a bifunctional catalyst **72** bearing a guanidine moiety as Brønsted base and two thioureas as H-bond donor groups was effective in catalysing the Mannich reaction between *N*-Boc imines and malonates.[96] The catalyst was also able to promote the 1,4-type Friedel-Crafts reaction between phenols and nitroolefins.[97]

Johnston *et al.* reported that a bisamidine salt **73** was effective in the nitro-Mannich reaction between a range of aromatic *N*-Boc aldimines and nitroalkanes.[98] A later report from the same authors described that the basicity of the amidine catalyst could be enhanced by the addition of electron donating groups to the aromatic ring, increasing reaction rates in the nitro-Mannich reaction.[99] In 2007, Ooi and co-workers disclosed the first chiral P-1 phosphazene possessing a *P*-spirocyclic structure **74** as an effective organocatalyst in the Henry addition of nitroalkanes to a range of aldehydes with excellent levels of diastereo- and enantiocontrol.[100] The same catalyst system has found subsequent applications in a range of other reactions such as the enantioselective hydrophosphonylation of aldehydes and dimethylphosphite,[101] the addition of azlactones to imines[102] and in conjugate additions to activated α,β-unsaturated esters.[103,104]

Since the commencement of the DPhil project, two research groups reported the development of new classes of asymmetric organocatalysts incorporating superbases. In 2012, Lambert *et al.* published the use of chiral cyclopropenimines bearing a hydroxyl group such as **75** as highly effective catalysts in the enantioselective conjugate addition of

glycine imines such as **77** to acrylates.[84] The authors proposed that the increased basicity of cyclopropenimines relative to guanidines was responsible for the observed enhanced rate of reaction for the cyclopropenimine catalyst relative to Ishikawa's chiral guanidine catalyst **70** in the conjugate addition reaction of **77** to **78** (Table 2).



77 **78** **79**

Entry	Catalyst	pK_{BH+}	Loading /mol%	Time	Yield/ %	ee /%
1	**70**	23.56[a]	20	3 days	98	93
2	**75**	26.9[b]	10	5 min	99	91

Table 2 Addition of glycine imine 77 **to methyl acrylate catalysed by** 70 **or** 75 **with comparative pK_{BH+} values included in MeCN of structurally related achiral superbases; [a] pK_{BH+} of BTMG; [b] pK_{BH+} of** 66 **(Figure 6).**

The subsequent year, the authors demonstrated that their cyclopropenimine catalyst was also able to promote the Mannich reaction between *N*-Boc protected imines and glycine imines on gram scale with excellent levels of stereocontrol.[105] The mechanism of the conjugate addition to acrylates was probed from both a kinetic and computational perspective and a comprehensive screen of catalysts was performed.[106,107]

In another recent report on chiral organosuperbases, Terada described the enantioselective α-amination of cyclic ketones using a bis(guanidino)iminophosphorane catalyst **76**, in a catalyst design incorporating the salient structural features of Ooi's P1-phosphazene catalyst.[108]

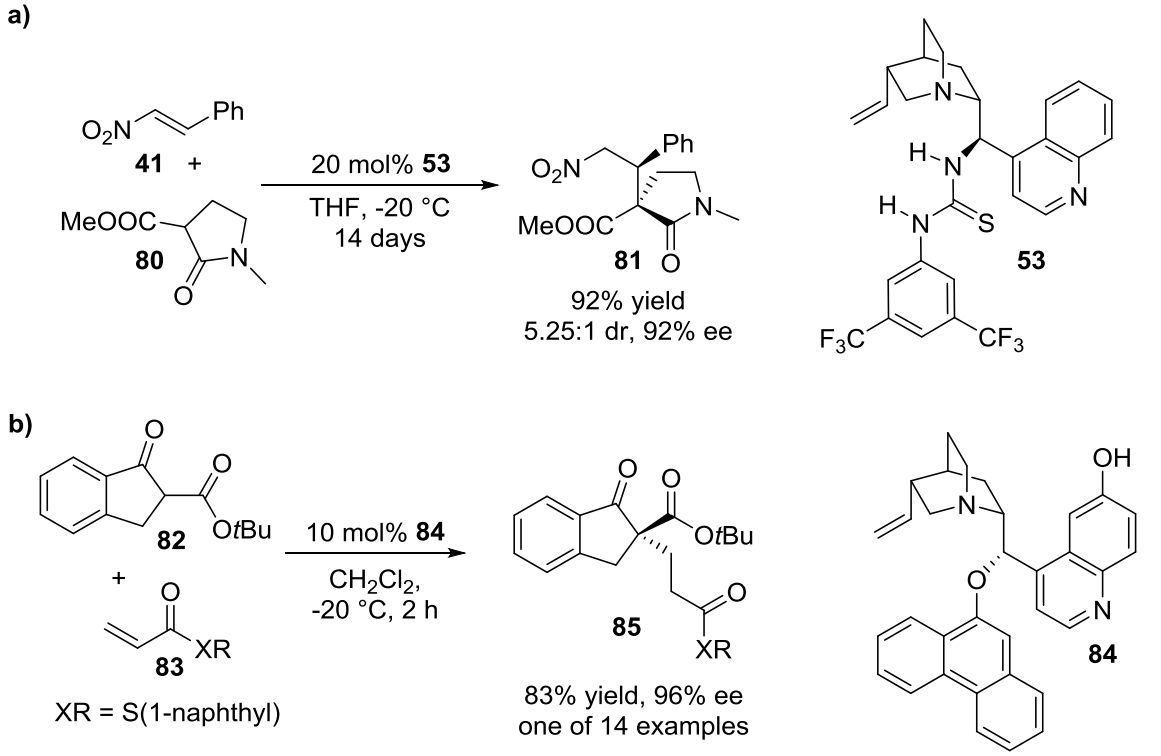
1.6 Limitations of Tertiary Amine Bifunctional H-Bond Donor Organocatalysis and DPhil Aims

The field of organocatalysis has advanced tremendously since its inception with the rational design of new catalysts enabling the discovery of numerous novel asymmetric transformations. The historical examples of metal-free catalysts predominantly used single

enantiomer natural products such as quinine to catalyse a reaction. Over the last decade, with the development of effective H-bond donor groups such as the thiourea, many new organocatalyst designs feature these with a chiral backbone derived from a natural product or other readily available chiral building block. These bifunctional Brønsted base H/bond donor catalysts include structures such as Takemoto's cyclohexyl diamine derived catalyst **42** and the cinchona alkaloid thiourea catalysts such as **53** (Figure 4). The catalysts typically include a tertiary amine as the Brønsted base and have been broadly effective in a range of transformations (*vide supra*).

We recognised however, that there were instances in the literature where some limitations of tertiary amine Brønsted base H-bond donor catalysts became apparent. Long reaction times (1 – 2 days) and high catalyst loadings (10 – 20 mol%) are typical and therefore from an industrial perspective, addressing these considerations would be highly beneficial in order for organocatalysis to be used as a widespread green technology. One example that particularly drew our attention was work published within the Dixon group where the authors investigated the conjugate addition between β-amido ester **80** and nitrostyrene **41** using a cinchona derived bifunctional thiourea catalyst **53** (Scheme 9a).[109] The reaction required 20 mol% catalyst and a 14 day reaction time to afford the Michael adduct **81** in good yield and enantioselectivity at –20 °C. The authors also reported that the reaction to synthesise rac-**81** with 20 mol% DABCO, an achiral tertiary amine base, at room temperature necessitated a three day reaction time. This reaction is therefore an example where the Brønsted base bifunctional H-bond donor catalysts were operating at their limits of reactivity. A possible explanation for the low reactivity observed in this reaction under tertiary amine catalysis is the relatively high pK_a value of **80**. In Takemoto's seminal papers on the conjugate addition of 1,3-dicarbonyls a correlation was observed between the acidity of the pro-nucleophile and the rate of reaction (*vide supra*). Therefore if the pK_a

value of the pro-nucleophile is too high for the pK_{BH+} of the Brønsted base of the catalyst the reaction will proceed much slower. Although, the exact pK_a value of **80** is unknown it can probably be reasonably estimated at around 18 in DMSO, similar to that of β-ketoamides and therefore is an example of a low acidity pro-nucleophile that is just in range of tertiary amine bifunctional organocatalysts.



Scheme 9 a) Conjugate addition of cyclic β-amido ester 80 **to nitrostyrene catalysed by cinchona derived bifunctional thiourea catalyst** 53**; b) addition of β-ketoester** 82 **to α,β-acrylic ester** 83 **catalysed by 10 mol%** 84**.**

In a separate publication, the Dixon group also inadvertently highlighted another limitation of tertiary amine Brønsted base bifunctional organocatalysts when they reported the conjugate addition between various β-ketoesters such as **82** and activated acrylic ester derivatives **83** (Scheme 9b).[110] The reaction proceeded smoothly to afford the Michael adduct **85** bearing a fully substituted carbon atom in good yield and with excellent levels of enantiocontrol in just two hours. For the reaction to proceed however, it was necessary to use an activated acrylic ester derivative. Moreover, the use of activated esters reduces the atom economy of the transformation and additional steps are required for their installation and removal. In an initial screen of reactivity using DABCO the authors found that the

Michael addition did not occur with ethyl acrylate **86** as the electrophile even after 7 days at room temperature. However, when the ester group was substituted to an aryl thioamide moiety, the reaction was complete in just 30 minutes (Table 3).

Entry	Electrophile	XR	Time[a]	Conversion/ %
1	**83**	S(1-naphthyl)	30 min	>95
2	**86**	OEt	7 days	0

Table 3 Select examples of Rigby and Dixon's reactivity study in the optimisation of the Michael addition of 82 **to α,β-unsaturated esters; reactions were performed with 10 mol% DABCO at rt (Scheme 9b).**

Additionally, a closer inspection of pro-nucleophiles/electrophile combinations reported in the literature highlighted that only the most reactive combinations were amenable to asymmetric union under tertiary amine Brønsted base bifunctional H-bond donor catalysis. Aldimines **87**, imines derived from aldehydes are used routinely whereas additions to ketimines are much less prevalent (Figure 10). Nitro-olefins **88** are excellent Michael acceptors that have been used extensively with a wide foray of pro-nucleophiles. Other electrophiles such as enals and enones (**89**) have also been utilised due to their relatively low lying LUMO. In addition, the carbonyls of these electrophiles readily undergo condensation with primary and secondary amines making them amenable to iminium catalysis. Addition reactions to low energy electrophiles such as α,β-unsaturated esters, on the other hand are much more challenging due to the mesomerically electron donating OR group. Iminium catalysis is not viable for these electrophiles and to address the poor reactivity, ester surrogates such as imides **90a**, oxazolidinones **90b**, *N*-acyl pyrroles **90c** or thioamides **90d** have been utilised. Additional steps, however, are required in a synthesis for their installation and removal. Extending the range of electrophiles amenable to organocatalysis to include simple α,β-unsaturated esters such as acrylic, methacrylic and crotonic esters and other feedstock chemicals would represent significant progress in the field of asymmetric catalysis.

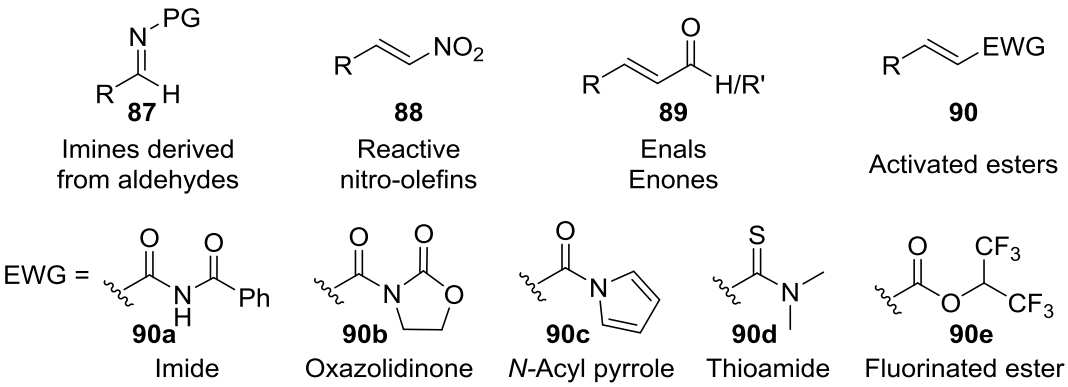


Figure 10 Examples of prevalent electrophiles in organocatalysis.

In a similar vein, only relatively high acidity pro-nucleophiles are amenable to tertiary amine bifunctional organocatalysis (Figure 11). The pK_a value of the carbon or hetero-centred acid must be appropriately matched to the pK_{BH+} of the catalyst. Therefore pro-nucleophiles such as acetyl acetone and other 1,3 di-carbonyls are commonly used whereas high pK_a carbon centred acids such as the solvents ethyl acetate and acetonitrile with pK_a values in DMSO of 29.5 and 31.5 respectively require inorganic bases to be deprotonated.

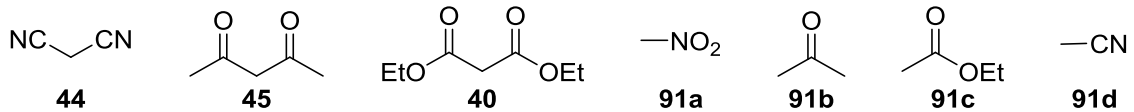


Figure 11 pK_a values in DMSO of a range of carbon centred acids.[57,58,111,112] The pK_{BH+} value of triethylamine is 9.0 in DMSO.[113]

One solution to address the limits of reactivity of bifunctional organocatalysts is to consider catalyst designs that incorporate alternative Brønsted bases to tertiary amines such as superbases (Figure 12). Several groups have successfully used chiral organosuperbases such as guanidines, P-1 phosphazenes and cyclopropenimines as effective organocatalysts (Figure 9) although arguably these catalyst designs do not allow for ready tunability and library generation which would facilitate catalyst optimisation.

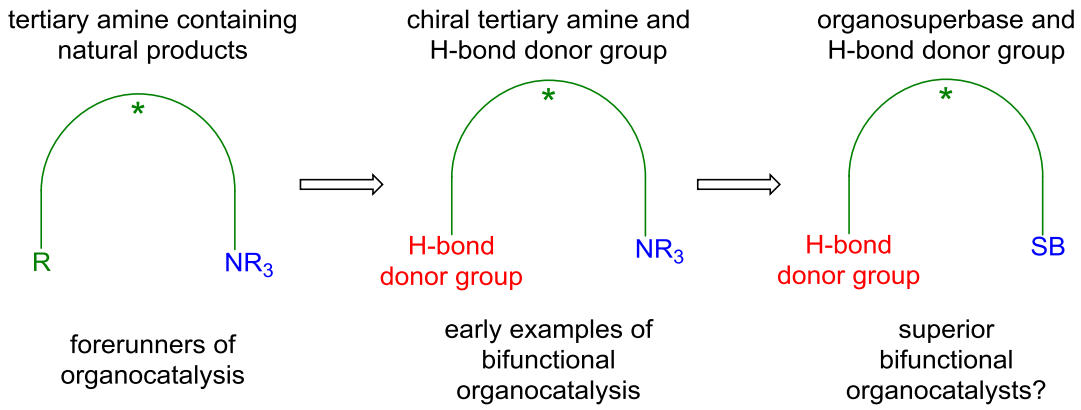
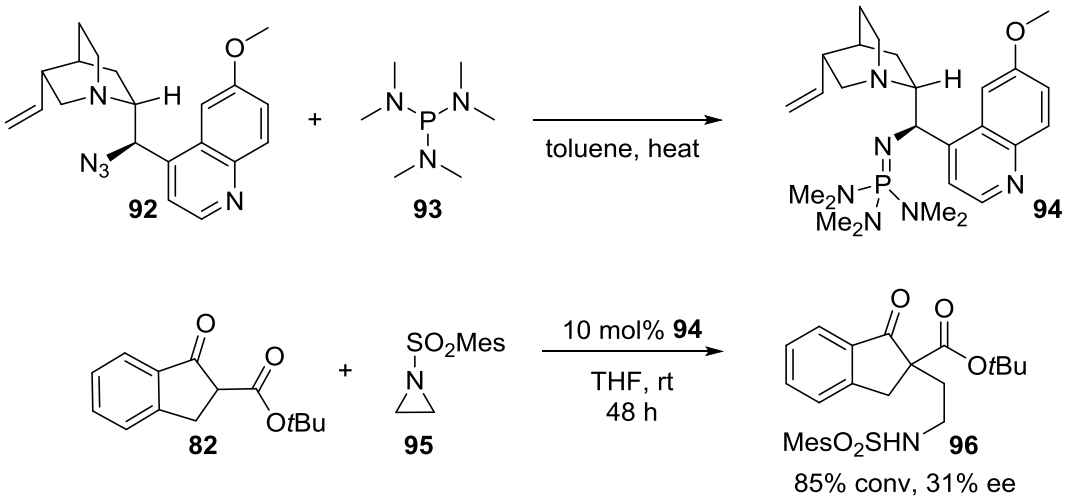


Figure 12 Schematic of the evolution of bifunctional organocatalysis and proposed design of new organocatalysts containing an organosuperbase; SB represents a superbase.

For several years the Dixon group explored the incorporation of an organosuperbase into a chiral scaffold in an attempt to synthesise superior organocatalysts to tertiary amine Brønsted base organocatalysts (Scheme 10).[114] A late stage generation of the Brønsted base was beneficial to avoid handling of the strongly basic compound and therefore the Staudinger reaction between azide **92** and tris(dimethylamino)phosphine **93** to afford a chiral P-1 phosphazene **94** was chosen.



Scheme 10 Synthesis of a chiral P-1 phosphazene 94 ***via*** **the Staudinger reaction and evaluation in the enantioselective ring opening of aziridines.**

The P-1 phosphazenes were catalytically active in the ring opening of aziridines such as **95** using **82** as a pro-nucleophile, a reaction that required the use of superbases to proceed and afforded the product in moderate levels of enantiocontrol. The synthesis of the P-1 phosphazenes was, however, challenging as the Staudinger reaction required prolonged heating. Therefore the generation of a library of catalysts that incorporated a H-bond group

and the P1-phosphazene would be problematic. Although this catalyst design was promising, the difficulties associated with the synthesis of the superbase led us to consider alternative Brønsted bases.

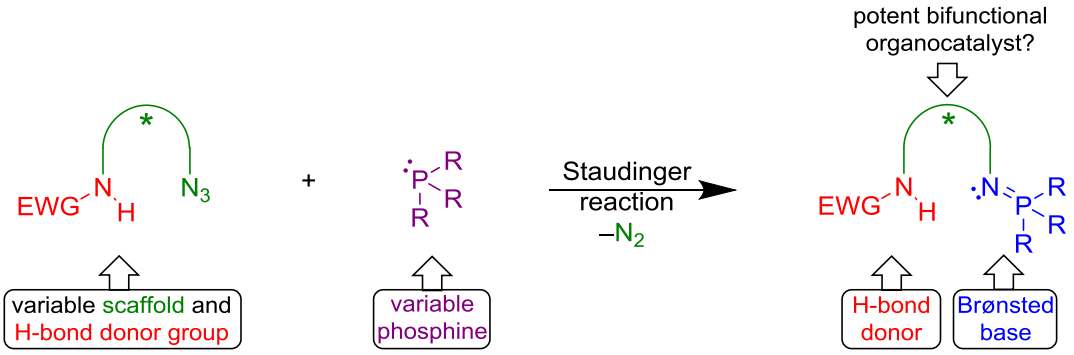
We believed, therefore that a new class of catalyst that successfully incorporated an effective hydrogen bond-donor group and an organosuperbase which demonstrated good reactivity across a wide-ranging spectrum of transformations, would be a notable and powerful contribution to the field of bifunctional organocatalysis. A modular catalyst design with a late generation of the Brønsted base to minimise difficulties working with highly basic moieties was desirable. Ready tuning of the catalyst pK_{BH+} to match the acidity of the pro-nucleophile would be advantageous. Furthermore, the modular design would facilitate the generation of a catalyst library to expedite catalyst optimisation.

The broad aims of this thesis were, therefore, to design a new class of bifunctional organocatalysts and assess their performance in a variety of reactions. More specifically, we sought to apply them to the asymmetric union of new and challenging pro-nucleophile/electrophile combinations such as reactions involving ketimines and simple α,β-unsaturated esters. A primary objective throughout this DPhil was to demonstrate the applicability of the organocatalysts on preparative scale with the focus on minimising reaction times and catalyst loadings which are two of the primary limitations of Brønsted base bifunctional H-bond donor organocatalysts. Finally, establishing a catalyst library that encompassed a broad range of structural diversity would facilitate catalyst optimisation in reactions of interest.

2 Concept, Design and Synthesis of a New Class of Organosuperbase Catalysts

2.1 Concept of Bifunctional Iminophosphorane Catalysts

From the onset, our catalyst design incorporated a strong Brønsted base with a H-bond donor group linked *via* an appropriate chiral scaffold. We also recognised that a late stage generation of the Brønsted moiety would be beneficial, as this would greatly simplify the synthesis, purification and handling of these strongly basic compounds. Building on the prior work in the Dixon group on chiral superbases and the synthesis of P-1 phosphazenes *via* the Staudinger reaction (Scheme 10), we considered triaryliminophosphoranes, the intermediates formed in the Staudinger reaction between an organoazide and a trivalent phosphine, as the crux of our catalyst design (Scheme 11).

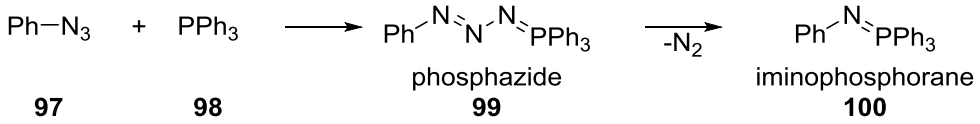


Scheme 11 Concept and design of a new class of bifunctional organocatalysts.

The active bifunctional iminophosphorane (BIMP) catalysts could be readily generated in one step by treating a chiral azide bearing a H-bond donor group with a trivalent phosphine. The modular design would allow the ready generation of a library of catalysts to expedite identification of the optimal catalyst.

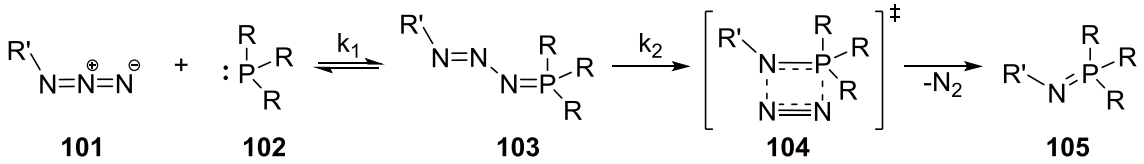
2.2 History of the Staudinger Reaction and Uses of Triaryliminophosphoranes

Hermann Staudinger and Jules Meyer, in 1919, reported the reaction between phenyl azide **97** and triphenylphosphine **98** to afford an iminophosphorane **100**,[115] in a transformation that would later be known as the Staudinger reaction (Scheme 12).[116,117]



Scheme 12 Staudinger's seminal report on the synthesis of iminophosphoranes.

Mechanistic studies on the Staudinger reaction revealed that the rate equation is approximately first order with respect to both the trivalent phosphine **102** and the azide **101** (Scheme 13). Deviations from the second rate order, result from the stability of the phosphazide intermediate **103** which determines the overall kinetics. The rate of reaction is dependent on both the electronic and steric properties of the azide, phosphine and the phosphazide.[118]



Scheme 13 Mechanism of the Staudinger reaction.

The first step involves the reversible nucleophilic attack of the trivalent phosphorous atom at the terminal nitrogen of the azide to afford the phosphazide **103**. These are generally unstable intermediates, decomposing with loss of nitrogen to the iminophosphorane *via* the 4-membered transition state **104** in a 4π electrocyclization and retro [2+2] cycloaddition, however in particular cases they can be isolated. The rate of thermolysis of the phosphazide is shown to have little solvent dependency which is consistent with a pericyclic process.[119] Isotopic labelling studies showed that the proximal nitrogen of the azide to the R' group remained in the iminophosphorane.[120,121] EPR spectroscopy did not reveal the presence of radicals in the rearrangement[122] and importantly the Staudinger

reaction proceeds with retention of configuration of the phosphorous moiety if the trivalent phosphine is chiral.[123,124]

Staudinger detected the intermediate phosphazide at very low temperature[125] but others can be detected at ambient temperature such as **106** (Figure 13).[126] X-ray crystallography revealed that the phosphazide **106** is acyclic and the central N-N linker has *E*-configuration and partial double bond characteristics.[116,127] An isolated report described the phosphazides as less basic than their iminophosphorane counterparts and that protonation occurs at the N atom adjacent to phosphorous.[128]

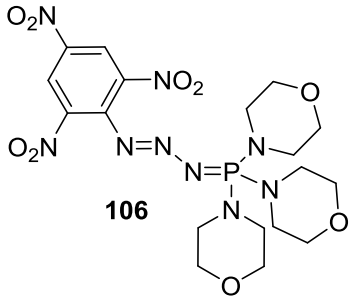


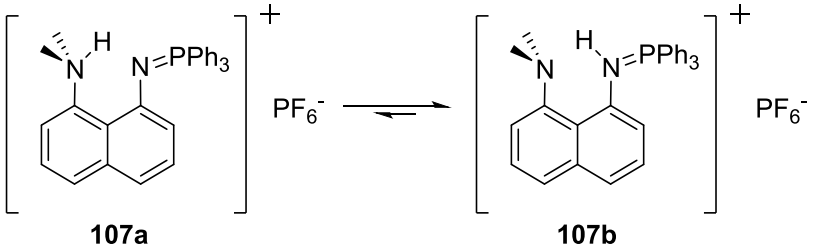
Figure 13 Example of a stable phosphazide.

There have been numerous reports in the literature of the use of triaryliminophosphoranes as Lewis bases.[129,130] The nitrogen lone pair acts as a two electron σ donor and although iminophosphoranes are relatively labile ligands, they have found uses in a number of metal catalysed reactions such as hydrogenation,[131] cross-couplings[132] and olefin polymerisation.[133]

Synthetically, the most prevalent occurrence of iminophosphoranes is as an intermediate in the Staudinger reduction of azides where they are subsequently hydrolysed to the amine and triphenylphosphine oxide. Another use exploits the strongly nucleophilic character of the nitrogen ylide of an iminophosphorane which enables it to react with a range of electrophiles such as carbonyls to form imines *via* the aza-Wittig reaction.[134] Iminophosphoranes have also found applications in bioorganic chemistry in the Staudinger ligation – a transformation that is becoming increasingly useful in the bioconjugation of molecules due to its high chemoselectivity and excellent yields *in vitro*.[135,136]

2.3 Determination of pK_{BH+} Values of Triaryliminophosphoranes

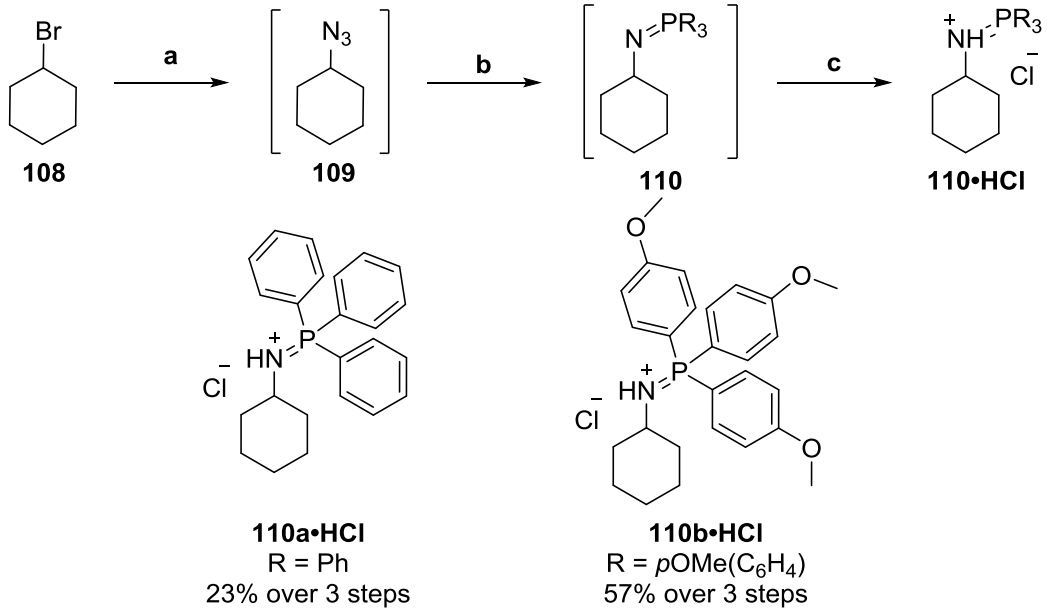
Triaryliminophosphoranes, due to the high energy σ donor orbitals of the nitrogen are effective Lewis bases; however, their ability to act as Brønsted bases has been much less explored. To the best of our knowledge there have been no reports of their use as Brønsted bases. An isolated report in the literature describing triaryliminophosphorane substituted proton sponges **107** indicated that triaryliminophosphoranes were stronger bases than amines (Scheme 14).[137,138] The authors concluded however, that since the iminophosphorane moiety decomposed upon removal of the acidic proton, these reagents would not be synthetically useful.[139]



Scheme 14 Iminophosphorane substituted proton sponge and qualitative basicity measurement.

We initially sought to quantify the basicity of triaryliminophosphoranes and accordingly synthesised two model iminophosphoranes derived from cyclohexyl azide. Cyclohexyl bromide **108** was treated with NaN_3 in DMSO and then with triphenylphosphine (Scheme 15). To avoid isolation of the small and potentially explosive azide **109**, upon work up of the S_N2 reaction, the azide was kept in solution and used *in situ*. The Staudinger reaction was allowed to occur for 24 h at rt in Et_2O and then anhydrous hydrogen chloride in Et_2O was added. The resultant precipitate was collected and purified by silica gel chromatography to afford **110a•HCl** in 23% yield over three steps. The triphenyl iminophosphorane was stored as the hydrochloride salt due to its increased hydrolytic stability compared to the free base form. Analogously, the reaction was

performed using tris 4-methoxyphenylphosphine, a more electron rich phosphine, to afford the salt **110b•HCl** in 57% yield over three steps.[i]



Scheme 15 Synthesis of iminophosphoranes derived from cyclohexyl azide as their hydrochloride salts; a: NaN_3, DMSO, 60 °C, 16 h; b: PPh_3 or *p*-$(OCH_3C_6H_4)_3P$, Et_2O, rt, 20 h; c: 2 M HCl in Et_2O, rt, 1 h.

We elected to use NMR spectroscopy for pK_a determination.[140-142] By exploiting the different chemical shifts of the protonated and free base forms of a Brønsted base and using equimolar quantities of a base of known basicity, the pK_{BH+} can be rapidly determined.

$$HA + B^- \overset{K_1}{\rightleftharpoons} A^- + HB \text{ where } K_1 = \frac{[A^-][HB]}{[HA][B^-]} = \frac{[A^-]^2}{[HA]^2}$$

On the NMR timescale the rate of proton exchange is fast and therefore the observed chemical shift is the weighted average of the free base and protonated forms. This is represented by the equation $\delta_{obs} = x_1\delta_1 + x_2\delta_2$, where δ_1 and δ_2 are the chemical shifts in ppm of the protonated and free base forms and x_1 and x_2 are their respective mole fractions. As $x_1 + x_2 = 1$ the equation can be rewritten as:

$$\delta_{obs} = x_1\delta_1 + (1 - x_1)\delta_2 = \delta_2 + x_1(\delta_1 - \delta_2)$$

[i] The yield of **110a•HCl** was calculated from cyclohexyl bromide whereas the yield for **110b•HCl** was calculated based on tris(4-methoxyphenylphosphine) and 2 eq of cyclohexyl bromide was used.

$$\therefore x_1 = \frac{(\delta_{obs} - \delta_2)}{(\delta_1 - \delta_2)}$$

K_1 can be represented in terms of the pK_a values of the base of known basicity and that of the unknown basicity.

$$K_1 = \frac{[A^-][H^+]}{[HA]} \div \frac{[B^-][H^+]}{[HB]} = \frac{K_a}{K_b}$$

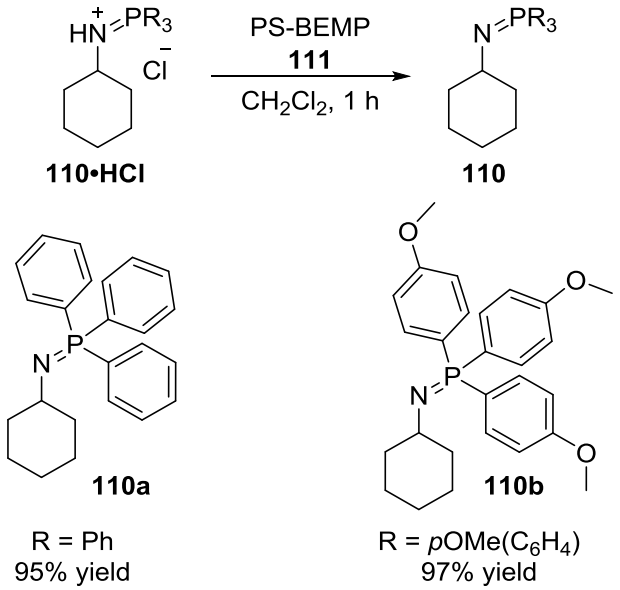
$$\therefore logK_1 = logK_a - logK_b$$

$$\text{since } pK_a = -logK_a \text{ and } pK_b = -logK_b \ \therefore pK_a = pK_b - logK_1$$

$$\text{where } K_1 = \frac{{x_2}^2}{{x_1}^2} = \frac{(1-x_1)^2}{{x_1}^2} \text{ and } pK_b \text{ is a known value}$$

The pK_{BH+} values of many organosuperbases are measured in acetonitrile and therefore d_3-MeCN was used as solvent in the NMR experiments.[77] The free base form of the iminophosphoranes were conveniently generated by stirring the salt at rt with PS-BEMP for 1 h and then filtering off the polymer supported base to afford essentially pure iminophosphorane (Scheme 16).[ii] The NMR spectra were measured for both the salt and free base and compared. The ^{1}H NMR shift of the CH adjacent to the iminophosphorane shifted slightly in the two spectra, as did the ^{13}C peak. The difference in the ^{1}H NMR chemical shifts of the C<u>H</u>N=PR$_3$ signal of the salt and free base were 0.16 ppm for **110a** and 0.15 ppm for **110b**. The ^{13}C signals of <u>C</u>HN=PR$_3$ shifted 0.26 ppm for **110a** and 0.62 ppm for **110b** whereas the difference in the ^{31}P NMR spectra was 26 and 25 ppm respectively for **110a** and **110b**. Accordingly, we elected to use the ^{13}C and ^{31}P chemical shifts to independently determine the pK_{BH+} of triaryliminophosphoranes.

[ii] The iminophosphoranes partially hydrolysed in the NMR tube (Figure 15b) and trace phosphine oxide was observable (~10%). Removing the water content from the solvent would increase the hydrolytic stability of the iminophosphorane. However, no oxide was observed in the spectrum of the salt and less than 0.5% oxide was present in the pK_{BH+} determination experiment (Figure 15c).



Scheme 16 Synthesis of free base iminophosphoranes by treatment with PS-BEMP.

The choice of the base of known pK_{BH+} value was important as it needed to be of comparable strength to that which was being determined and after several trials TMG (pK_{BH+} in MeCN of 23.3)[143,144] was found to be ideal.[iii]

Entry	110a•HCl		110b•HCl	
	^{13}C NMR	^{31}P NMR	^{13}C NMR	^{31}P NMR
Exp.1	22.7	23.0	25.1	24.8
Exp.2	22.8	22.9	25.1	24.9
Exp.3	22.6	23.2	25.2	25.0
Average	*22.7*	*23.0*	*25.1*	*24.9*

Table 4 Estimated pK_{BH+} values of 110a**•HCl and** 110b**•HCl in CD_3CN determined by ^{13}C and ^{31}P NMR.**

[iii] The pK_{BH+} determination experiments were performed in collaboration with Dr M. G. Núñez.

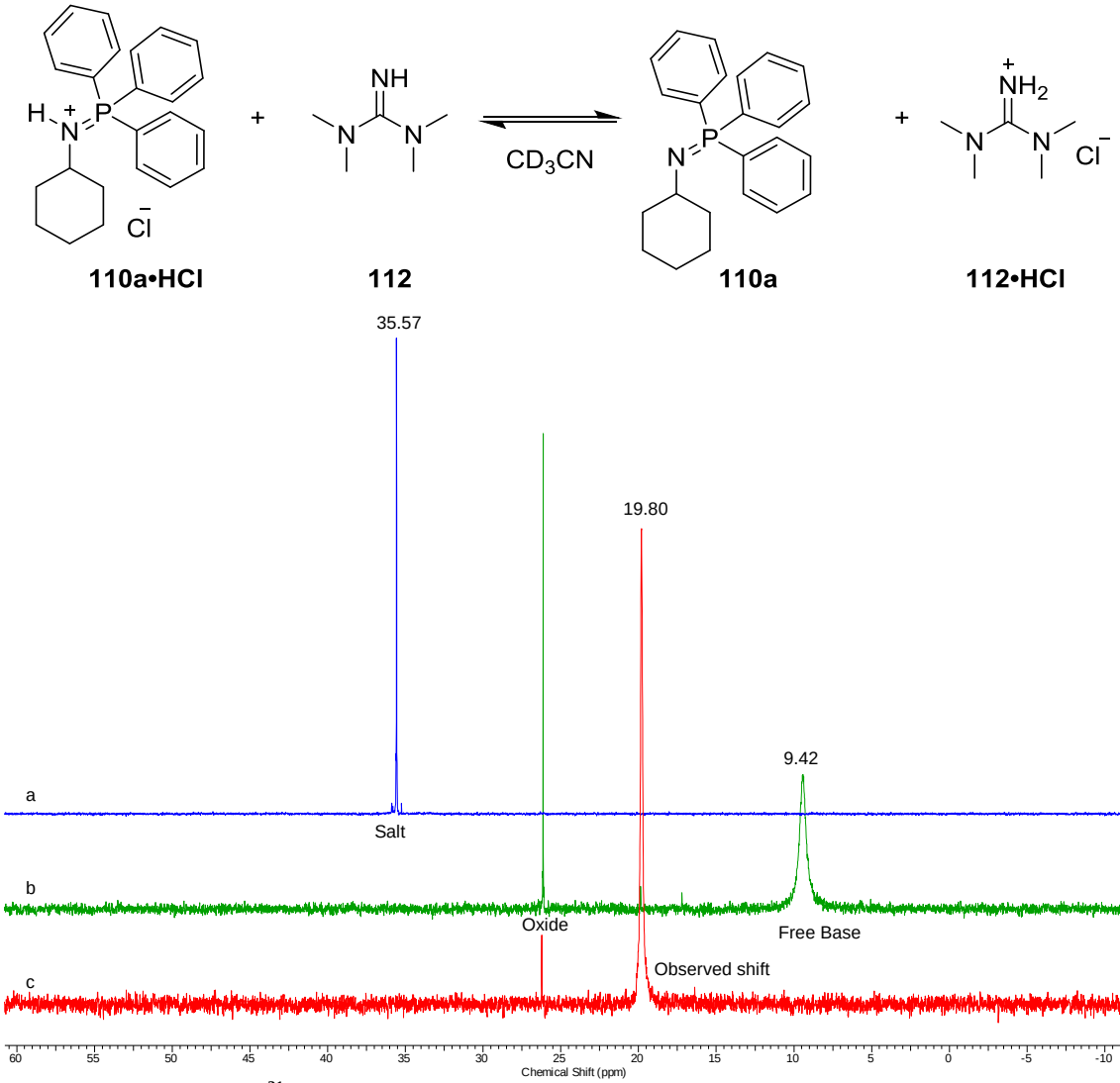
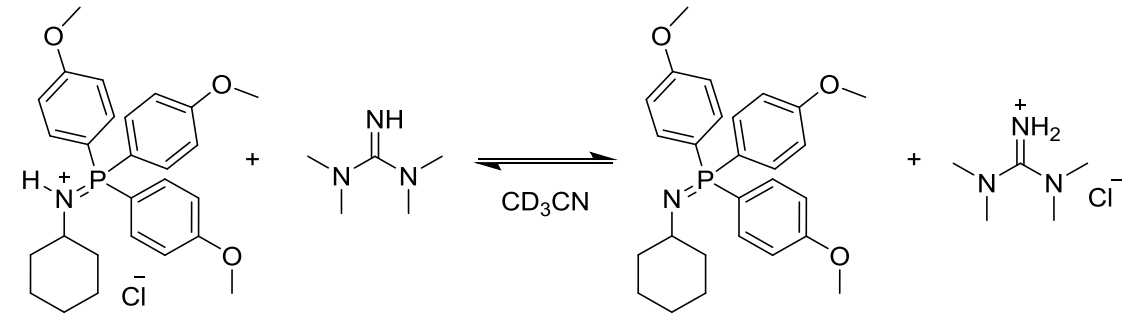


Figure 14 Representative ^{31}P NMR spectra for the determination of the pK_{BH+} of triaryliminophosphorane 110a•HCl **in d_3-MeCN; a) ^{31}P NMR spectrum of** 110a•HCl**; b) ^{31}P NMR spectrum of** 110a **(trace phosphine oxide observable at 25.4 ppm due to partial hydrolysis of the iminophosphorane in d_3-MeCN); c) ^{31}P NMR spectrum of the experiment between equimolar** 110a•HCl **and TMG** 112**.**

The pK_{BH+} of the triphenylphosphine derived iminophosphorane was determined to be 22.7 in acetonitrile and therefore comparable to other organosuperbases such as BTMG and DBU **62** (Figure 16 and Table 4). Importantly, the pK_{BH+} of the iminophosphorane was found to be around 4 orders of magnitude greater than that of triethylamine.



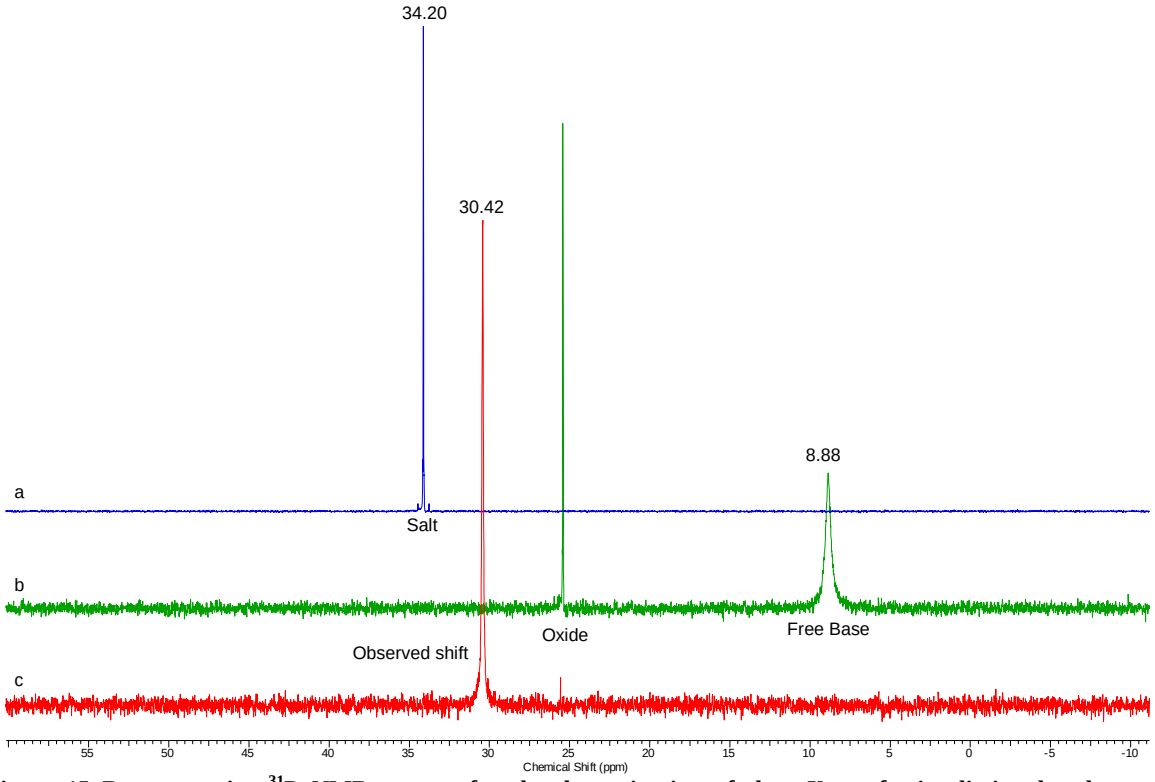


Figure 15 Representative ^{31}P NMR spectra for the determination of the pK_{BH+} of triaryliminophosphorane 110b•HCl **in d_3-MeCN; a) ^{31}P NMR spectrum of** 110b•HCl**; b) ^{31}P NMR spectrum of** 110b **(trace phosphine oxide observable at 25.4 ppm due to partial hydrolysis of the iminophosphorane in d_3-MeCN); c) ^{31}P NMR spectrum of the experiment between equimolar** 110b•HCl **and TMG** 112**.**

Significantly, when performing the same experiments on the tris(4-methoxyphenyl)phosphine derived iminophosphorane **110b•HCl** the pK_{BH+} value was found to have increased by two units to 25.0 (Figure 15 and Table 4).[iv]

[iv] The synthesis of tris(4-chlorophenyl)phosphine derived iminophosphorane of cyclohexyl azide was attempted but under the described conditions an intractable and insoluble mixture was obtained thus preventing pK_{BH+} determination experiments.

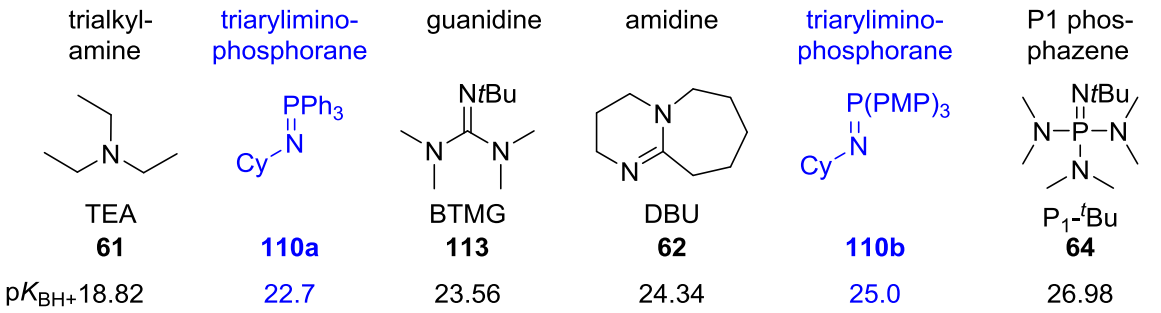


Figure 16 pK_{BH+} of triethylamine and some common organosuperbases. Two novel triaryliminophosphorane bases are also included.

The ease with which the basicity of the iminophosphorane could be tuned by simply varying the electronics of the phosphine moiety was extremely encouraging, as fine-tuning of the catalyst basicity would be beneficial during reaction optimisation. The highly basic iminophosphorane moiety was readily synthesised in good yields under mild conditions from an azide and commercially available phosphine. The late stage generation of the organosuperbase under mild conditions would not only allow for rapid library generation between a range of azides and phosphines but also alleviate the problems associated with the purification and handling of highly basic and polar compounds. Thus, a catalyst design integrating triaryliminophosphoranes as the Brønsted base appeared to be attractive due to its modularity and the ready synthesis of triaryliminophosphoranes.

With quantification of the basicity complete, we next needed to incorporate iminophosphoranes into a chiral scaffold bearing an effective hydrogen bond donor group and evaluate their performance in a range of asymmetric transformations.

2.4 Design and Synthesis of Bifunctional Iminophosphorane Catalysts

The design of an effective asymmetric bifunctional organocatalyst requires judicious incorporation of the H-bond donor group and Brønsted base. Drawing inspiration from existing tertiary amine bifunctional organocatalyst designs (Figure 4) the recurrent 3,5-$(CF_3)_2C_6H_3$ thiourea motif was selected as the hydrogen bond donor group. The use of chiral vicinal 1,2-diamines as a linker between the hydrogen bond donor group and the

Brønsted base predominates the literature. Pedrosa's bifunctional organocatalyst design **54**, utilising chiral vicinal diamines derived from α-amino acids as the chiral linker between the base and H-bond donor group, appealed to us due to its simplicity. Our initial catalyst design is given in Figure 17.

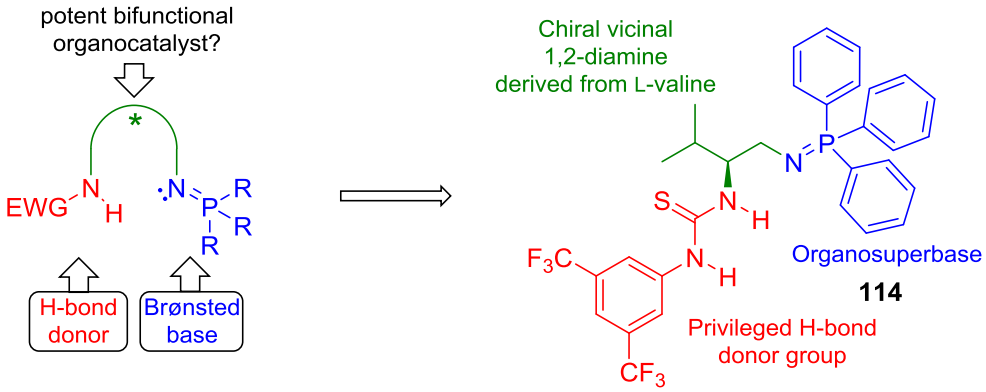
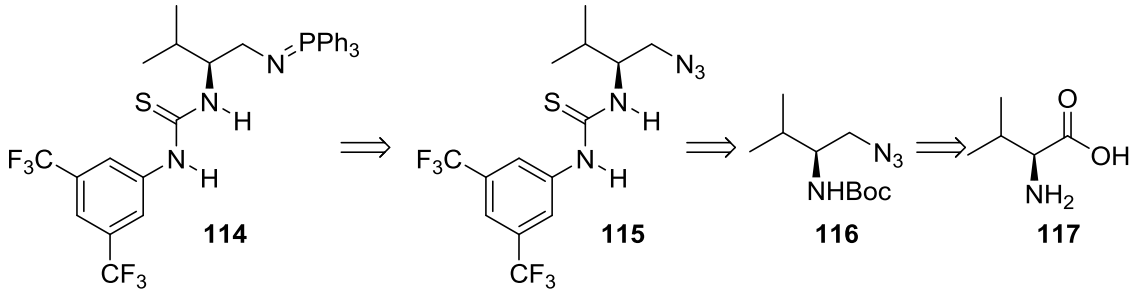


Figure 17 Initial design of a BIMP catalyst incorporating the 3,5-$(CF_3)_2C_6H_3$ thiourea and a triaryliminophosphorane linked by a chiral 1,2-vicinal diamine derived from L-valine.

The BIMP catalyst **114** could be synthesised by the Staudinger reaction between triphenylphosphine **98** and the chiral azide **115** bearing the 3,5-$(CF_3)_2C_6H_3$ thiourea (Scheme 17). The catalysts could be made *in situ* by premixing equimolar quantities of the catalytically inactive azide and phosphine. The catalyst precursor bearing the H-bond donor could be synthesised from the *N*-Boc protected amino azide **116** and 3,5-$(CF_3)_2C_6H_3$ isothiocyanate. The *N*-Boc protected amino azide **116** would be readily synthesised from the α-amino acid L-valine.



Scheme 17 Retrosynthetic analysis of BIMP catalysts.

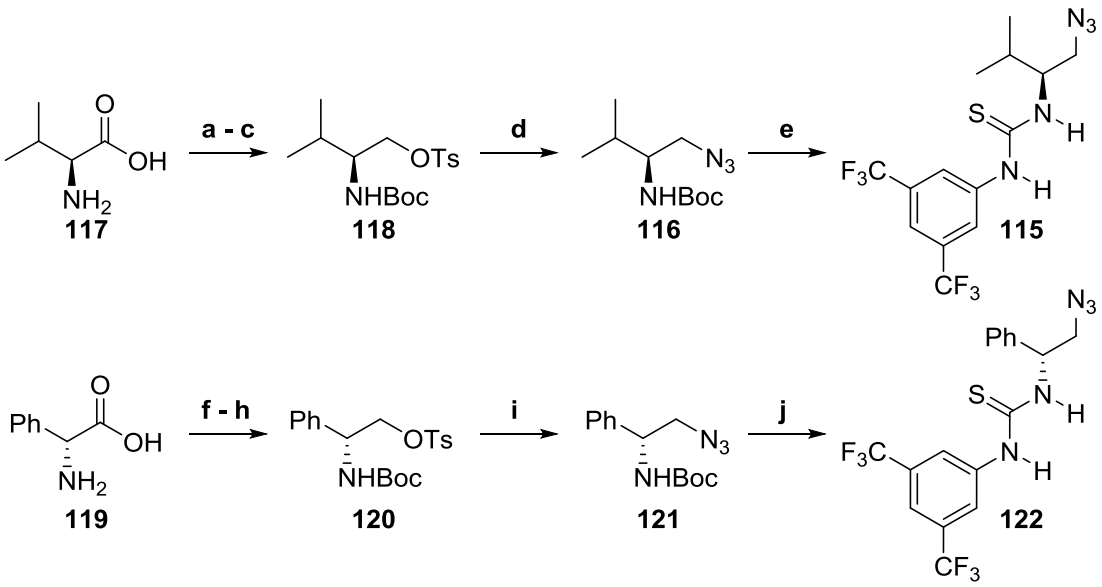
Structural variations to the catalyst backbone would be facile due to the widespread availability of many natural and unnatural α-amino acids. In addition, the modular design of the catalyst would readily allow the generation of a diverse catalyst library. A range of

azides containing various H-bond donor groups could easily be synthesised from the common *N*-Boc protected amino azide **116** with a variety of isocyanates, isothiocyanates and acid chlorides.

2.4.1 Synthesis of L-Valine and D-Phenylglycine Derived BIMP Pre-Catalysts

L-Valine was reduced to the amino alcohol without racemisation by *in situ* generated BH_3 according to McKennon *et al.*[145] and then the amine was *N*-Boc protected in 68% yield over two steps. Tosylation of the alcohol under standard conditions afforded **118** in 68% yield and subsequent S_N2 displacement of the tosylate with sodium azide gave the *N*-Boc protected amino azide **116** in 51% yield. Removal of the *N*-Boc group by treatment with neat trifluoroacetic acid, basification with aqueous sodium hydroxide and then addition to 3,5-bis(trifluoromethyl)phenyl isothiocyanate afforded the thiourea azide **115** in 56% yield (Scheme 18).

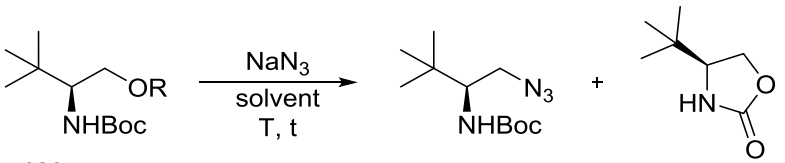
The D-phenylglycine derived precatalyst was synthesised in an analogous manner to the L-valine precatalyst. The tosylate **120** was synthesised in 48% yield over three steps and was displaced with sodium azide in 76% yield to afford **121**. The catalyst precursor **122** was synthesised by removal of the *N*-Boc group and addition to 3,5-bis(trifluoromethyl)phenyl isothiocyanate in 81% yield.



Scheme 18 Synthesis of 115 **derived from L-valine and** 122 **and derived from D-phenylglycine. a: $NaBH_4$, I_2, THF, reflux; b: Boc_2O, NEt_3, CH_2Cl_2, 68% over 2 steps; c:TsCl, NEt_3, CH_2Cl_2, 68%; d: NaN_3, DMF, 45 °C, 51%; e: TFA, then 3,5-$(CF_3)_2C_6H_3NCS$, 56%; f: $NaBH_4$, I_2, THF, reflux; g: Boc_2O, NEt_3, CH_2Cl_2; h:TsCl, NEt_3, CH_2Cl_2, 48% over 3 steps; i: NaN_3, DMF, 45 °C, 76%; j: TFA, then 3,5-$(CF_3)_2C_6H_3NCS$, 81%.**

*2.4.2 Synthesis of L-*tert*-Leucine Derived BIMP Pre-Catalyst*

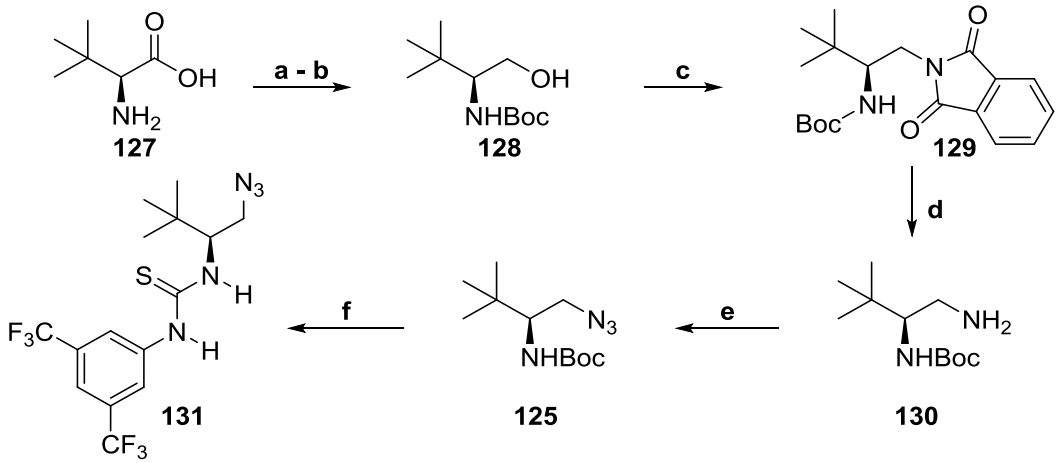
The synthesis of a catalyst precursor incorporating a *tert*-butyl group at the stereogenic centre required an alternative strategy to that described above (Scheme 20). Reduction of L-*tert*-leucine **127** and subsequent *N*-Boc protection afforded the amino alcohol **128** in 70% yield. However when the tosylate **123** (or mesylate **124**) was treated with sodium azide the yields of the desired amino azide **125** were found to be low due to the competing formation of the undesired oxazolidinone side product **126** (Scheme 19).



Entry	R =	Solvent	T (˚C), t (h)	Yield 125 (%)	Yield 126 (%)
1	Ts	DMF	60 ˚C, 8 h	32	26
2	Ms	DMF	80 ˚C, 1 h	32[a]	52[a]
3	Ms	DMSO	50 ˚C, 5 h	6[a]	54[a]

Scheme 19 Formation of undesired oxazolidinone by-product; [a] conversion was measured by integration of the *tert*-butyl signals by ^{1}H NMR.

A viable alternative was to perform a Mitsunobu reaction on **128** to substitute the hydroxyl moiety with phthalimide to afford **129** in 89% yield (Scheme 20). The phthalimide protecting group was removed by treatment with hydrazine monohydrate in refluxing ethanol to afford the diamine **130** in quantitative yield. The amino azide **125** was synthesised by treatment of the diamine with the recently developed diazotransfer reagent,[146] $N_3SO_2Im.HCl$ **133**•HCl and 1 mol% $CuSO_4$•$5H_2O$, to afford the desired product in 85% isolated yield on a 1.25 g scale. Subsequent *N*-Boc deprotection and coupling afforded **131** in 88% yield. Furthermore the structure of **131** was confirmed by single crystal analysis (Figure 18).



Scheme 20 Synthesis of 131 ***via*** **a Mitsunobu-Gabriel diazotransfer sequence; a: $NaBH_4$, I_2, THF, reflux; b: Boc_2O, NEt_3, CH_2Cl_2, 70% over 2 steps; c: DIAD, PPh_3, phthalimide, THF, 89%; d: $N_2H_4.H_2O$, EtOH, reflux, 99%; e: $N_3SO_2Im.HCl$, K_2CO_3, $CuSO_4$•$5H_2O$, MeOH, 85%; f: TFA, then 3,5-$(CF_3)_2C_6H_3NCS$, 88%.**

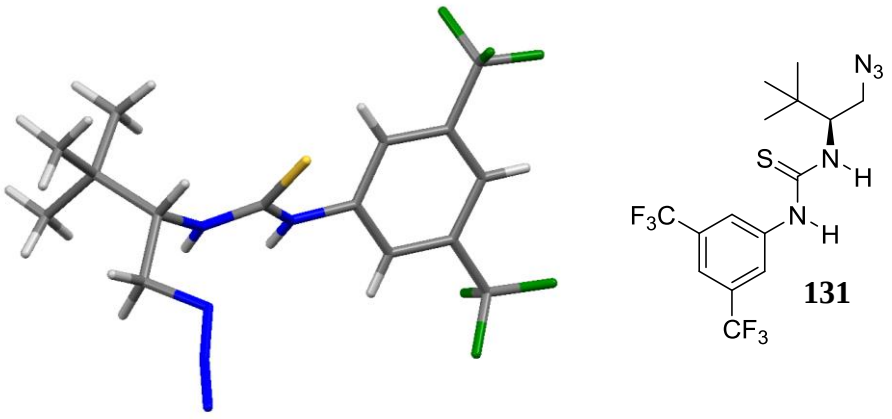
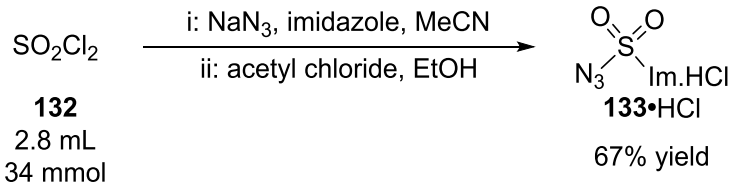


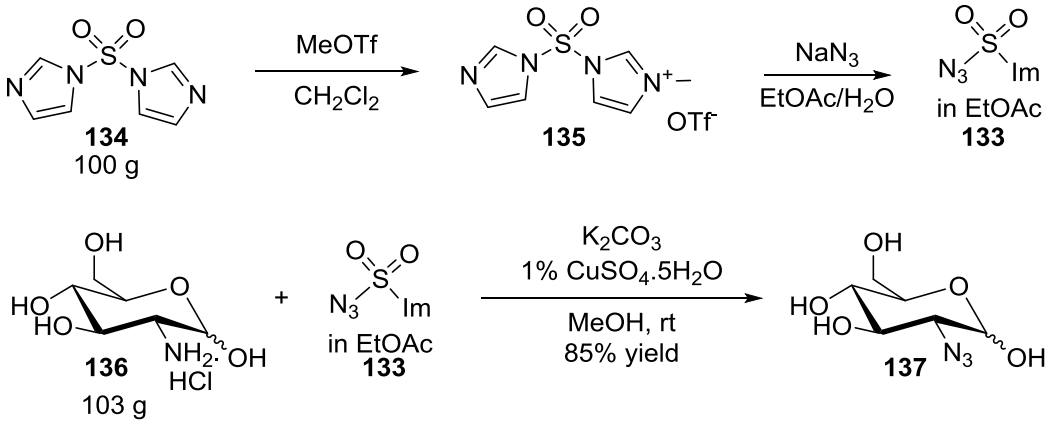
Figure 18 Single X-ray crystal structure of 131**.**

The diazotransfer reagent **133** was initially synthesised as the hydrochloride salt. Treatment of sulfuryl chloride **132** with one equivalent of sodium azide, imidazole and subsequent protonation with hydrogen chloride in EtOH afforded the reagent **133**•HCl as a precipitate which was collected in 67% isolated yield (Scheme 21).



Scheme 21 Synthesis of isolated diazotransfer reagent 134**•HCl.**

Whilst the reagent is believed to be more stable than some other diazotransfer reagents such as TfN_3, the procedure should be performed taking appropriate precautions. The authors published an amendment to their original paper where they reported that an explosion had occurred when mother liquors were being concentrated *in vacuo*.[147] There have also been reports of the formation of hydrazoic acid and sulfuryl diazide[148] side products which are known to be highly explosive.[149] A study on the thermal and kinetic stability of **133**•HCl demonstrated it to be shock-sensitive and that other salts were more stable although these would be more difficult to synthesise.[150]

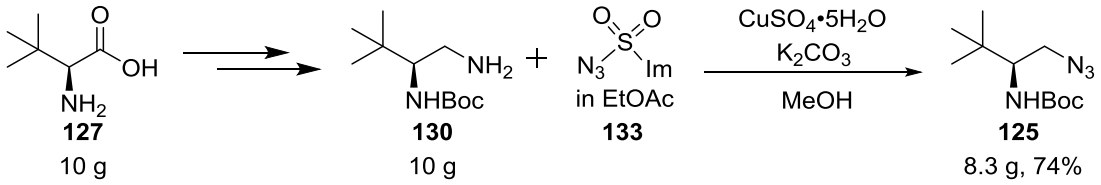


Scheme 22 Synthesis of *in-situ* diazotransfer reagent 133 **and application on scale to the azidation of glucosamine.**

The development of a safer alternative has been sought by various groups and recently the *in situ* use of **133** has been described (Scheme 22).[148] The authors describe the synthesis of **133** on a 100 g scale by treatment of sulfuryl diimidazole **134** with substoichiometric

(0.90 eq) methyl triflate in quantitative yield. The activated imidazole could be displaced with sodium azide to afford **133** as a stock solution in EtOAc. They demonstrated the azidation reaction on a hundred gram scale of glucosamine **136** with comparable yields to when the purified reagent was used.

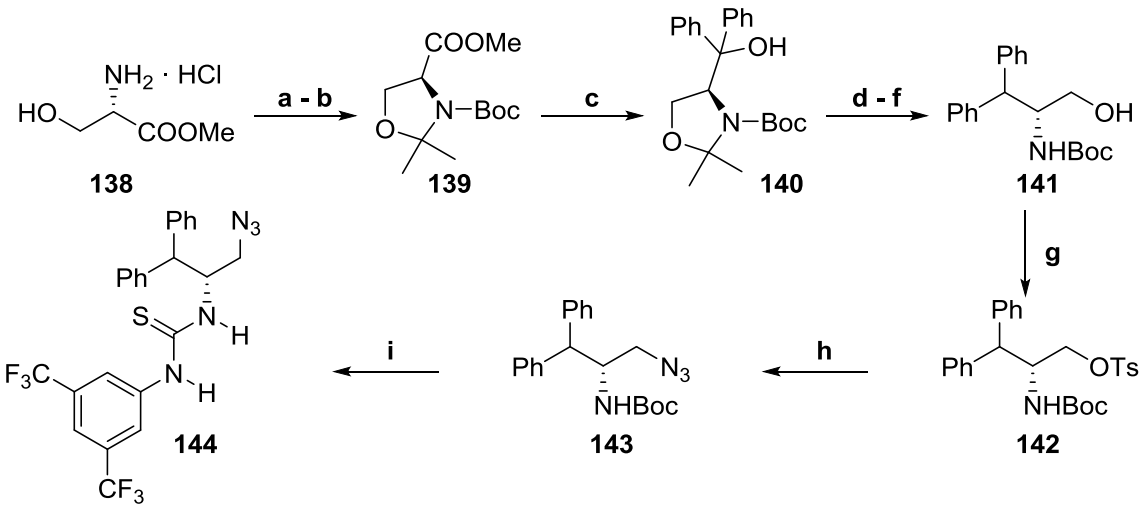
Encouraged by the scale-up capabilities of the diazotransfer reagent, we then performed the synthesis of amino azide **125** on a 10 g scale in a satisfactory 74% isolated yield (Scheme 23).



Scheme 23 Synthesis of 125 **using *in situ* generated diazotransfer reagent.**

2.4.3 Synthesis of BIMP Catalyst Precursor Derived from L-Serine

To install the benzhydryl moiety at the alpha position of the stereogenic centre L-serine methyl ester hydrochloride **138** was used as the starting material; this was *N*-Boc protected and then treated with 2,2-dimethoxypropane to afford **139** (Scheme 24). Nucleophilic attack with phenyl magnesium bromide afforded **140** and removal of the benzylic alcohol was accomplished by hydrogenation in formic acid to give the amino alcohol **141** in 68% yield. Under the same conditions used for the L-valine and D-phenylglycine scaffolds (Section 2.4.1) the tosylate **142** was obtained in 83% yield, substitution afforded the amino azide **143** in 68% yield. Lastly, the catalyst precursor **144** was synthesised in 76% yield.

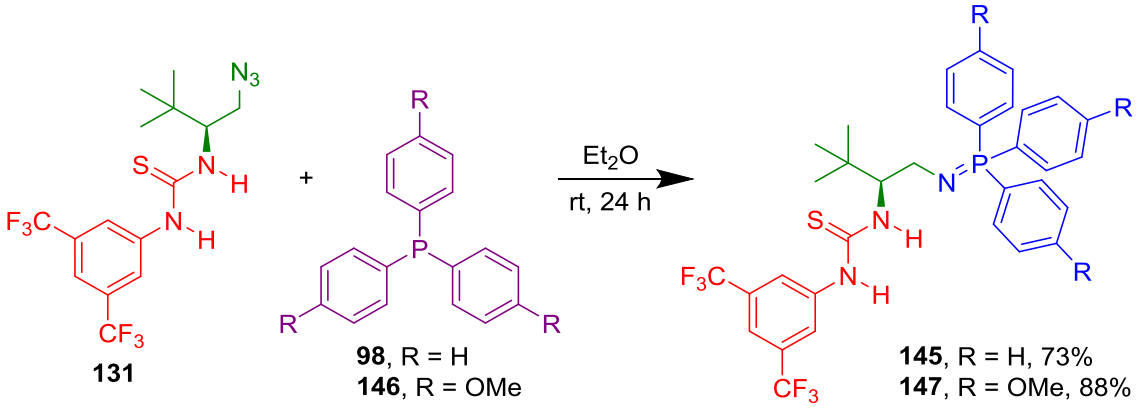


Scheme 24 Synthesis of benzhydryl BIMP precatalyst 144 **from L-serine methyl ester hydrochloride; a: Boc_2O, NEt_3, THF, 50 °C; b: 2,2-dimethoxypropane, BF_3•Et_2O, 99% yield over 2 steps; c: PhMgBr, THF, –20 °C, 54%;d: H_2, $Pd(OH)_2$, HCO_2H, 60 °C; e: NaOH, MeOH/H_2O, reflux; f: Boc_2O, NEt_3, CH_2Cl_2, 68% over 3 steps; g: TsCl, NEt_3, CH_2Cl_2, rt, 83%; h: NaN_3, DMF, 50 °C, 68%; i: TFA then 3,5-$(CF_3)_2C_6H_3NCS$, 76%.**

2.5 Synthesis and Characterisation of Bifunctional Iminophosphoranes

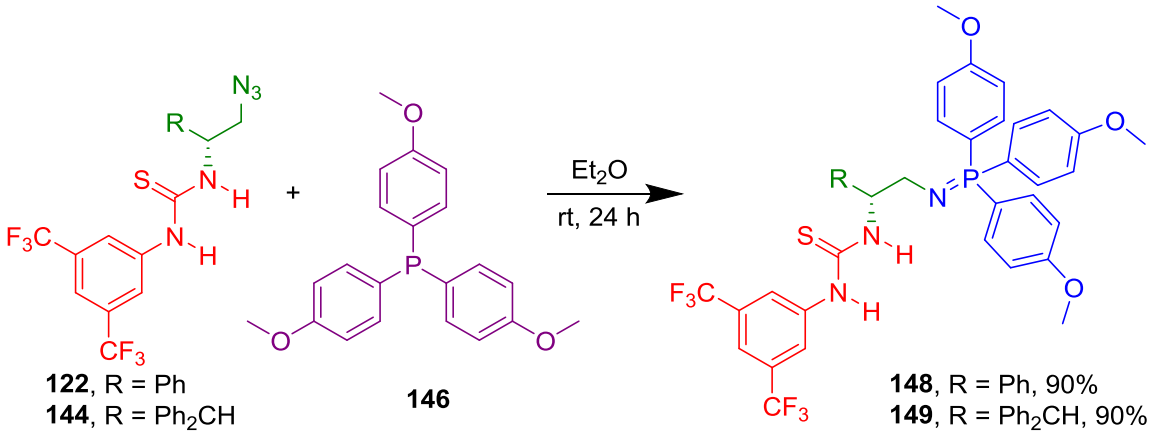
With the synthesis of catalyst precursors complete, the isolation and purification of the bifunctional iminophosphoranes was investigated. L-*tert*-Leucine derived azide **131** was reacted with one equivalent of triphenylphosphine **98** in Et_2O at rt for 24 h (Scheme 25). The volatiles were removed *in vacuo* and the catalyst was triturated by addition of pentane to afford the bifunctional iminophosphorane **145** as a colourless powder in 73% yield after filtration.[v] The bifunctional iminophosphorane **147** was synthesised by the addition of tris(4-methoxyphenyl)phosphine **146** to **131** and isolated in 88% yield after precipitation and filtration from the reaction mixture. The synthesis of the iminophosphorane can be readily performed on gram scale, although necessary precaution for the evolution of nitrogen gas should be taken.

[v] The low yield is due to difficulties encountered during filtration on moderate scale and should be higher when the reaction is performed on larger scale.



Scheme 25 Isolation of L-*tert*-leucine derived bifunctional iminophosphoranes 145 **and** 147**.**

Similarly, bifunctional iminophosphoranes **148** and **149** derived from D-phenylglycine and L-serine respectively were synthesised by treatment of the corresponding azide with equimolar tris(4-methoxyphenyl)phosphine **146** and both were isolated in 90% yield (Scheme 26).



Scheme 26 Isolation of BIMP catalysts derived from D-phenylglycine and L-serine.

The bifunctional iminophosphorane catalysts were fully characterised by NMR spectroscopy and HRMS but unambiguous confirmation of the bifunctional iminophosphoranes was made by single X-ray crystallography.[vi] Crystals of **147** and **148** were grown of sufficient quality for single crystal X-ray diffraction showing the key nitrogen phosphorous bond. The N=P bond was found to be 1.59 Å which is consistent with that reported in the literature for other triaryliminophosphoranes.[138,151]

[vi] The bifunctional iminophosphorane catalysts show interesting dynamic behaviour in solution. See Chapter 5 for details.

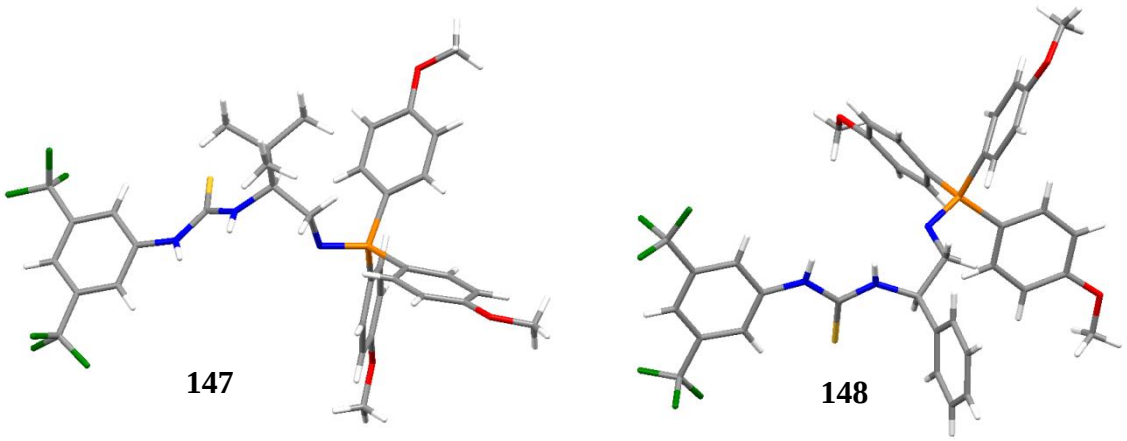


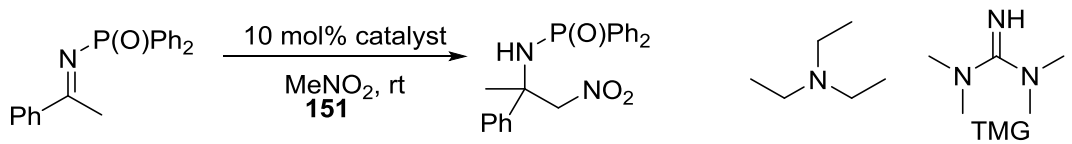
Figure 19 Single X-ray crystal structures of 147 **and** 148**.**

With a preliminary catalyst precursor library and select examples of isolated bifunctional iminophosphoranes in hand, we were ready to evaluate their efficacy in a range of challenging asymmetric reactions.

3 Development of an Organocatalytic Ketimine Nitro-Mannich Reaction

3.1 Chapter Overview

This chapter describes the application of the BIMP organocatalysts to the first general organocatalytic ketimine nitro-Mannich reaction.[vii] The products formed from the nitro-Mannich reaction, β-nitro amines, are synthetically valuable building blocks that allow the construction of 1,2-diamines and α-amino acids (*vide infra*). In comparison to the well-developed organocatalytic aldimine nitro-Mannich reaction, the corresponding reaction to ketimines (imines derived from ketones) has no general solution. Terada *et al.* described the racemic reaction between *N*-diphenylphosphinoyl ketimine **150a** and nitromethane to afford the β-nitroamine adduct **152a** (Scheme 27).[152] Organosuperbases such as TMG **112** were required to catalyse the reaction and importantly triethylamine was ineffective. We postulated that as the BIMP catalysts possess similar basicity to TMG, they may also be efficacious in this reaction. The combination of both a challenging and synthetically useful reaction provided us with an ideal platform to showcase the performance of our newly developed BIMP catalysts. We therefore actively sought the development of the first general enantioselective organocatalytic ketimine nitro-Mannich reaction.



150a **152a** **61** **112**

No reaction 14 h, 91%

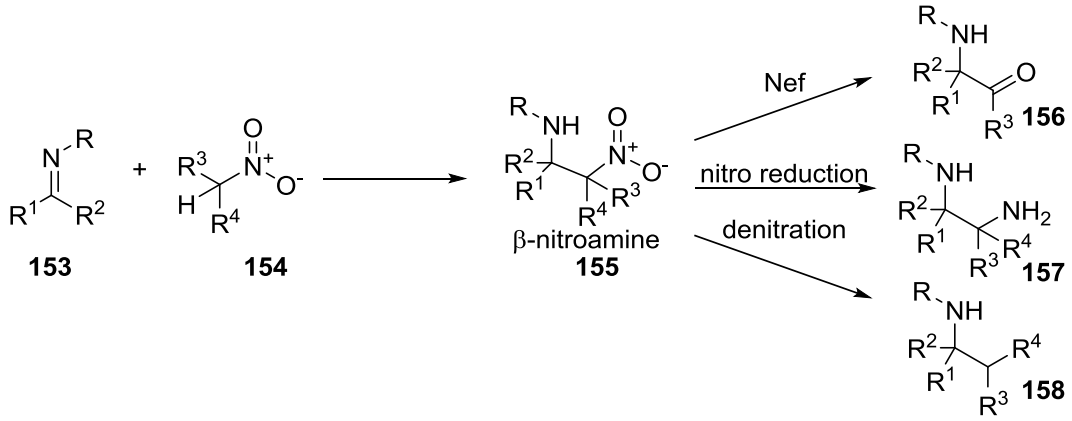
Scheme 27 Terada's racemic organocatalytic ketimine nitro-Mannich reaction between ketimine 150a **and nitromethane requiring the use of organosuperbases to proceed.**

[vii] The work disclosed in this chapter was performed in collaboration with Dr M. G. Núñez who made the initial discovery of the BIMP catalysed ketimine nitro-Mannich reaction prior to the start of the DPhil project. All of the results have been included in this chapter for completeness.

3.2 Introduction and History of the Nitro-Mannich Reaction

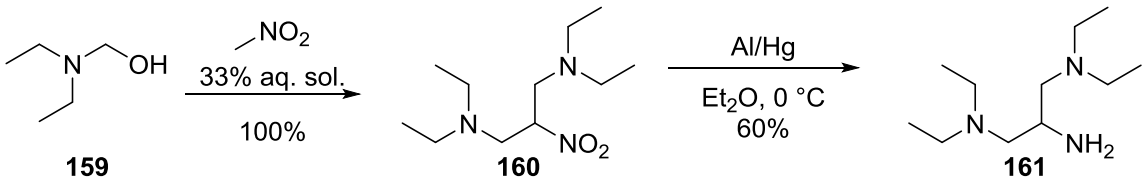
3.2.1 Importance of the Nitro-Mannich Reaction and Early Examples

The addition of a carbon centred acid across a carbon-heteroatom double bond is a fundamental reaction in organic chemistry[153] and includes transformations such as the aldol,[154] Henry[155,156] and Mannich reactions.[157] The nitro-Mannich or aza-Henry reaction is the formation of a β-nitroamine **155** by the addition of a nitroalkane **154** *via* a nitronate to an imine **153**.[71] The β-nitroamine adducts are synthetically useful building blocks, as the nitro group can be transformed into a carbonyl **156** *via* the Nef reaction[158] or reduced to form 1,2-diamines **157**.[159] Alternatively the nitro group can be removed to yield the monoamine **158** (Scheme 28).[160]



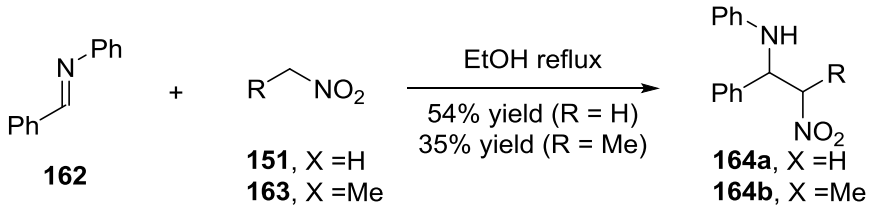
Scheme 28 Summary of the nitro-Mannich reaction and selected chemical transformations.

The nitro-Mannich reaction was first reported by Louis Henry in 1896[161] and the early reports described the addition of nitroalkanes to imines synthesised *in situ* by the dehydration of hemiaminals such as **159**.[161-163] Cerf de Mauny performed a systematic study on Henry's earlier nitro-Mannich reaction and isolated the bis nitro-Mannich adduct **160** in quantitative yield (Scheme 29).[164] The nitro group was reduced to the amine **161** by aluminium amalgam and the reaction scope was extended to higher order nitroalkanes to form the corresponding β-nitroamine in excellent yields.



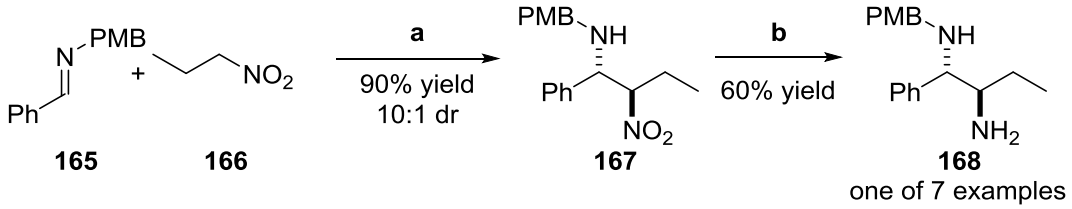
Scheme 29 Cerf de Mauny's nitro-Mannich reaction.

The first nitro-Mannich reaction using preformed imines was not described until 1950 by Hurd and Strong,[165] using benzaldehyde derived imine **162** to form the β-nitroamine product in modest yields (Scheme 30).



Scheme 30 Hurd and Strong's nitro-Mannich reaction using preformed imines.

Anderson and co-workers, at the turn of the 21st century, reported the first diastereoselective acyclic nitro-Mannich reaction with the addition of preformed nitronates at –78 °C to *N*-PMB imines **165** (Scheme 31).[166] After quenching the reaction mixture with AcOH, the β-nitroamines **167** were formed in good yields with good levels of diastereocontrol and the products were derivatised to 1,2-diamines **168**.

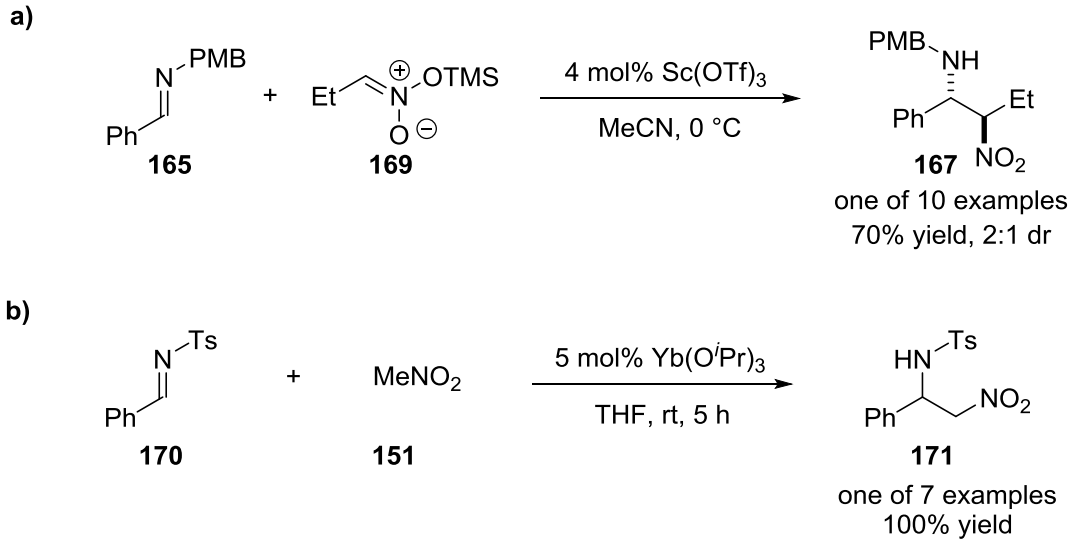


Scheme 31 Anderson's diastereoselective nitro-Mannich reaction from preformed nitronates and *N*-PMB imines. a: ^{n}BuLi, THF, –78 °C then AcOH; b: SmI_2, THF/MeOH.

3.2.2 Catalytic Aldimine Nitro-Mannich Reactions

In 2000, Anderson disclosed that the addition of the TMS trapped nitronate **169** to *N*-PMB and *N*-PMP protected imines could be catalysed by just 4 mol% of $Sc(OTf)_3$ in good yields and with moderate levels of diastereocontrol (Scheme 32a).[167] Following on from Anderson's seminal work, Qian and co-workers discovered that $Yb(O^{i}Pr)_3$ was also an effective catalyst in the nitro-Mannich reaction of nitromethane to *N*-tosyl imines **170**

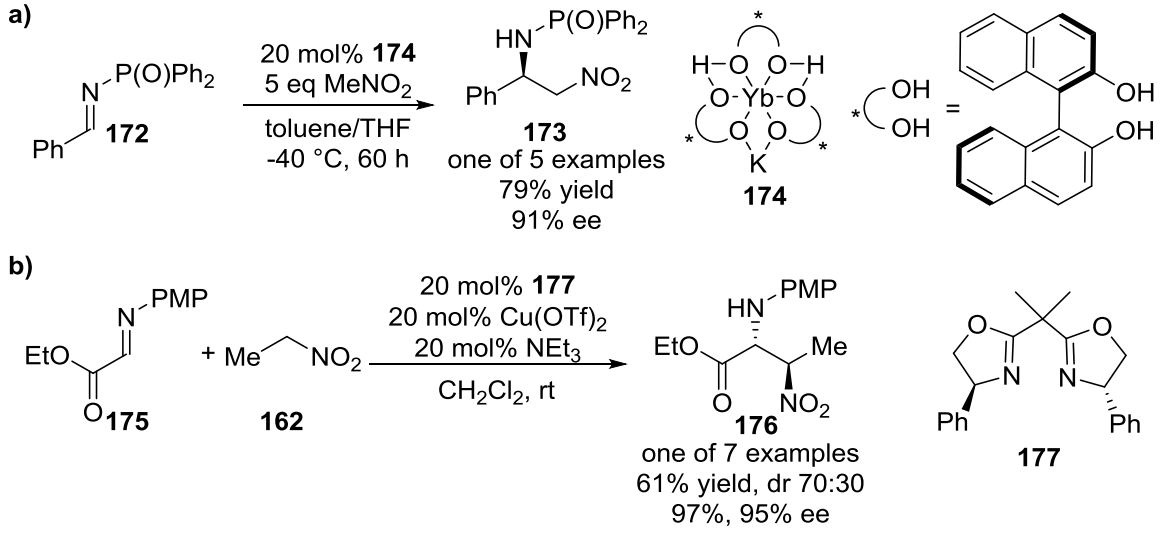
(Scheme 32b),[168] demonstrating that the reaction could proceed catalytically under mild conditions.



Scheme 32 a) Anderson's $Sc(OTf)_3$ catalysed nitro-Mannich reaction using TMS protected nitronates; b) Qian's $Yb(O^iPr)_3$ catalysed nitro-Mannich reaction between nitromethane and *N*-tosyl imines.

3.2.3 Enantioselective Metal Catalysed Aldimine Nitro-Mannich Reactions

In 1999, Shibasaki *et al.* described the first enantioselective nitro-Mannich reaction utilizing the binaphthol ligated Yb/K heterobimetallic complex **174** to catalyse the addition of nitromethane to *N*-diphenylphosphoryl imines **172** (Scheme 33a).[169] The reactions necessitated high catalyst loadings (20 mol%) and reaction times were long, however the products were afforded in good yields and enantioselectivities. The same group subsequently published the use of a binaphthoxide Al/Li bimetallic catalyst to extend the scope to higher order nitroalkanes.[170]

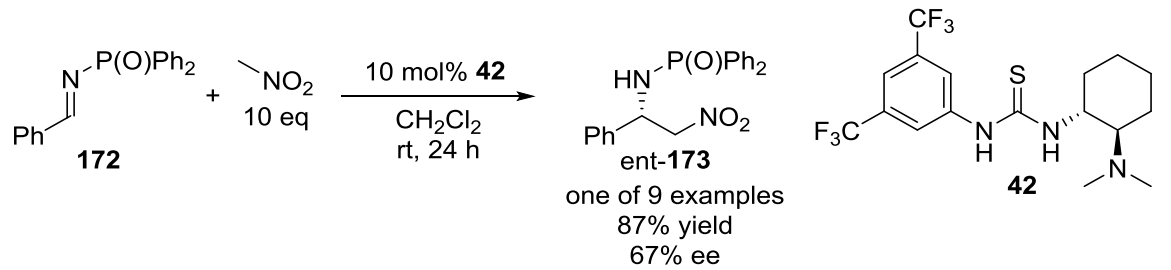


Scheme 33 a) Shibasaki's enantioselective nitro-Mannich reaction catalysed by bimetallic complex 174**; b) Jørgensen's Cu(II)-BOX catalysed nitro-Mannich reaction to α-iminoesters.**

In 2001, Jørgensen and co-workers reported the enantioselective nitro-Mannich reaction of nitroalkanes to *N*-PMP-α-iminoesters **175** catalysed by 20 mol% $Cu(OTf)_2$, bisoxazoline BOX ligand **177** and triethylamine. Although, the reaction scope was limited to **175**, a range of nitroalkanes were well tolerated.[171]

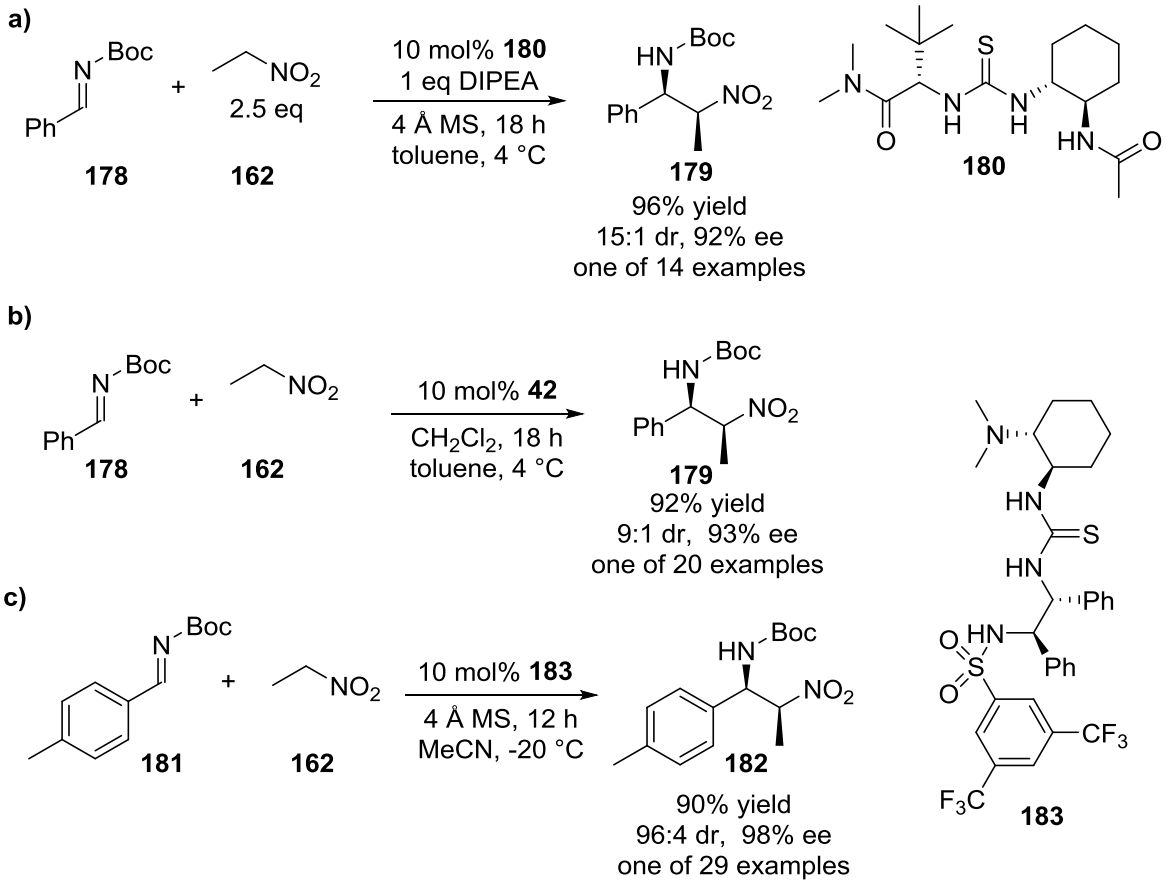
3.2.4 Enantioselective Organocatalytic Aldimine Nitro-Mannich Reactions

The first enantioselective organocatalytic nitro-Mannich reaction was disclosed by Takemoto *et al.* in 2006 (Scheme 34). Cyclohexyl diamine derived bifunctional thiourea **42** catalysed the addition of nitroalkanes to a range of *N*-DPP aromatic aldimines such as **172** with moderate levels of enantiocontrol.[172] The reaction was also applicable to nitroethane with no loss of enantiocontrol and with modest diastereocontrol (2.7:1 dr, 67% ee).



Scheme 34 Takemoto's organocatalytic enantioselective nitro-Mannich reaction of nitromethane to *N*–DPP aldimines.

Following Takemoto's publication, several other groups developed novel thiourea based organocatalysts for the asymmetric organocatalytic nitro-Mannich reaction. Jacobsen and co-workers reported the nitro-Mannich reaction of aromatic *N*-Boc imines such as **178** and nitroalkanes.[49] Due to the absence of a Brønsted base moiety on catalyst **180**, the addition of one equivalent of DIPEA, a tertiary amine, was required for the reaction to proceed. The reaction was applicable to a variety of imines, including two heteroaromatic substrates, which afforded the β-nitroamines **179** with excellent levels of *syn* diastereoselectivity and enantioselectivity (Scheme 35a). The reaction was extended to nitromethane with no loss of enantiocontrol, however the authors noted that much longer reaction times were required.



Scheme 35 a) Jacobsen's thiourea catalysed nitro-Mannich reaction to the *syn* β-nitroamine; b) Takemoto's nitro-Mannich reaction using *N*-Boc aryl imines; c) Wang's nitro-Mannich reaction using a sulfonamide thiourea bifunctional catalyst 183**.**

Takemoto and co-workers subsequently improved on their previous report by using *N*-Boc imines **178** instead of *N*-DPP imines (Scheme 35b).[173] The β-nitroamines were formed

with excellent levels of enantio- and diastereocontrol. The authors' rationale for the observed stereochemistry is that the thiourea and protonated tertiary amine simultaneously coordinate the nitronate and the *N*-Boc imine **178** (Figure 20).

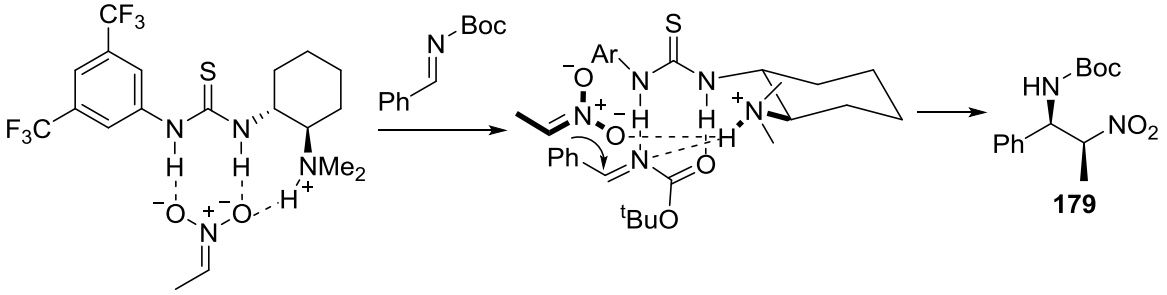
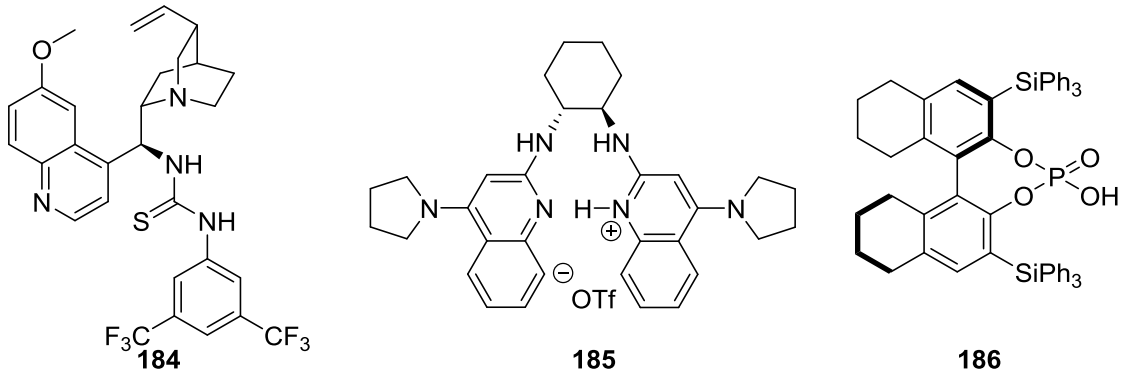


Figure 20 Proposed activation mode in the nitro-Mannich reaction of nitroethane and *N*-Boc phenyl aldimine 178 **catalysed by** 42**.**

Wang *et al.* discovered that their sulfonamide thiourea bifunctional catalyst **183** was highly effective in catalysing the nitro-Mannich of *N*-Boc imines **181** and nitroalkanes with excellent levels of enantio- and diastereocontrol (typically 98-99% ee and >19:1 dr).[174] A wide range of imines were tolerated, including an aliphatic example (Scheme 35c).



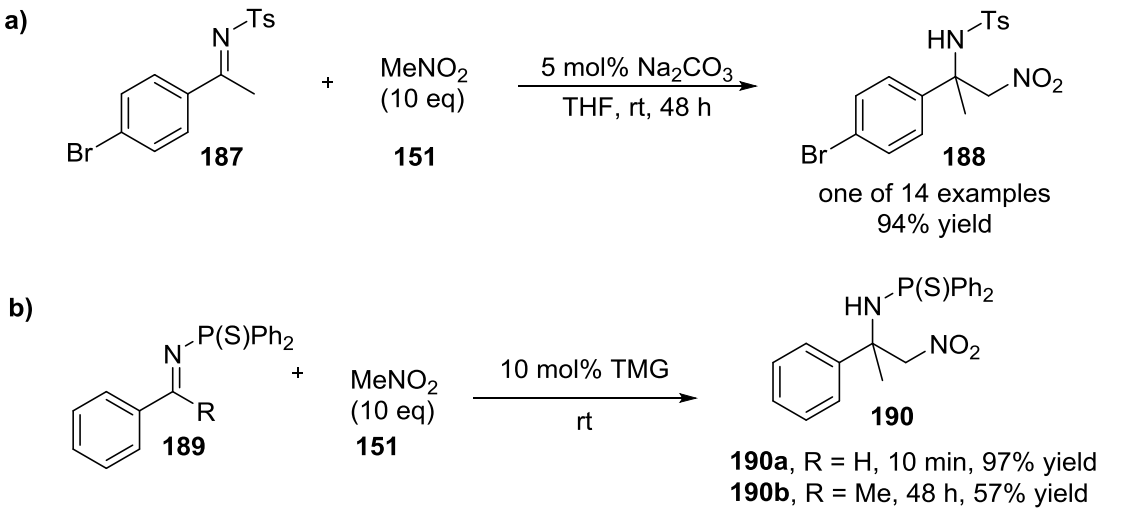
184 Ricci **185** Johnston **186** Rueping

Figure 21 A selection of organocatalysts used in the enantioselective aldimine nitro-Mannich reaction.

The addition of nitroalkanes to aldimines has been documented with a variety of other organocatalysts such as Ricci's report using a quinine-derived thiourea catalyst **184**,[175] Johnston's bis-amidine salt **185**[98,99,176] and Rueping's phosphoric acid **186**.[177] Comprehensive reviews on the nitro-Mannich reaction can be found in the literature[71] and only selected notable contributions have been mentioned here.

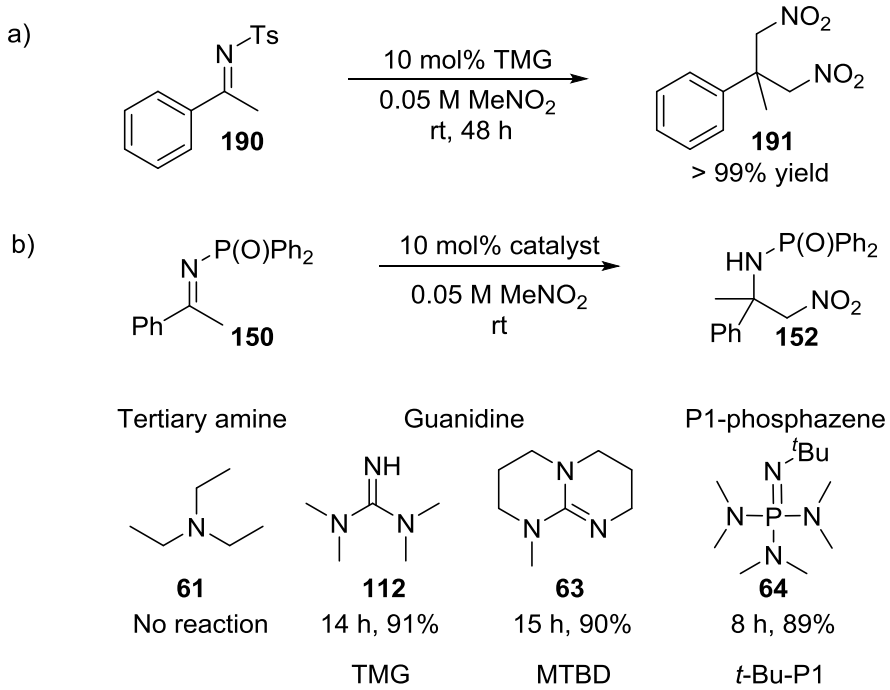
3.2.5 Examples of Ketimine Nitro-Mannich Reactions

In contrast to the well-developed asymmetric nitro-Mannich reaction to imines derived from aldehydes, the corresponding reaction of ketimines has been much less studied. The enantioselective addition of nucleophiles into prochiral imines or ketones to afford the amine or alcohol bearing a fully substituted carbon atom is synthetically much more challenging. Enantiofacial discrimination between the two faces of the electrophile becomes harder due to the smaller difference in size and electronic effects of the two substituents. Moreover, the electrophilicity of the imine or ketone is also much lower due to the inductive effects of two electron donating groups.[178,179] An early report in 2008 by Feng *et al.* on the ketimine nitro-Mannich reaction described the addition of nitromethane into *N*-tosyl ketimines **187** using catalytic Na_2CO_3 to afford the racemic products in good yields (Scheme 36a).[180] Zhou and co-workers disclosed the addition of nitromethane to *N*-thiophosphoryl imines **189** derived from both aldimines and ketimines.[181] Interestingly, whilst the reactions with aldimines **189a** proceeded smoothly under standard tertiary amine Brønsted base H-bond donor bifunctional organocatalysis, the analogous reaction with ketimines **189b** necessitated the use of the superbase TMG to afford the racemate (Scheme 36b).



Scheme 36 a) Addition of $MeNO_2$ to *N*-Ts ketimines 187 **catalysed by Na_2CO_3; b) TMG catalysed nitro-Mannich reaction of *N*-thiophosphoryl imines** 188**.**

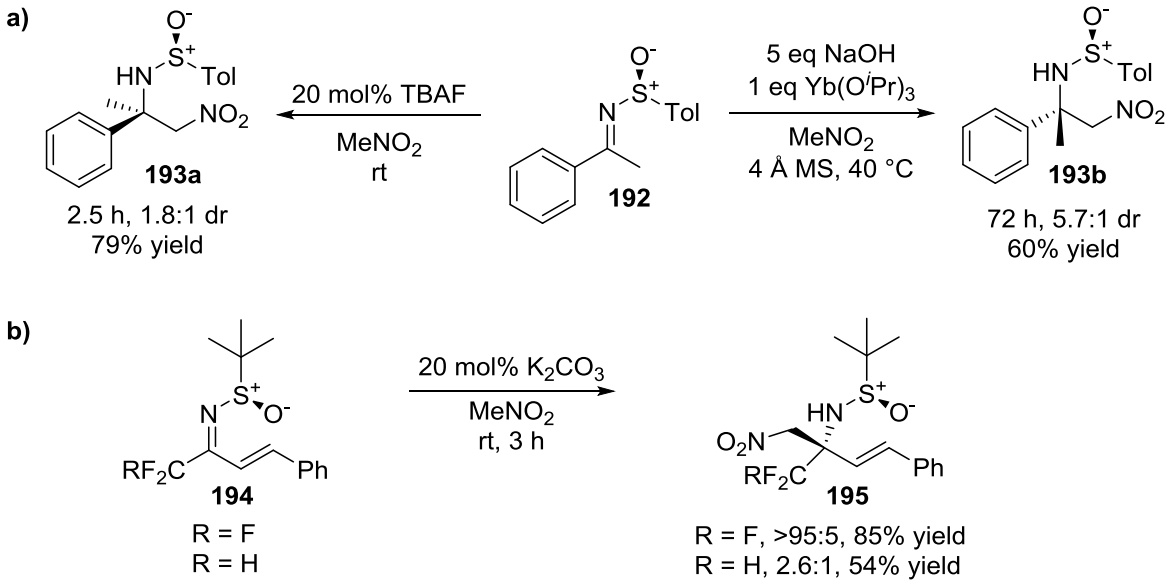
In 2007, Terada *et al.* described the first nitro-Mannich reaction of nitromethane to ketimines catalysed by an organic base and found that the reaction required the use of superbases.[152] They investigated several protecting groups on the imine and found that when using *N*-tosyl ketimine, the β-nitroamine adduct was not obtained; the exclusive formation of the bis-nitro addition product was observed instead. This is presumably due to the enhanced leaving ability of the NHTs moiety (Scheme 37a). With *N*-benzyl or *N*-phenyl ketimines, no product was observed but when *N*-diphenylphosphinoyl (*N*-DPP) ketimine was used the reaction proceeded smoothly. A brief optimisation of the reaction conditions revealed that reaction rates rapidly diminished when nitromethane was not used as solvent and that organosuperbases such as guanidines and P-1 phosphazenes were required to catalyse the reaction. Importantly, triethylamine was ineffective in promoting this transformation, thus suggesting that tertiary amine bifunctional organocatalysts would also be impotent as catalysts in an asymmetric variant (Scheme 37b).



Scheme 37 Terada's organocatalytic nitro-Mannich ketimine addition of nitromethane to *N*-DPP ketimines.

There have been several reports of the diastereoselective nitro-Mannich ketimine reaction, including that by Ruano and Cid, disclosing the use of chiral *N*-sulfinyl imines **192** for

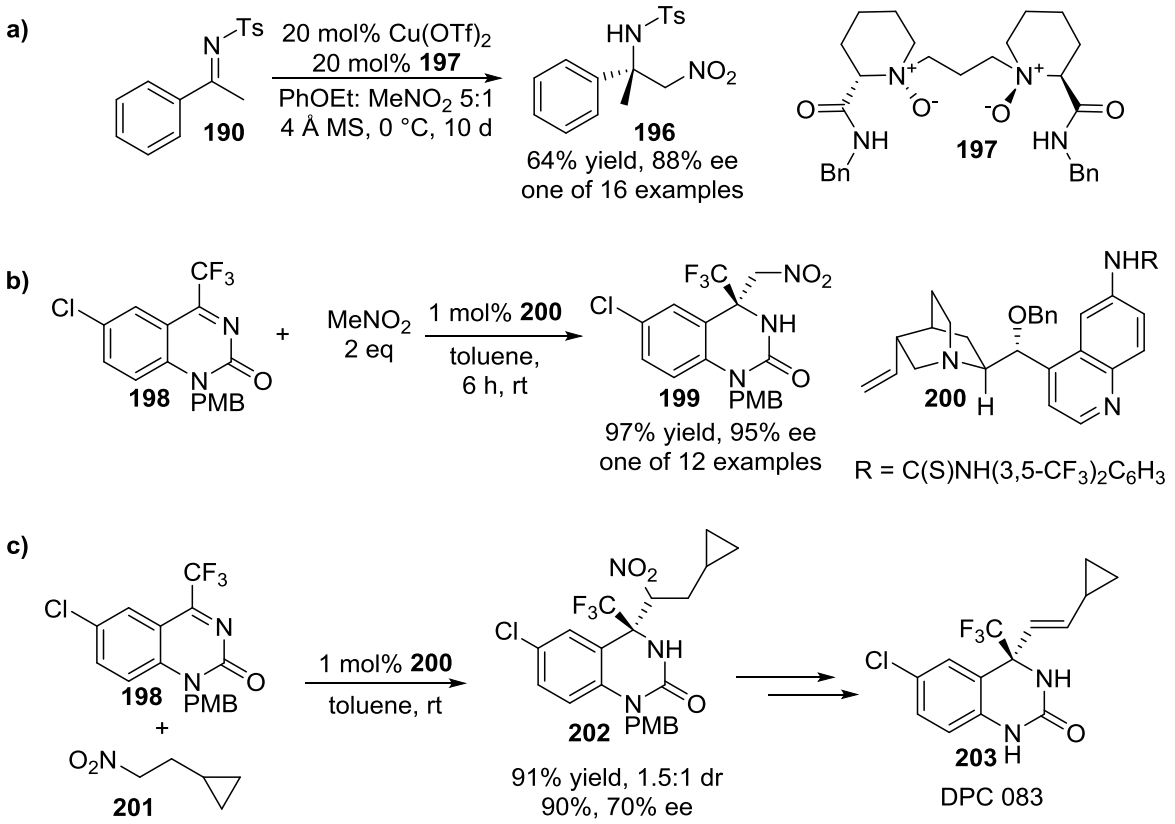
both aldimines and ketimines using either NaOH or catalytic TBAF to afford the nitro-Mannich adducts **193** with moderate to excellent levels of diastereocontrol. However, the reaction with ketimines required the use of stoichiometric $Yb(O^iPr)_3$ to increase the reaction rate (Scheme 38a).[182] In a similar report, Liu described the diastereoselective nitro-Mannich reaction to fluoroalkyl α,β-unsaturated *N*-sulfinyl ketimines **194** requiring the use of 20 mol% K_2CO_3 for the reaction to proceed (Scheme 38b).[183]



Scheme 38 a) Ruano and Cid's diastereoselective nitro-Mannich reaction to *N*-sulfinyl ketimines; b) Liu's diastereoselective nitro-Mannich reaction to fluoroalkyl α,β-unsaturated *N*-sulfinyl ketimines.

The first enantioselective nitro-Mannich reaction of nitromethane to ketimines was reported by Feng *et al.* in 2008. The authors required the use of 20 mol% of a chiral *N*,*N*'-dioxide **197** Cu(I) complex to catalyse the formation of the β-nitroamine **196** bearing a fully substituted carbon with good to excellent levels of enantiocontrol, albeit with long reaction times and high catalyst loadings (Scheme 39a).[184] Wang and co-workers published the first organocatalytic variant, employing a cinchona alkaloid derived thiourea catalyst **200** to effectively catalyse the addition of nitroalkanes to cyclic trifluoromethyl ketimines **198** (Scheme 39b).[185] They were able to demonstrate that catalyst loadings as low as 1 mol% were viable, however, the presence of the CF_3 moiety was critical for reactivity.

This methodology could be applied to the elegant synthesis of the anti-HIV drug candidate DPC 083 **203** (Scheme 39c).



Scheme 39 a) Feng's Cu(I) catalysed enantioselective nitro-Mannich ketimine reaction, b) Wang's organocatalytic nitro-Mannich reaction to cyclic trifluoromethyl ketimines, c) synthesis of anti-HIV candidate DPC 083.

The lack of a general organocatalytic strategy for the enantioselective formation of β-nitroamines bearing a fully substituted carbon centre and the requirement of organosuperbases for the racemic reaction to proceed presented us with an ideal opportunity to showcase our new bifunctional iminophosphorane catalysts. Using Terada *et al.*'s optimised conditions, we thus chose *N*-DPP ketimine **150a** as the electrophile and nitromethane as the pro-nucleophile to establish a proof of principle using a BIMP catalyst.

3.3 Synthesis of N-*Diphenylphosphinoyl Ketimine 150a*

N-Phosphinoyl, in particular *N*-diphenylphosphinoyl (*N*-DPP), imines are an increasingly important class of imines in asymmetric synthesis.[186] *N*-DPP imines **172** are less electrophilic than the corresponding *N*-tosyl[187] and *N*-carbamoyl imines **170** and **178**;[188] a

trend that has recently been quantified by Mayr and co-workers (Figure 22).[189,190] The *N*-protected aldimines are more reactive than the parent carbonyl compound **2** and presumably the electrophilicity trends can be extended to ketimines. The greater reactivity of *N*-tosyl imines with respect to *N*-alkyl and *N*-DPP imines was observed in Terada's racemic ketimine nitro-Mannich report (Scheme 37).

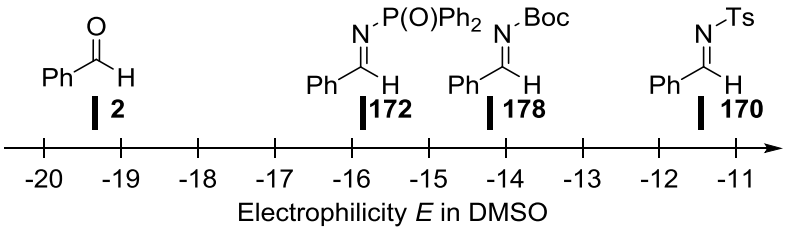
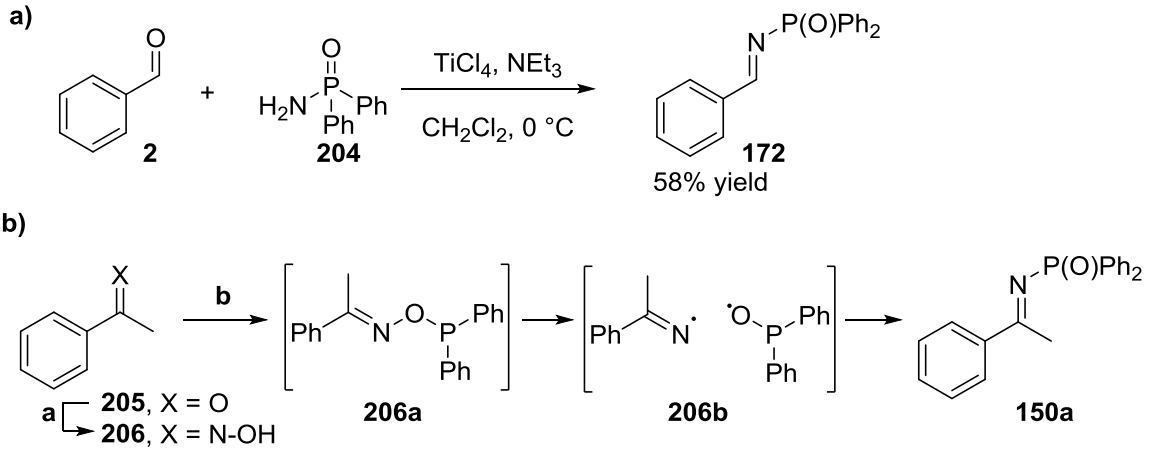


Figure 22 Mayr's quantification of imine electrophilicity.[189,190]

In the presence of a chiral catalyst, providing that the imine is prochiral, the nucleophilic attack onto the imine C=N double bond can result in the formation of enantioenriched products due to differences in addition rates to each face. The polar functional groups of the protecting group lower the LUMO of the imine and can provide greater enantiofacial discrimination and hence enantioselectivities upon addition.

The lower electrophilicity of *N*-DPP imines facilitates their handling and purification by increasing their hydrolytic stability. Furthermore, in many cases they can be purified by flash column chromatography. *N*-DPP aldimines can be synthesised by the $TiCl_4$ mediated condensation of the aldehyde with diphenylphosphinamide **204** according to a procedure developed by Jennings and co-workers (Scheme 40a).[191] The yield for the analogous reaction to synthesise *N*-DPP ketimines derived from acetophenone is, however, much lower due to the lower electrophilicity of the ketone and competing enolisation. The predominant and most general synthesis of both *N*-DPP aldimines and ketimines is the reaction between the corresponding oxime and chlorodiphenylphosphine, first reported in 1968 by Kruglyak *et al.*.[192] The oxime is treated at low temperature (typically –40 °C) in the presence of a tertiary amine base with the dropwise addition of

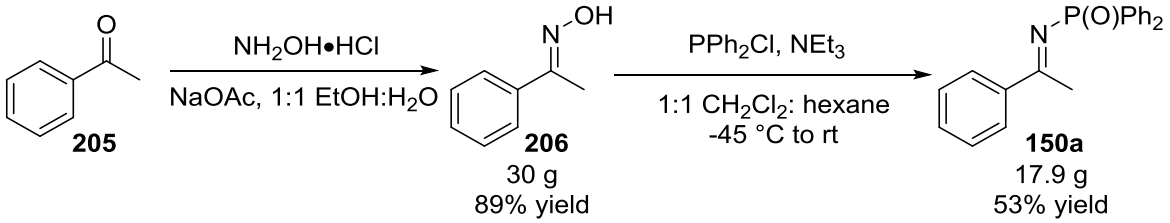
chlorodiphenylphosphine. After complete addition of the phosphorus (III) reagent, the reaction mixture is slowly warmed to rt and stirred overnight (Scheme 40b).



Scheme 40 a) Synthesis of *N*-DPP aldimines by condensation of diphenylphosphinamide and benzaldehyde; b) Synthesis of *N*-DPP ketimines 150a ***via*** **treatment of the oxime with chlorodiphenylphosphine and Hudson's proposed mechanism for the reaction: a) NH_2OH•HCl, NaOAc; b) PPh_2Cl, NEt_3, CH_2Cl_2:hexane, –45 °C.**

The mechanism[193,194] is believed to involve initial nucleophilic attack of the oxime to the chlorodiphenylphosphine to form the intermediate **206a** which has been observed spectroscopically. Subsequent warming of the reaction causes homolytic fission of the N-O bond (observed by EPR spectroscopy) and radical recombination forms the *N*-DPP imine **150a**.

Although the reaction sequence outlined by Kruglyak and co-workers required two steps, the reactions did not necessitate Lewis acid additives to proceed and we therefore chose this method to synthesise **150a**.



Scheme 41 Synthesis of *N*-DPP ketimine 150a**.**

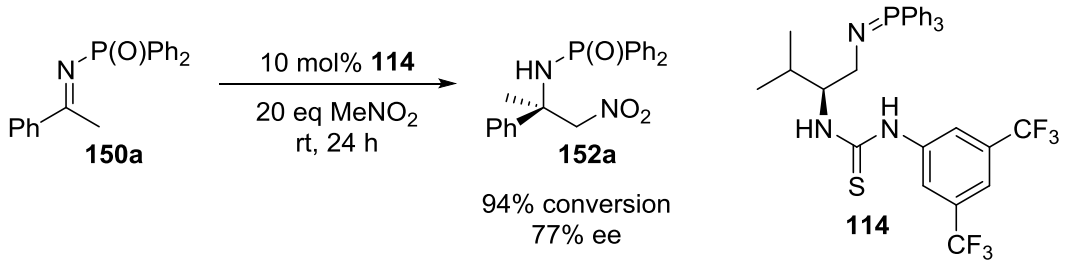
Accordingly, acetophenone was reacted with hydroxylamine hydrochloride and sodium acetate in equal volumes of ethanol and H_2O to afford, after distillation, 30 g of the oxime **206** in 89% yield (Scheme 41). The oxime was treated with chlorodiphenylphosphine and triethylamine at –45 °C and the reaction mixture was allowed to warm to room temperature

overnight. Ketimine **150a** was obtained in a reproducible 53% yield after purification by flash column chromatography (17.9 g of product obtained in the largest scale experiment). The moderate yield obtained for the ketimine is a reflection of its partial instability to silica gel; unfortunately, it was not possible to develop reliable crystallisation methods.

3.4 Ketimine Nitro-Mannich Reaction Proof of Principle and Catalyst Optimisation Studies

3.4.1 Proof of Principle

With copious quantities of ketimine **150a** in hand, the performance of the BIMP catalysts could be evaluated in the ketimine nitro-Mannich reaction. The L-valine derived BIMP **114** (chapter 2) was chosen as the initial catalyst to evaluate the reaction. An initial test reaction using 10 mol% **114** on a 0.2 mmol scale of **150a** with nitromethane (20 eq) as the solvent, was performed at rt (Scheme 42). To our delight, the adduct **152a** was formed with excellent conversion (94% by ^{1}H NMR after 24 h) and in high levels of enantioselectivity (77% ee).



Scheme 42 Proof of principle for the organocatalytic enantioselective ketimine nitro-Mannich reaction.

3.4.2 Optimisation of the Catalyst Scaffold

Following the successful proof of principle, a small library of catalysts with variations to the backbone, as the primary point of investigation, was synthesised. To expedite the screening process, the active catalysts were made *in situ* using equimolar quantities of the

corresponding azide and triphenylphosphine by stirring for 24 h in Et_2O, whereupon the solvent was removed then ketimine **150a** and nitromethane added (Figure 23).

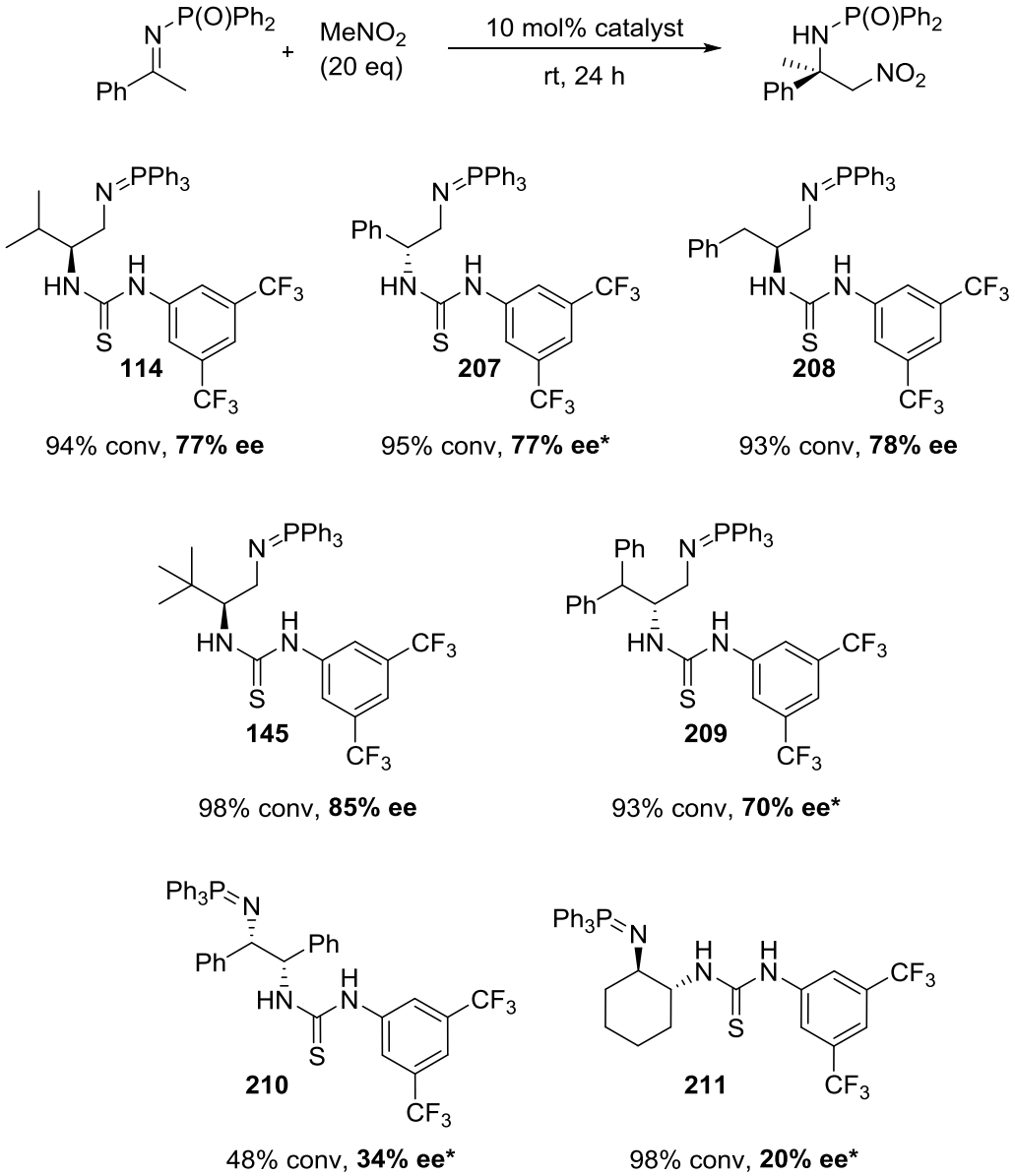


Figure 23 Catalyst backbone optimisation of the nitro-Mannich ketimine reaction; the use of * denotes the preferential formation of (*S*)152a inline with the opposite absolute configuration of the catalyst.

The reactions using D-phenylglycine derived catalyst **207** and L-phenylalanine derived catalyst **208** both afforded the product with high conversion and similar levels of enantiocontrol (77 and 78% ee respectively). The more sterically hindered catalyst **145** (derived from L-*tert*-leucine) afforded the product with enhanced levels of enantiocontrol (85% ee), whereas utilising the catalyst incorporating a benzhydryl group at the stereogenic centre **209** resulted in a decrease in the enantioselectivity (70% ee). A brief

exploration of other chiral 1,2-diamine building blocks as catalyst scaffolds, inspired by other bifunctional catalyst systems, did not enhance the levels of enantiocontrol although both the diphenylethylenediamine derived catalyst **210** (34% ee) and cyclohexyl diamine derived catalyst **211** (20% ee) were catalytically active in this transformation (Figure 23).

3.4.3 Effect of the Hydrogen-Bond Donor Group in the Ketimine Nitro-Mannich Reaction

With the optimal scaffold in hand, namely the one derived from L-*tert*-leucine, we subsequently investigated the effect of the H-bond donor group of the catalyst on the enantiocontrol imparted in the reaction.

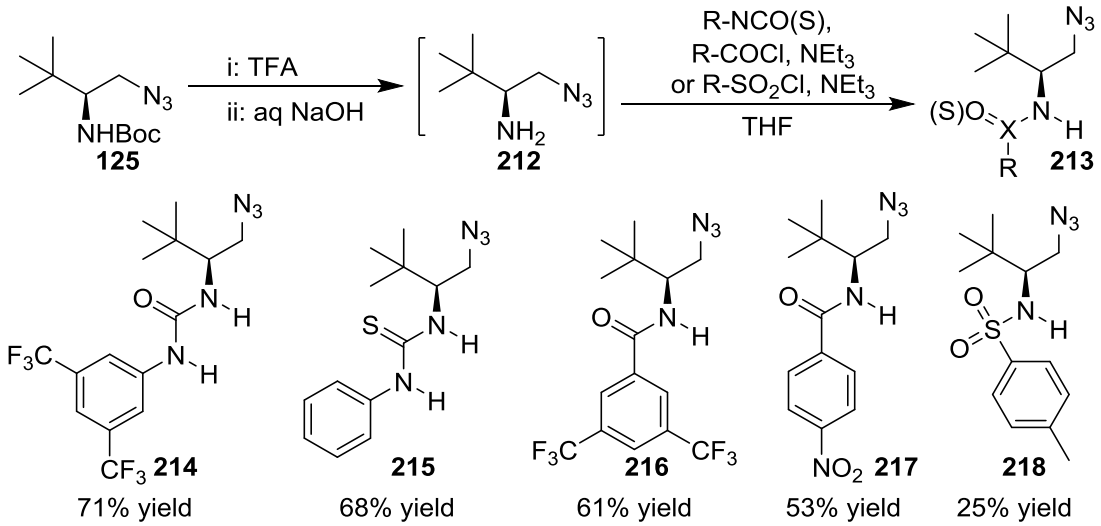


Figure 24 Synthesis of a range of BIMP catalyst precursors incorporating various H-bond donor groups from amino azide 125**.**

A range of azides bearing different hydrogen bond groups (including thiourea, urea, amide, carbamate and sulfonamide) were synthesised from the *N*-Boc protected amino azide **125** (Figure 24). The corresponding bifunctional iminophosphorane catalysts were made *in situ* by the addition of triphenylphosphine to the azide and then screened for efficacy in the reaction (Figure 25).

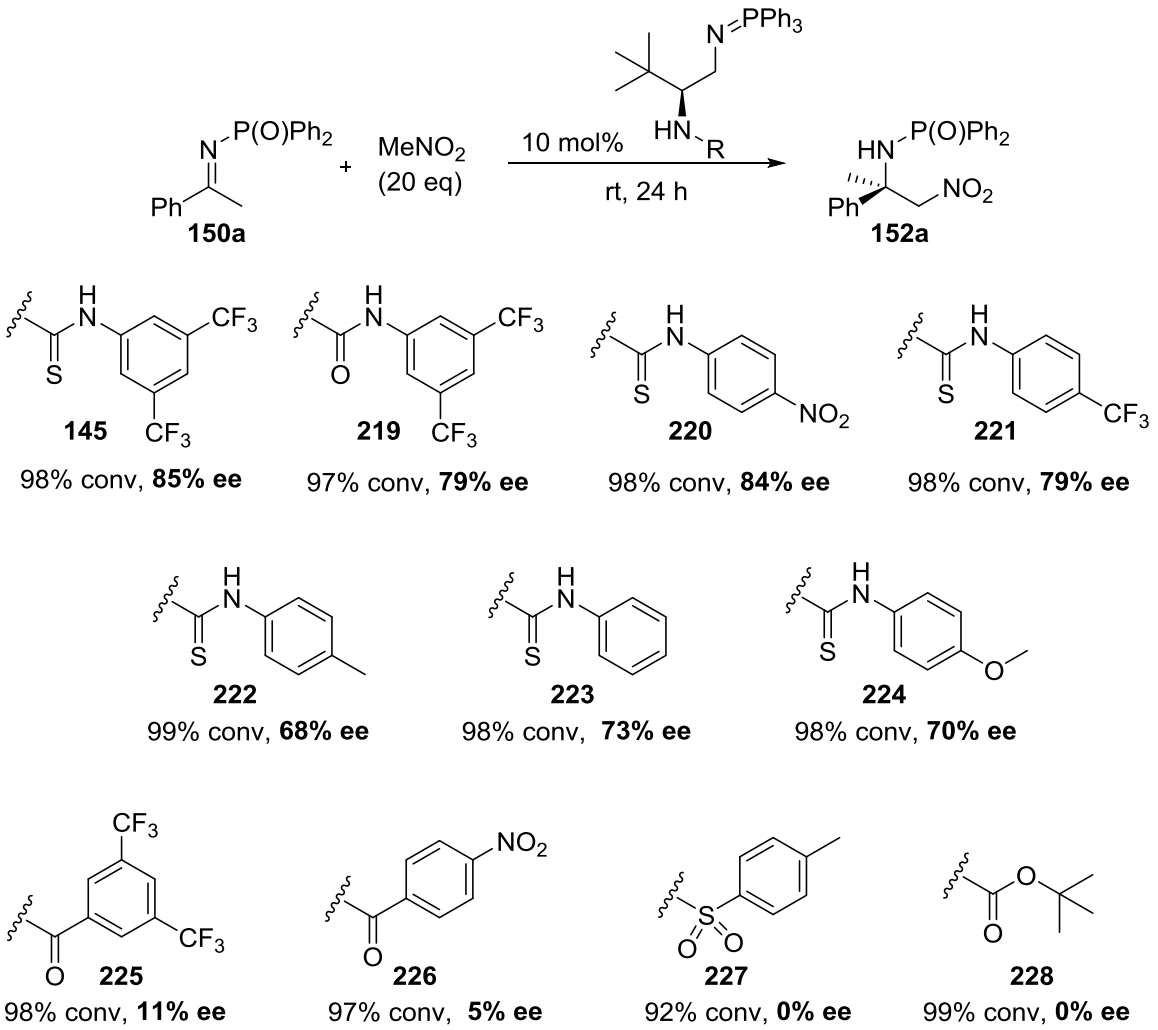


Figure 25 Investigation into the effect of the hydrogen donor group on the enantioselectivity in the ketimine nitro-Mannich reaction.

In all cases, the reactions proceeded with high levels of conversion to the product **152a**. When the urea **219** was used, a reduction in the enantioselectivity from 85% to 79% relative to the thiourea analogue **145** was observed, presumably due to the reduced acidity of the N-H and hence reduced H-bonding capability.[195] Thiourea **220** bearing a *p*-NO_2 phenyl group afforded **152a** with very similar levels of enantioselectivity to **145** (84% *vs* 85%), which we postulated to be due to the similar electron deficiencies on the aromatic ring. The use of more electron rich aryl thioureas resulted in a lowering of the enantioselectivity. When electron deficient amides were used as H-bond donor groups, the levels of enantiocontrol fell away drastically to 11% and 5% respectively for catalysts **225** and **226**. Catalysts **227** and **228** bearing sulfonamide and carbamate moieties respectively

as H-bond donor groups did not impart any enantiocontrol in the ketimine nitro-Mannich reaction.

These results are in agreement with work by Cheng and co-workers, who performed a comprehensive study into the structure-activity-enantioselectivity relationships of bifunctional thioureas in the conjugate addition between malonates and nitro-olefins.[196] They concluded that the enantioselectivity obtained for the product was dependent on the acidity of the thiourea moiety of the catalyst.

Whilst the data given in Figure 25 gives no indication of the rates of the catalysed reactions, as all reactions have reached complete conversion, a qualitative observation was made by TLC that the reaction catalysed by **228** proceeded faster than that catalysed by **145**. These findings are incongruous with other reports of thiourea H-bond donor groups enhancing the rates of organocatalysed reactions. The reaction using catalyst **145** containing the 3,5-$(CF_3)_2C_6H_3$ thiourea proceeded slower and with greater enantiocontrol than catalysts bearing a poor H-bond donor group. This may have resulted from the catalyst reducing the rate of formation of the minor enantiomer. An alternative explanation may be that as a result of the greater acidity of the protons of the 3,5-$(CF_3)_2C_6H_3$ thiourea relative to the NH of the carbamate of **228**, the basicity of the iminophosphorane moiety was reduced through inter and intramolecular H-bonding interactions. Therefore, the observed rate of reaction was decreased (see Chapter 5 for further discussion).

3.4.4 Effect of the Brønsted Basicity on the Ketimine Nitro-Mannich Reaction

The ability to tune the Brønsted basic moiety by changing the phosphine gave rise to the third, and arguably the greatest, variation to the catalyst library. We showed in section 2.3 that the basicity of the iminophosphorane could be tuned by changing the electronic characteristics of the phosphine. Electron deficient phosphines would decrease the basicity

of the iminophosphorane moiety due to stabilisation of the nitrogen lone pair by the electron withdrawing aromatic groups and conversely, more electron rich phosphines increase the basicity by stabilising the conjugate acid. Therefore, if the extent of deprotonation was key to the activation of low acidity pro-nucleophiles, then a marked increase in the rate of reaction when using electron rich iminophosphoranes as the catalysts would be observed. The effect of the pK_a of the iminophosphorane on the rate of the ketimine nitro-Mannich reaction was unknown and therefore experiments to verify this hypothesis would be worthy of investigation.

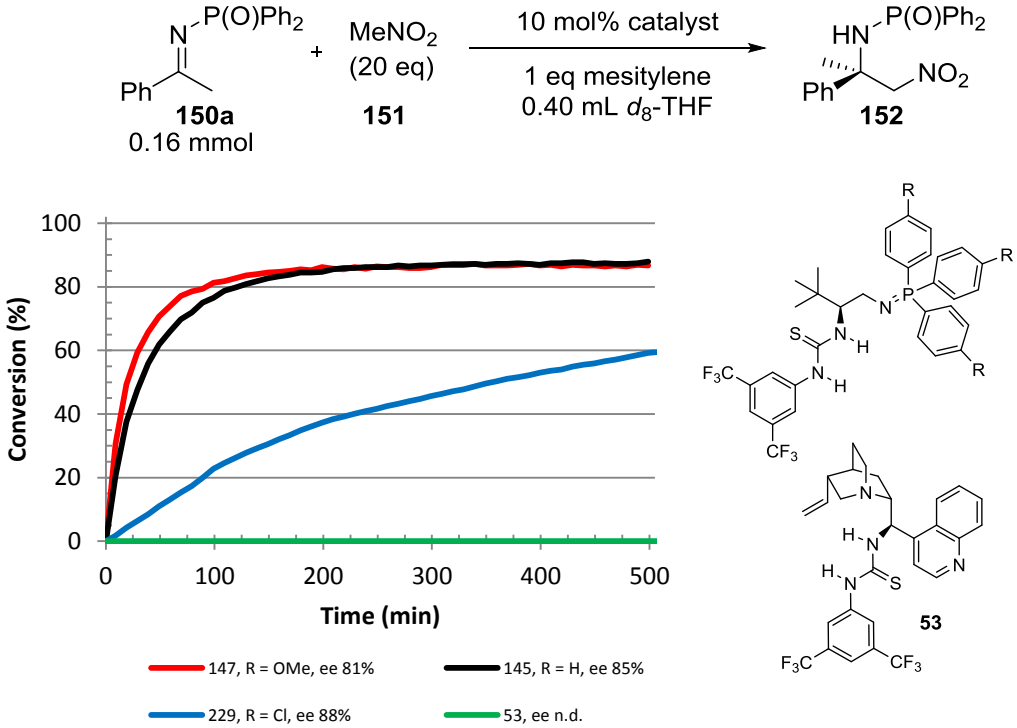


Figure 26 Rate of ketimine nitro-Mannich reaction as a function of iminophosphorane substituents and comparison with a cinchona alkaloid derived catalyst. The ee was determined in reactions performed under standard conditions with 10 mol% catalyst in 20 eq $MeNO_2$ and quenched after 24 h. ^{1}H NMR spectra were collected every 10 minutes. Reactions were performed on 0.16 mmol scale of 150a.

The formation of nitro-Mannich adduct **150a** as a function of time was conveniently measured by ^{1}H NMR kinetic experiments as they readily allow the conversion to be measured without disturbing the reaction medium. After some optimisation of the reaction conditions, reactions performed in d_8-THF on 0.16 mmol scale of **150a** using 10 mol% catalyst (synthesised *in situ* from the azide and the corresponding phosphine) and

mesitylene as an internal standard were found to be practical (Figure 26). The conversion was measured both against the internal standard and by starting material *vs* product for comparison.

The graph demonstrates that the reaction rate was governed by the aryl substituents of the iminophosphorane. The tris(4-chlorophophenylphosphine) derived catalyst **229** was approximately ten times slower than the triphenylphosphine derived catalyst **145** (90 minutes *versus* 9 minutes to reach 20% conversion respectively), consistent with an electron withdrawing group reducing the basicity of the iminophosphorane moiety. The reaction with catalyst **147** was slightly faster than that with **145**, presumably due to the greater basicity of the iminophosphorane moiety. As a comparison, the reaction was performed under identical conditions using cinchona-derived catalyst **53** and the conversion was found to be just 0.04% even after an extended reaction time of 32 h. The basicity of the Brønsted moiety is clearly having an effect on the rate of reaction. The enantioselectivity was found to vary slightly with the phosphine moiety with **147** affording the product in 81% ee whilst **229** afforded **152a** in 88% ee at rt after 24 h.[viii]

In a similar series of measurements, using the enantiomeric catalyst system derived from D-phenylglycine, the ^{1}H NMR kinetic experiment was performed employing more electron rich phosphine derived iminophosphoranes. As shown in Figure 27 catalyst **207** was approximately 4 times slower than the tris(4-methoxyphenylphosphine) derived catalyst **148**. Iminophosphorane catalysts **230** and **231** derived from tris(3,4-methoxyphenylphosphine) and tris(3,4,5-methoxyphenylphosphine)[ix] respectively, did not increase the rate of reaction significantly relative to **148**.

[viii] The enantioselectivities were obtained in separate experiments with 20 eq of $MeNO_2$ as solvent and 10 mol% catalyst (Table 5).
[ix] See section 8.2.11 for the synthesis of trivalent phosphines.

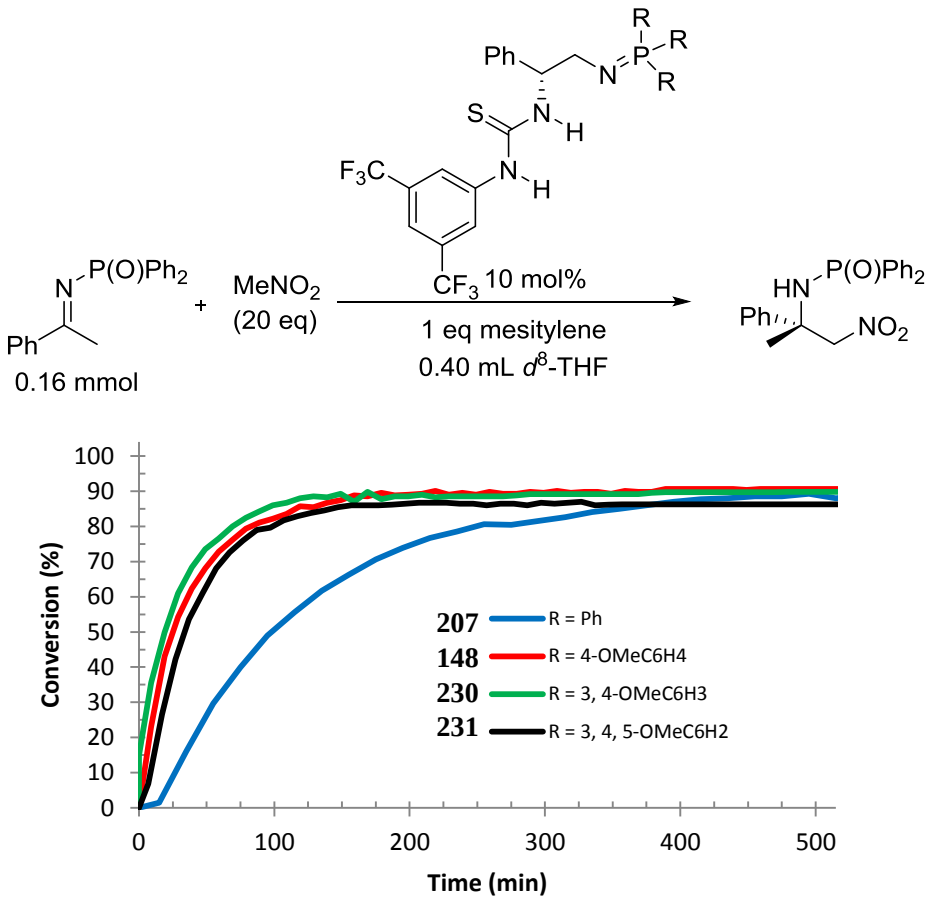
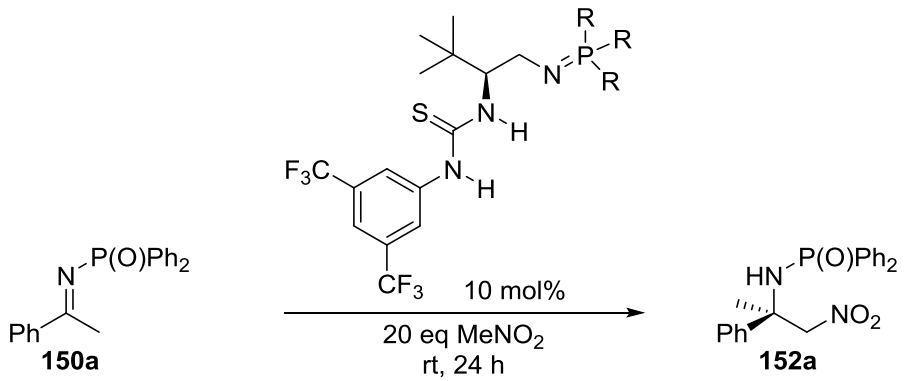


Figure 27 Rate of nitro-Mannich reaction as a function of increasing the number of methoxy substituents on the phosphine moiety. (See footnote xi for an explanation as to why no enantioselectivities are given in the graph).

The effect of the iminophosphorane moiety on the enantioselectivity obtained in the ketimine nitro-Mannich reaction was investigated using catalysts derived from L-*tert*-leucine (Table 5). The enantioselectivity using catalyst **147** was slightly diminished relative to **145** (85% *vs* 81% ee respectively, Table 5 entries 1 & 2). Iminophosphorane catalysts **232** and **233** imparted similar levels of enantiocontrol in the reaction to **147** (79% *vs* 81% ee Table 5, entries 2 – 4) whereas the enantioselectivity with the less Brønsted basic catalyst **229** was 88% (Table 5, entries 5). Therefore, as a trade-off between rate (Figure 26) and enantioselectivity (Table 5) we selected catalyst **145** as the optimal catalyst to investigate the scope of the ketimine nitro-Mannich reaction.



Entry	Catalyst	PR_3	Conversion / %	ee / %
1	**145**	PPh_3	98	85
2	**147**	$P(4\text{-}(OCH_3)C_6H_4)_3$	99	81
3	**232**	$P(3,4\text{-}(OCH_3)_2C_6H_3)_3$	99	79
4	**233**	$P(3,4,5\text{-}(OCH_3)_3C_6H_2)_3$	99	79
5	**229**	$P(4\text{-}ClC_6H_4)_3$	99	88

Table 5 Effect of the phosphine moiety on the enantioselectivity in the ketimine nitro-Mannich reaction. Reactions were performed on 0.20 mmol scale of 150a **and 20 eq of $MeNO_2$ and quenched after 24 h. Conversion determined by ^{1}H NMR.**

A brief screen of solvents was performed on the ketimine nitro-Mannich reaction of **150a** and nitromethane to determine whether the enantioselectivity could be enhanced (Table 6). Reactions were performed at rt for 24 h on a 0.20 mmol scale of **150a** with 10 mol% **145**, 20 equivalents of nitromethane and 0.40 mL of solvent. Conversion for all the solvents screened was high after 24 h (80 – 90%). The enantioselectivities were moderate to good (70 – 83% ee) across a range of aprotic solvents. The highest enantioselectivity in this series of experiments was obtained when CH_2Cl_2 was used as the solvent (80% conversion and 83% ee, Table 6, entry 2). The screen of solvents, however, did not increase the enantioselectivity higher than that obtained when the reaction was performed under neat conditions in the formation of **150a** (Table 6, entry 1). The scope of the ketimine nitro-Mannich reaction was therefore further probed performing the reactions using 20 equivalents of nitromethane as solvent.

Entry	Solvent	Conversion (%)	ee /%
1	-	98	85
2	CH_2Cl_2	80	83
3	EtOAc	88	75
4	Dioxane	89	70
5	Toluene	83	73
6	THF	87	72
7	MTBE	86	77

Table 6 Solvent screen for the ketimine nitro-Mannich reaction. Reactions were performed on 0.20 mmol of 150a **using 10 mol%** 145 **and 20 eq $MeNO_2$ in 0.40 mL of solvent at rt for 24 h.**

3.5 Probing the Scope of the Ketimine Nitro-Mannich Reaction

3.5.1 Synthesis of a Range of N-*DPP Ketimines*

With the optimal catalyst identified, a range of ketimines were synthesised in order to investigate the reaction scope (Figure 28). The ketimines **150** were prepared according to the method described in Section 3.3 in yields ranging from 37 to 62% from the parent oxime.

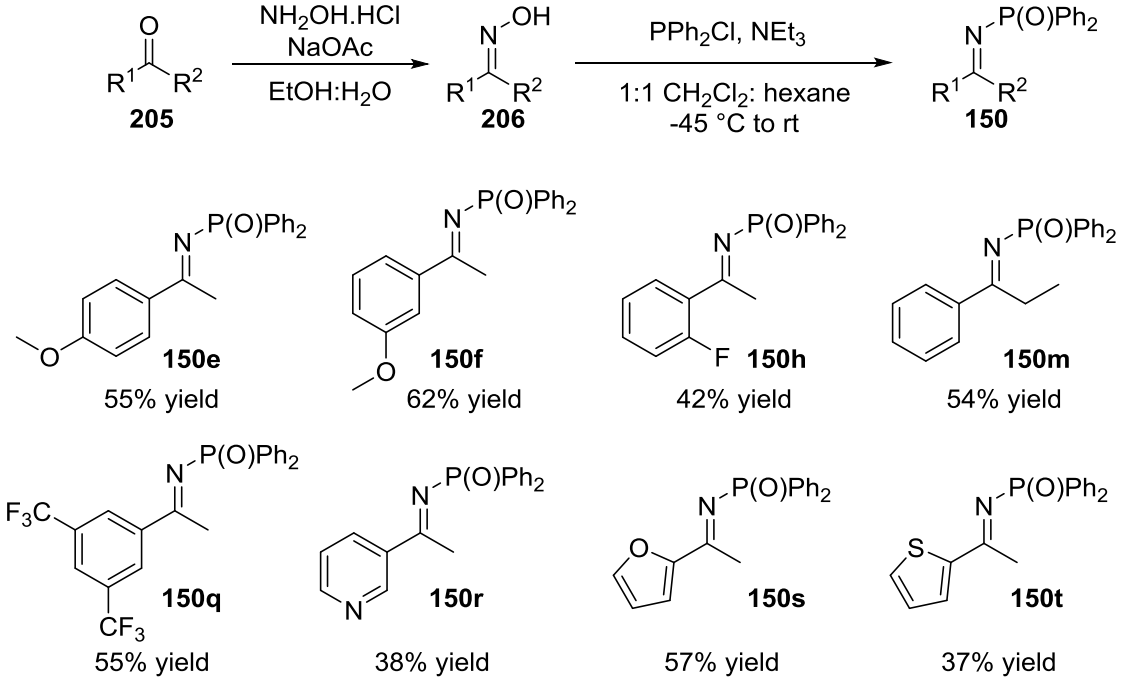


Figure 28 Two-step synthesis of a range of *N*-DPP ketimines *via* the oximes (synthesised in 60-85% yield). Yields are quoted for the second step.

The low yields were the result of the low stability of the ketimines to silica gel and difficulties in the separation of impurities. The ketimines could be purified by trituration with Et_2O after chromatography to increase the purity to >95%.[x]

3.5.2 Substrate Scope of the Ketimine Nitro-Mannich Reaction

Subsequent optimisation on ketimine **150a** demonstrated a moderate dependence of enantioselectivity in the ketimine nitro-Mannich reaction with respect to temperature. The reaction was performed at 0 °C using 10 mol% catalyst **145** in 20 equivalents of $MeNO_2$ and full conversion was observed after 24 h with an improvement of the enantioselectivity to 91%. Lowering the temperature further to –15 °C afforded **152a** in 89% conversion and 86% isolated yield after 96 h and with 95% ee. From a practical point of view four days was set as the maximum reaction time. Reactions were performed at both 0 and –15 °C for the ketimine substrates and the superior result with regards to both conversion and enantioselectivity retained (Figure 29).

[x] The other ketimines used in the methodology were synthesised by Dr Irene Ortin Remon and M.G.N..

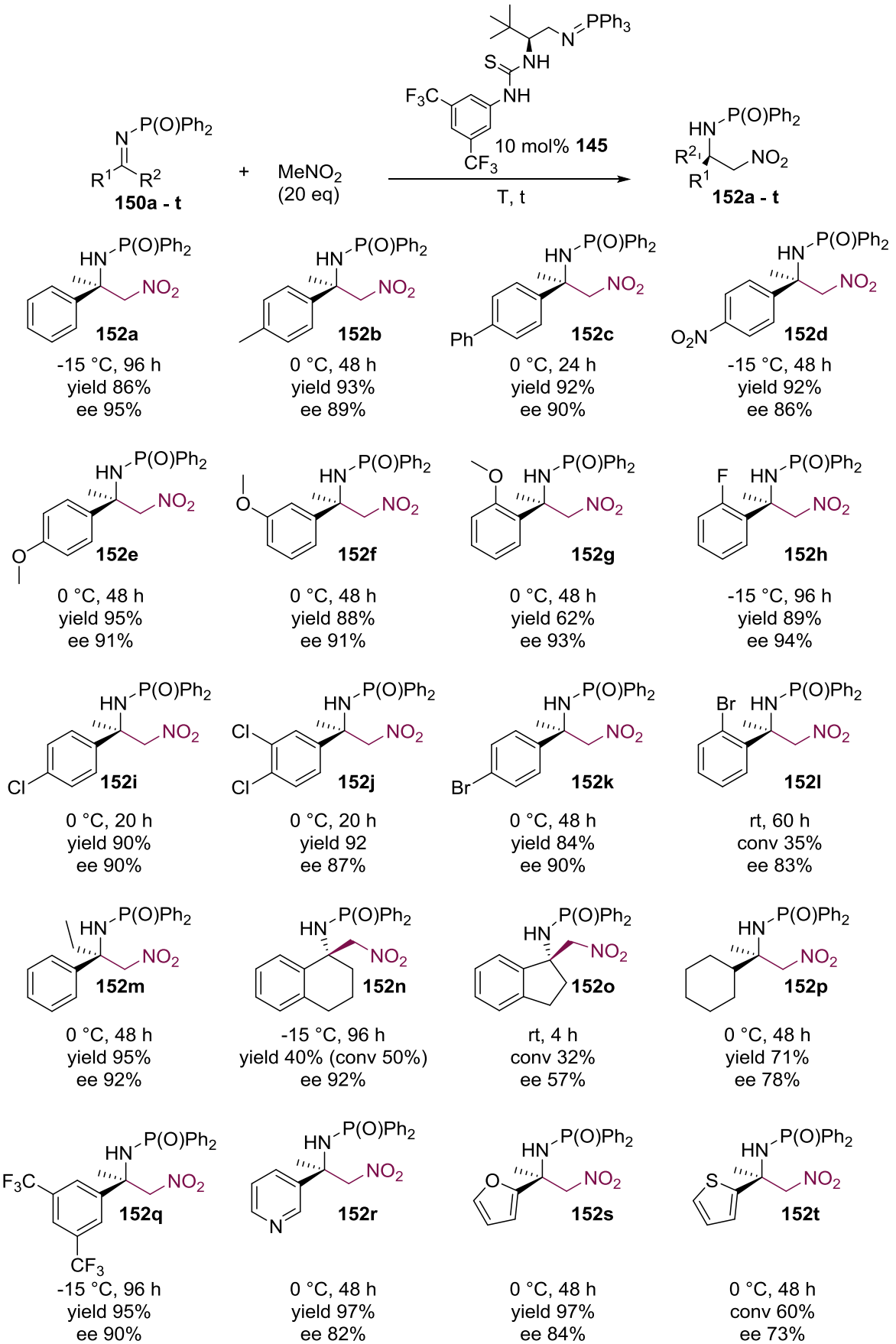
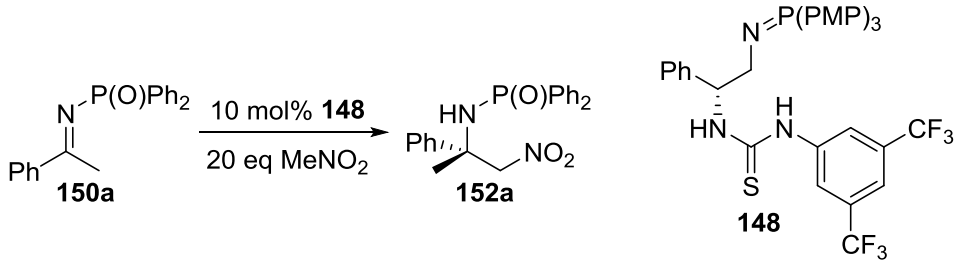


Figure 29 Scope of the ketimine nitro-Mannich reaction. Reactions were performed at both 0 and -15 °C with the superior result displayed. Reactions performed at 0 °C were left for a maximum of 48 h and 96 h for those at -15 °C.

A considerable range of aromatic ketimines were well-tolerated and afforded the corresponding β-nitroamines in excellent yields and enantioselectivities. Ketimines bearing substitution at the *meta* and *para* positions of the aromatic ring gave high levels of enantioselectivity although we found that only the more electron deficient substrates proceeded smoothly at -15 °C. Substitution of a methoxy group at the *ortho, meta* and *para* positions of the aryl ring afforded the nitro-Mannich adducts with enantioselectivities of 91 – 93%, however the yield was slightly diminished in the case of *o*-OMe ketimine **150g**. Having a smaller *ortho* substituent such as fluorine did not diminish the yield or enantioselectivity, however reactions performed using a ketimine substrate **150l** possessing a bromine substituent at the *ortho* position resulted in dramatically lower levels of reactivity, even at room temperature. The reaction scope was extended to include an ethyl group as the aliphatic residue of the ketimine with little effect on the yield and enantioselectivity. The yield for the nitro-Mannich adduct **152n**, derived from the cyclic 1-tetralone ketimine **150n** was diminished although the levels of enantiocontrol remained high. Indanone derived ketimine **150o** was much less reactive; performing the reaction at room temperature and quenching after 4 h was found to be a good balance of enantioselectivity and conversion. The reaction scope included the heteroaromatic 3-pyridyl **150r** and 2-furyl ketimine **150s** substrates with the respective β-nitroamines formed in excellent yields and good levels of enantiocontrol. The reaction with 2-thiophene **150t** was slower than that with 2-furyl and we postulated this was due to the presence of the large sulfur atom in close proximity to the site of electrophilic attack. The reaction was also applicable to an aliphatic ketimine **150p**; albeit with a moderate yield and levels of enantioselectivity. Having successfully demonstrated that a wide range of ketimines were well tolerated in the first general organocatalytic enantioselective ketimine nitro-Mannich reaction we did not explore the substrate scope further at this point.

3.5.3 Reversibility in the Ketimine Nitro-Mannich Reaction

During the course of our studies on the ketimine nitro-Mannich reaction we noted, that the enantioselectivity of the β-nitroamine products diminished over time under the reaction conditions.[xi] The reversibility was initially probed using D-phenylglycine derived catalyst **148** (Table 7). As the reaction using 20 eq of nitromethane as solvent is a suspension for much of its course and thus difficult to accurately sample, we performed separate experiments for each time interval. The enantioselectivity was found to be highest (76.5% ee) after two hours when the conversion was 90% and diminished to 60% after 48 h.



Entry	Time (h)	Conversion /%	ee /%
1	2	90	76.5
2	6	99	75
3	12	97	74
4	24	99	70
5	48	99	60

Table 7 Reversibility in the ketimine nitro-Mannich reaction using ketimine 150a **catalysed by** 148**. Each entry represents a separate experiment that was quenched by the addition of 1 M AcOH in CH_2Cl_2.**

The effect of the Brønsted basicity of the iminophosphorane catalyst on the rate of racemisation in the ketimine nitro-Mannich was also investigated. A series of nitro-Mannich reactions on ketimine **150a** using catalysts **229**, **145** and **147** were performed in

[xi] The reversibility of the nitro-Mannich reaction was discovered serendipitously when we decided to measure the ee of the reactions performed in the kinetic ^{1}H NMR study in Figure 27. Upon completion of the kinetic experiment the catalysts were not quenched and were therefore active over the course of several weeks. When the enantioselectivity was measured after several weeks, the ee with catalyst **207** was 26% ee whereas it was 0% with catalysts **148**, **230** and **231**.

CH_2Cl_2 with aliquots taken to determine the conversion and enantioselectivity (Figure 30). The rate of racemisation was found to be correlated to the strength of the Brønsted basicity.

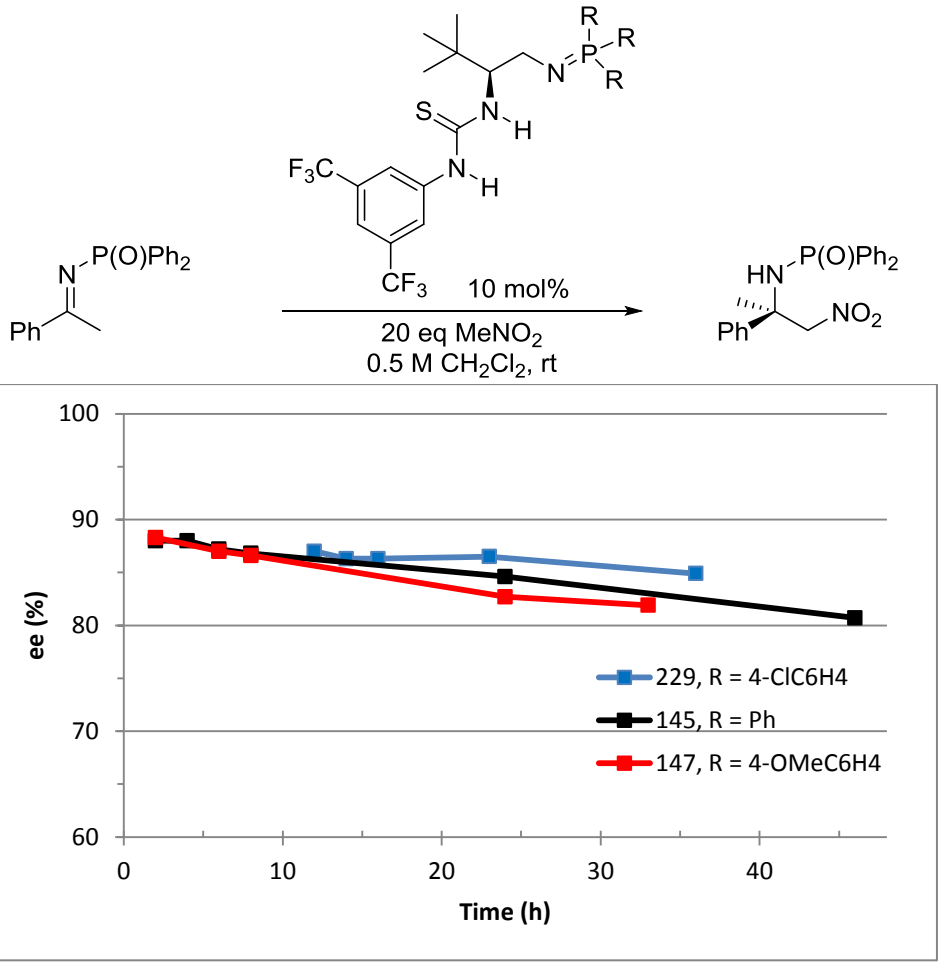


Figure 30 Graph comparing the effects of catalyst basicity on the ee in the ketimine nitro-Mannich reaction as a function of time. Reactions were performed on a 0.5 mmol scale of 150a **using 10 mol% catalyst in 1.0 mL of CH_2Cl_2. Conversion for** 152a **after 24 h was 99%, 91% and 87% for catalysts** 229, 145 **and** 147 **respectively.**

From these reversibility studies we concluded the absolute levels of enantiocontrol imparted by the catalysts **229**, **145** and **147** were very similar. The enhanced ee observed upon quenching the reactions after 24 h (Table 5) when the BIMP catalyst **229**, possessing the less Brønsted basic tris(4-chlorophenylphosphine) derived iminophosphorane was used, may have resulted from less extensive racemisation.

The retro-nitro-Mannich reaction occurred to afford the parent ketimine and the nitronate.[197] According to the Principle of Microscopic Reversibility,[198,199] the reverse reaction proceeded faster with the major enantiomer ((*R*)-**150a** when using BIMP catalysts derived from L-*tert*-leucine) as the activation energy was lower than for the minor

enantiomer in a qualititative simplified model of the overall reaction (Figure 31). In addition, the retro-nitro-Mannich reaction occurred preferentially for the major enantiomer as it was present in higher concentration than the minor.

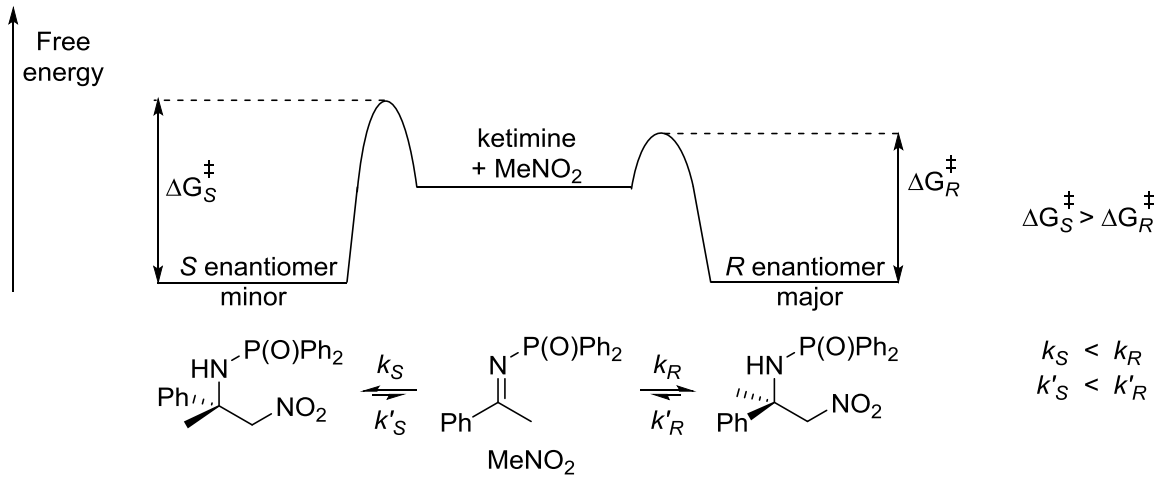
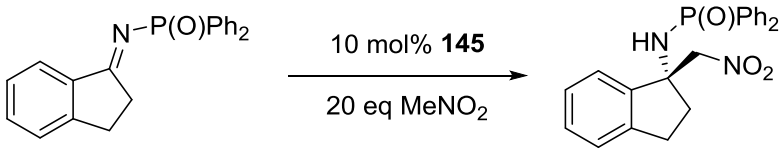


Figure 31 Simplified transition state diagram negating intermediary structures for the ketimine nitro-Mannich reaction catalysed by 147 **showing the retro-nitro-Mannich reaction occurred preferentially for the major enantiomer.**

As the inherent catalyst control in the reaction was not completely enantiospecific (15:1 selectivity, reflected in 88% ee) the ee of the product diminished over time. The minor enantiomer, (*S*)-**150a**, accumulated and if left long enough, the reaction would reach thermodynamic equilibrium and the two enantiomers would be present in equal quantities. The rate of the forward reaction was greater than that of the retro-nitro-Mannich reaction and therefore racemisation predominately occurred upon completion of the forward reaction. The more basic BIMP catalyst **147** derived from tris(4-methoxyphenylphosphine) increased the rate of the ketimine nitro-Mannich reaction relative to the less Brønsted basic catalyst **229** (Figure 26) and by extension also increased the rate of the retro reaction.

More drastic examples of reversibility issues were observed in the formation of **152o** from the indanone derived ketimine **150o**. At room temperature the enantiomeric excess was 71% ee after 2 h, but had decreased to 57% after an additional 2 h with only a modest conversion to 32% as determined by ^{1}H NMR (Table 8, Entries 1 & 2). Lowering the temperature – in an attempt to reduce the retro-nitro-Mannich reaction, consistent with the

Arrhenius equation – allowed the product to be formed in 87% ee although the rate of reaction was significantly reduced (Table 8, Entry 4).



Entry	Temp /°C	Time /h	Conversion /%	ee (%)
1	23	2	22	71
2	23	4	32	57
3	0	96	29	55
4	–20	96	15	87

Table 8 Addition of nitromethane to indanone derived ketimine. Reactions performed on 0.2 mmol scale of 150o **with 10 mol%** 145 **in 20 eq of $MeNO_2$.**

For a reaction to proceed, in the absence of external factors, the free energy of the products is lower than the reagents and therefore ΔG_R is negative (Figure 32, scenario A). Conversely if ΔG_R is positive in a reaction then the equilibrium will predominantly lie towards the reactants (scenario C).

In the ketimine nitro-Mannich reaction employing **150a** (Figure 30), the high conversion of the product **152a** was an example of scenario A (Figure 32). However, in the ketimine nitro-Mannich reaction to afford **152o** the rates of racemisation and low conversions to the product suggested that the difference in free energies of reactants and products was less than that observed in the formation of **152a** (i. e. ΔG_R was less negative).

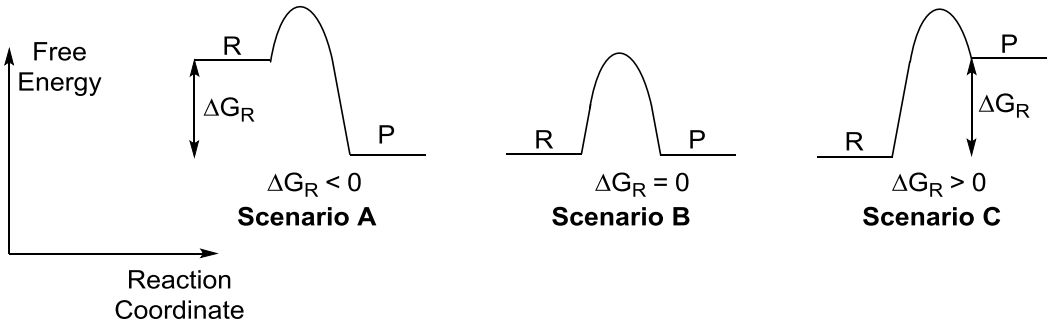
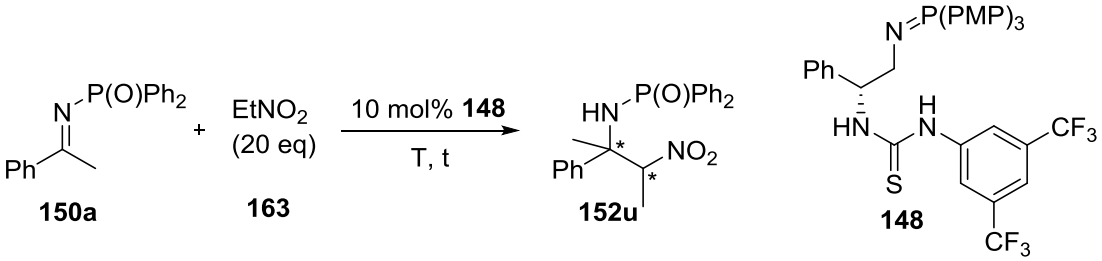


Figure 32 Schematic representation of reactants and products in trivialised reactions with different free energies.

When we tried to extend the reaction scope to higher order nitroalkanes (such as nitroethane) we were also faced with competing retro-nitro-Mannich reactions. Using

20 eq of nitroethane as solvent, the conversion to **152u** was just 63% after 96 h with 10 mol% **148**. The levels of diastereo- and enantiocontrol were very low (Table 9, Entry 1). Repeating the reaction and quenching after one hour revealed 30% conversion and modest enantioselectivities of 27 and 53% (Table 9, Entry 2). By performing the reactions at lower temperatures we were able to increase the ee up to 72% (Table 9, Entry 4) albeit with very low levels of conversion. The observed conversion of 63% after 96 h (Table 9, Entry 1) was a reflection of the equilibrium position between the starting materials and products when 20 eq of nitroethane was used; presumably the ee could be reduced to 0 for both diastereomers at equilibrium.

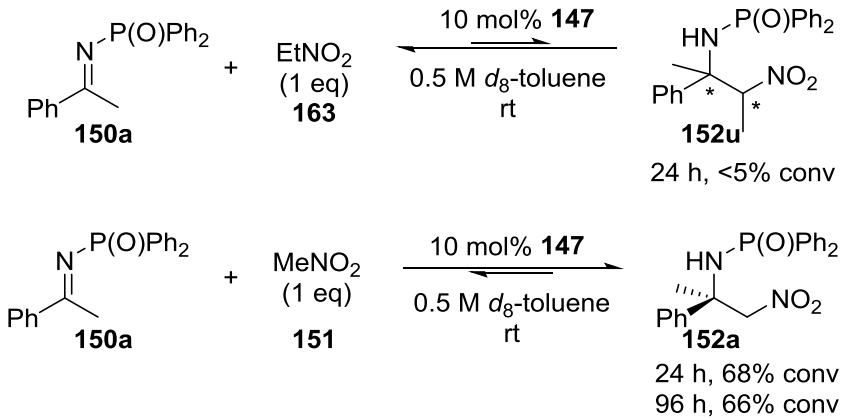


Entry	Temp /°C	Time /h	Conversion /%	dr	ee /%
1	23	96	63	2.4: 1	5, 3
2	23	1	36	1.2: 1	27, 53
3	0	1	30	2.7: 1	64, 64
4	-20	1	8	1: 1.6	66, 72

Table 9 Ketimine nitro-Mannich reaction of nitroethane to *N*-DPP ketimine 150a **to afford** 152u**.**

In an attempt to measure the equilibrium position in the ketimine nitro-Mannich reaction with nitroethane, equimolar quantities of nitroethane and ketimine **150a** were reacted with 10 mol% **147** at rt in d_8-toluene (Scheme 43). The conversion after 24 h to **152u** with one equivalent of nitroethane was less than 5% by ^{1}H NMR. Unfortunately only one data point was taken and therefore there was no evidence whether the low conversion was as a result of kinetic or thermodynamic effects; however if the reaction mixture had reached equilibrium, then this reaction was an example of scenario C (Figure 32). To the reaction mixture was subsequently added 9 equivalents of nitroethane and the conversion after a

further 72 h was found to be 27% by ^{1}H NMR. This was consistent with Le Chatelier's principle where the equilibrium position was shifted as a result of the extra equivalents of nitroethane. The analogous reaction was performed using one equivalent of nitromethane and the ^{1}H NMR conversion was 68% after 24 h and 66% after 96 h and thus the conversion was a reflection of the equilibrium position.[xii]



Scheme 43 Ketimine nitro-Mannich reaction of nitromethane and nitroethane to ketimine 150a **catalysed by** 147**. Reactions performed with one equivalent of nitroalkane in d_8-toluene.**

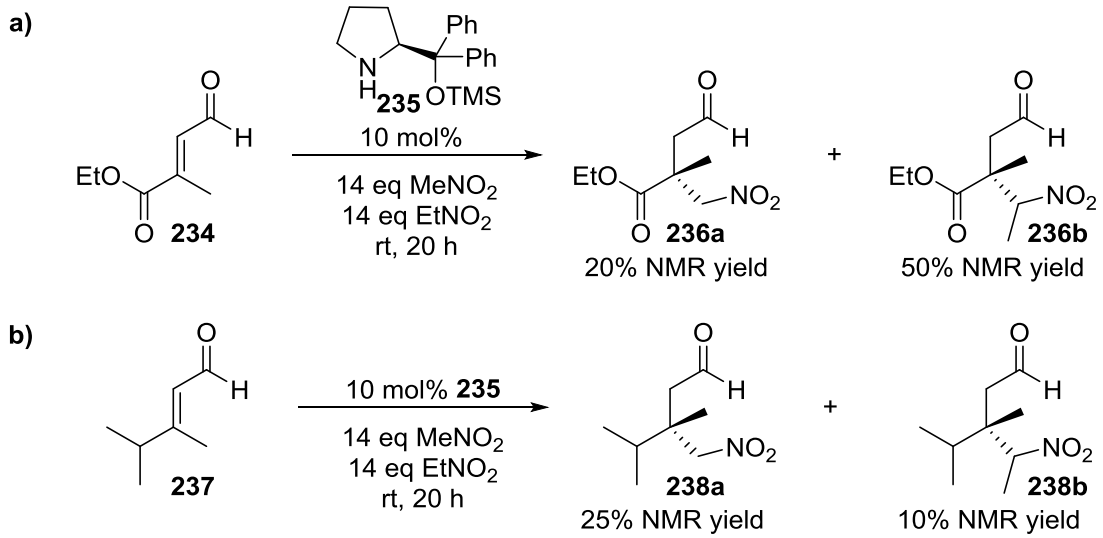
The faster retro-nitro-Mannich reaction, when using nitroethane as the pro-nucleophile relative to nitromethane was likely due to increased repulsive steric interactions at the contiguous tertiary and fully substituted carbon centres of **152u**. The increased acidity of nitroethane compared to nitromethane (16.7 vs 17.2 in DMSO respectively),[200] due to the greater stability of the more substituted nitronate anion may also have been a contributing factor. An interesting extension to these experiments would be the addition of nitromethane in the presence of a Brønsted base catalyst such as **147** to a solution of rac-**152u** to observe the relative conversions of the two nitro-Mannich adducts and their respective enantioselectivities.

[xii] In hindsight, these reactions should have been followed more closely over time with respect to both the conversion and enantiocontrol to unambiguously determine whether the conversion data shown in Scheme 43 are thermodynamic concentrations.

152u **152a**

Figure 33 Increased repulsive steric interactions for nitro-Mannich adduct 152u **relative to** 152a**.**

In a recent comprehensive study on the Michael addition of nitromethane and nitroethane to β,β-disubstituted α,β-unsaturated aldehydes under iminium catalysis, Hayashi and co-workers reported very similar observations (Scheme 44).[201] They observed that conjugate additions with nitroethane proceeded faster than those with nitromethane and postulated this to be due to the increased acidity of the pro-nucleophile. The retro-Michael reaction also proceeded faster with nitroethane but it only occurred at room temperature or above. Competing kinetic experiments using equimolar quantities of the nitroalkanes revealed nitroethane reacted faster with **234** (Scheme 44a). However, when the steric bulk at the β-position was increased further with **237** the reaction with nitromethane was more rapid (Scheme 44b).



Scheme 44 Hayashi's conjugate addition of nitromethane to β,β-disubstituted α,β-unsaturated enals using L-prolinol catalyst 235**. a) Competing addition between nitromethane and nitroethane to** 234 **showing the reaction proceeds faster with $EtNO_2$; b) Competing addition between nitromethane and nitroethane to** 237 **showing the reaction proceeds faster with $MeNO_2$.**

Further studies on the retro ketimine-nitro-Mannich reaction are required to fully understand the various competing kinetic and thermodynamic factors. As a first port of call, performing analogous experiments to those carried out by Hayashi and co-workers to

establish which of the nitroalkanes reacts faster with **150a** would be informative. Qualitatively from the data shown in Table 9 and by comparison to ketimine nitro-Mannich reactions performed with nitromethane the reactions proceeded slower with nitroethane. These results are consistent to those reported by Hayashi when very sterically hindered β,β-disubstituted α,β-unsaturated enals were used (Scheme 44b).

3.5.4 Origins of Enantiocontrol in the Ketimine Nitro-Mannich Reaction

Computational analysis, in collaboration with the Paton Group provided us with a putative working model for the observed enantioselectivity. The thiourea efficiently bound the nitronate formed from the reversible deprotonation of nitromethane. The N-H of the protonated iminophosphorane could then act as an effective H-bond donor group to the *N*-DPP group and align the ketimine. The attack of the nitronate then proceeded preferentially to the *si* face of the ketimine (Figure 34). The lower enantioselectivity observed with less acidic H-bond donor groups probably resulted from less efficient binding of the nitronate.

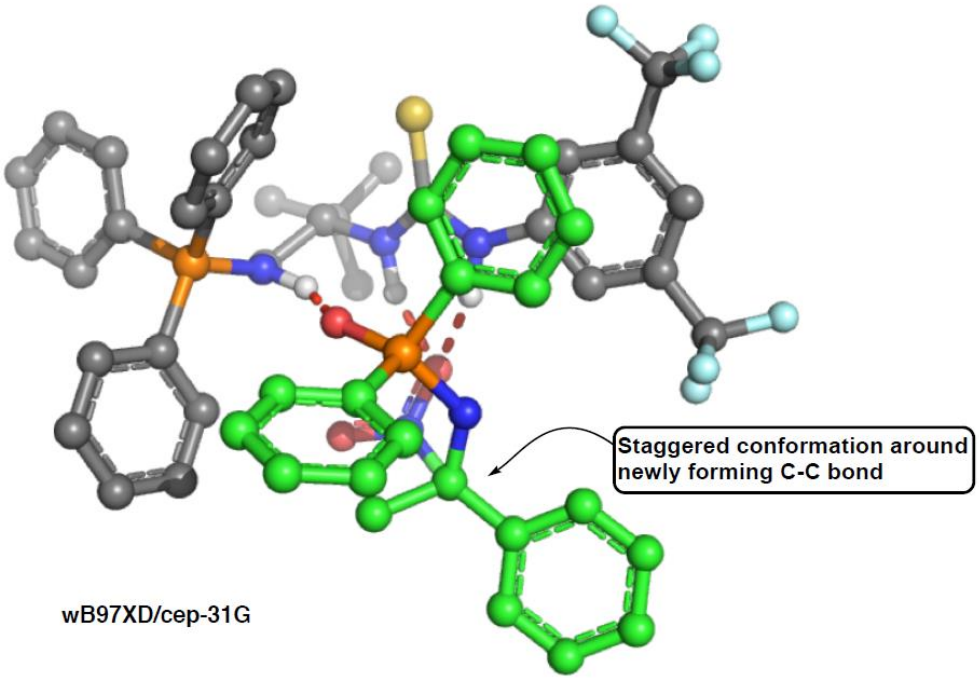
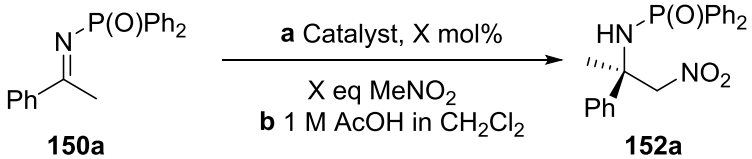


Figure 34 Working model of the nitro-Mannich ketimine reaction. Calculations by Dr Robert Paton and Adam Madarasz: Quantum-guided molecular mechanics (Q2MM); Monte Carlo conformational search of the transition structures, followed by full DFT optimisations.

3.6 Preparative Scale Synthesis of 150a and Derivatisation

With the substrate scope completed, we next focussed on performing the ketimine nitro-Mannich reaction on a preparative scale. In the substrate scope, carried out on a 0.2 mmol scale, 15 mg of catalyst were used for typically around 65 mg of substrate. Whilst acceptable for a methodology, as maximising enantioselectivity was the principle objective, it was impractical in any scale-up procedure. For a catalyst to be used on scale, low catalyst loadings and reaction times are paramount.



150a **152a**

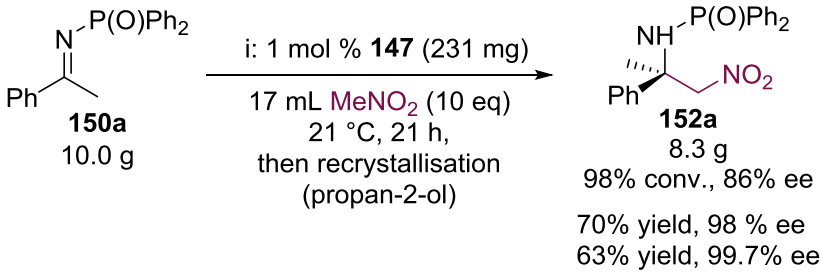
Entry	Mass (g)	Catalyst, Eq, (mol%)	Time (h)	Crude conversion/ *ee* (%/%)	Purification	Yield/ ee (%/%)
1	0.20	**145**, 10[a]	6	92, *87*	Recryst. (EtOAc)	29, *98.5*
2	0.043	**147**, 10[a]	2	99, *83.5*	-	-
3	0.043	**147**, 10[a]	2	99, *86*	-	-
4	2.00	**147**, 1	50	90, *86*	Recryst. (EtOAc)	47, *99*
5	0.43	**147**, 1	25	>90	Filt. (EtOAc)	56, *98*
6	2.0	**147**, 1	20	>90	Filt. (EtOH)	26, *99.3*
7	1.0	**147**, 0.5	46	~30	-	-
8	1.0	**147**, 1	20[c]	96, *79*	Recryst. (EtOAc)	42, *98*
9	1.0	**145**, 1	120	75, -	-	-
10	1.0	**147**, 1[b]	42[c]	90, *84*	Recryst. (EtOAc)	38, *99*
11	1.0	**147**, 1	22[c]	>90, *82*	Recryst. (2 x *i*PrOH)	59, *99.3*
12	1.0	**147**, 1	22[d]	*85*	Filt. (*i*PrOH)	35, *98.5*
13	0.50	**147**, 1	21	90	Recryst. (2 x *i*PrOH)	46, *99.7*
14	10.0	**147**, 1	21	98, *86*	Recryst. (*i*PrOH)	70, *98*

Table 10 Optimisation studies for the preparative synthesis of 152a; [a] 20 eq $MeNO_2$ used; [b] Reaction performed at 13 °C; [c] reaction quenched by elution through silica gel; [d] purification by filtration of the reaction mixture.

From the onset, we wanted to optimise the reaction conditions so that the reaction would be operationally simple, complete within a 24 h timeframe and did not necessitate purification by chromatography (silica or preparative chiral HPLC) to afford enantiomerically pure product. As a starting point, the reaction was repeated on 43 mg of

150a using 10 mol% **147** and was found to be complete after just 2 h with a crude ee of 84% (Table 10, Entry 2). Reducing the equivalents of nitromethane to 10 increased the enantioselectivity to 86% ee and the high conversion maintained (Table 10, Entry 3). Significantly, when the catalyst loading of **147** was lowered down to 1 mol% the reaction proceeded to greater than 90% conversion within 25 h (Table 10, Entries 5 and 6) and with maintained enantioselectivity of 86% (Table 10, Entry 4). When the catalyst loading was dropped to 0.5 mol% of **147** only 30% conversion was reached after 2 days. For comparison, the loading was dropped to 1 mol% using the triphenylphosphine derived BIMP **145**; however the reaction only reached 75% conversion after 5 days (Table 10, Entry 9).

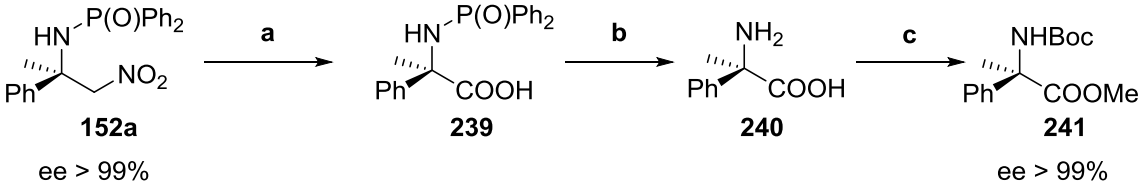
As the reaction mixture is a slurry due to the high concentration of the reagents and high crystallinity of the products we tried to simply filter the reaction mixture upon completion with minimal washings employing either EtOAc or EtOH. This proved to be possible with excellent enhancement in the enantioselectivities (98 and 99.3% ee respectively), but the yields of the isolated crystals were insufficient (Table 10, Entries 5 and 6). A screen of solvents of crystallisation for **152a** revealed excellent yields and enhancements in the ee when using refluxing isopropanol (Table 10, Entries 11 and 13).



Scheme 45 Preparative synthesis of 152a**.**

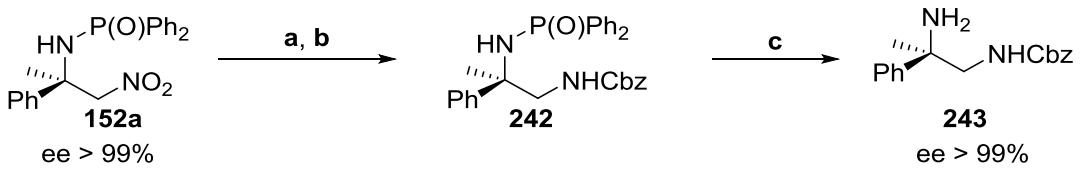
Taking all these considerations into account, the reaction was finally performed on a 10 g scale of ketimine **150a** with 231 mg of catalyst **147**. After 21 h, the conversion to **152a** was found to be 98% by ^{1}H NMR and the enantiomeric excess of the crude mixture was 86%. The reaction was quenched using 1 M AcOH in CH_2Cl_2, excess $MeNO_2$ and CH_2Cl_2 were

removed *in vacuo* and a slow crystallisation from ^{i}PrOH afforded **152a** in 70% yield and 98% ee. A second recrystallisation gave **152a** in 63 % isolated yield and 99.7% ee (Table 10, Entry 14 and Scheme 45).



Scheme 46 Derivatisation of 152a **to the α-amino acid *via* an oxidative Nef reaction; a: $KMnO_4$, KOH, KH_2PO_4, ^{t}BuOH, rt, 3 h; b: 6 M HCl, rt, 16 h, 57% yield over 2 steps; c: $SOCl_2$, MeOH, reflux, 9 h, then Boc_2O, $NaHCO_3$, 70 °C, 12 h, 65% yield over 2 steps.**

To demonstrate the synthetic utility of the enantiopure β-nitroamine, we derivatised **152a** to the α-amino acid **240** (Scheme 46). An oxidative Nef reaction transformed the nitro group to the carboxylic acid yielding **239**. Removal of the *N*-DPP protecting group under strong acid afforded **240** in 57% yield over two steps. In order to determine that no racemisation had occurred during the derivatisation the α-amino acid was esterified to the methyl ester and then *N*-Boc protected to afford **241** in 65% yield over two steps.



Scheme 47 Derivatisation of 152a **to the enantiopure diamine; a: $NaBH_4$, $NiCl_2$•$6H_2O$, MeOH, 0 °C, 30 min, 84% yield; b: CbzCl, Na_2CO_3, H_2O: dioxane, rt, 16 h, 90%; c: 12 M HCl, MeOH, rt, 13 h, 81%.**

The 1,2-diamine **243** was synthesised by the sequential reduction of the nitro group followed by removal of the *N*-DPP protecting group (Scheme 47). It was necessary to perform the reactions in that order as the presence of the nitro group prevented the ready cleavage of the protecting group.

3.7 Conclusion

We successfully developed the first general organocatalytic enantioselective ketimine nitro-Mannich reaction. Considerable effort was exercised to identify the optimal catalyst

and reaction conditions. Under the optimised conditions, twenty ketimine substrates were trialled in the nitro-Mannich reaction demonstrating the broad scope of the reaction. Complications arose with the discovery of the competing retro-nitro-Mannich reaction, but by performing the reactions at low temperature and quenching the catalyst upon completion of the reaction, optimal levels of enantiocontrol could be achieved. The strength of the Brønsted base was also found to be critical in determining whether any enantiocontrol was observable at appreciable levels of conversion. The BIMP catalysts appeared to have struck an optimal window between appropriate basicity strength to catalyse the forward reaction efficiently and prevent the retro-nitro-Mannich reaction from occurring too rapidly. We were able to perform the reaction on a 10 g preparative scale with just 1 mol% catalyst to afford the enantiopure β-nitroamine in good yields. Furthermore, the β-nitroamine product was derivatised to a 1,2-diamine and α-amino acid bearing a fully substituted carbon in a demonstration of synthetic utility.

4 Sulfa-Michael Addition to α,β-Unsaturated Esters

4.1 Chapter Overview

This chapter describes the first general enantioselective conjugate addition of alkyl and benzyl thiols to unactivated α-substituted α,β-unsaturated esters.[xiii] Reports in the literature of organocatalytic conjugate addition reactions to unactivated α,β-unsaturated esters are sparse and no true unactivated α or β-substituted α,β-unsaturated esters have been used. With the overall aim of demonstrating the applicability of the BIMP catalysts across a broad spectrum of pro-nucleophile/electrophile combinations, developing an efficient methodology involving low energy electrophiles – feedstock chemicals – would be a good gauge of performance. Building on the catalysts developed for the ketimine nitro-Mannich reaction, initial reactivity was identified but the reaction necessitated the development of new generations of bifunctional iminophosphorane catalysts. The scope was broadly applicable to a range of alkyl and benzyl thiols and α-substituted acrylates. Investigations into the scale-up capabilities of the reaction were performed and derivatisation of the β-mercaptoester moieties undertaken.

4.2 Introduction

Sulfur, in a variety of oxidation states, is omnipresent in biological processes and is found in many of the top selling drug molecules (Figure 35). The increasing requirement for chiral single enantiomer drug molecules has led to the development of a variety of methods for the catalytic formation of C-S bonds.[202] The sulfa-Michael addition (SMA) of thiols to

[xiii] The work disclosed in this chapter was performed in conjunction with Christopher Sandford, a part II student under the supervision of A.J.M.F. and all of the results have been included in this chapter for completeness.

a range of α,β-unsaturated systems predominates the literature, owing to the high nucleophilicity and synthetic utility of the sulfur moiety.[203] The oxidation state of the thiol moiety can be manipulated or the sulfur atom can be used for the installation of various other functional groups. The use of α-substituted α,β-unsaturated esters as electrophiles in the SMA allows the formation of β-mercaptoesters bearing a tertiary α-stereocenter. Examples of drug molecules containing this functionality include penicillin G **245** and (–)-Captopril **246** (Figure 35).

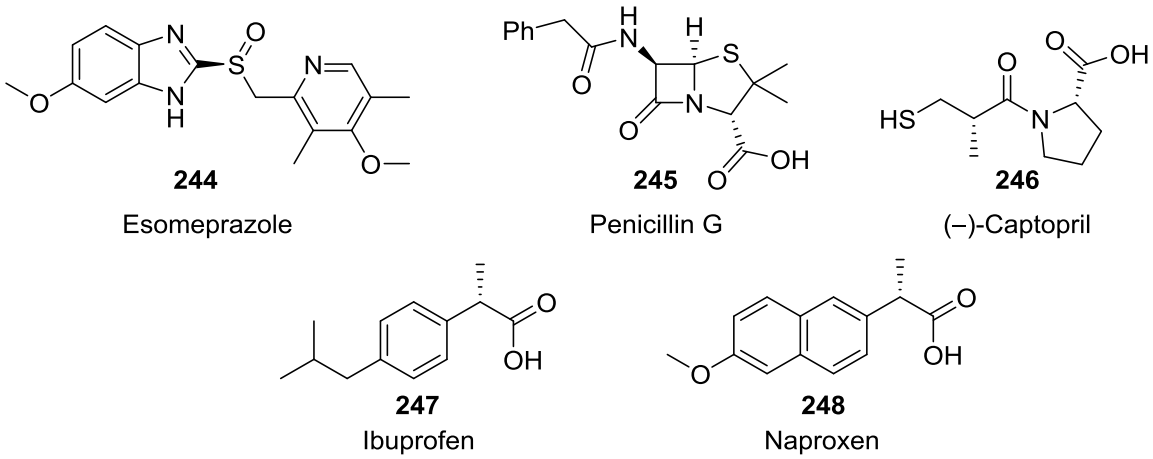


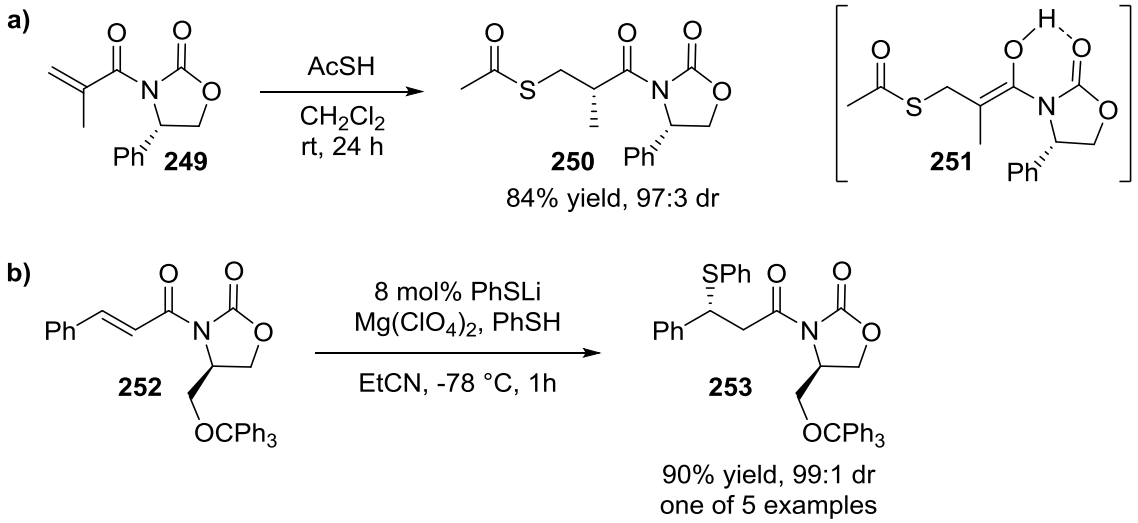
Figure 35 Examples of single enantiomer biologically significant sulfur containing molecules and drug molecules that can readily be accessed by cleavage of the C-S bond.

For all β-mercaptoesters with substitution at the α-position other than a methyl group, reductive cleavage of the C-S bond formed during the conjugate addition yields ester products with an α-stereocenter. This strategy provides direct access to biologically significant molecules such as the nonsteroidal anti-inflammatory drugs (NSAID) Ibuprofen **247** and Naproxen **248** (Figure 35).

4.2.1 Diastereoselective Conjugate Additions of Mercaptans

Several research groups have disclosed SMA reactions of mercaptans to α,β-unsaturated ester surrogates containing a chiral auxiliary with high levels of diastereocontrol. In 1995, Wu and co-workers disclosed the addition of thioacetic acid to α-substituted α,β-unsaturated oxazolidinone **249** which proceeded at room temperature in the absence of a

catalyst with high levels of diastereocontrol (Scheme 48a).[204] The authors proposed that the high levels of diastereocontrol observed in the formation of **250** arose from preferential protonation of the more accessible *re*-face of the intermediate enol **251**.



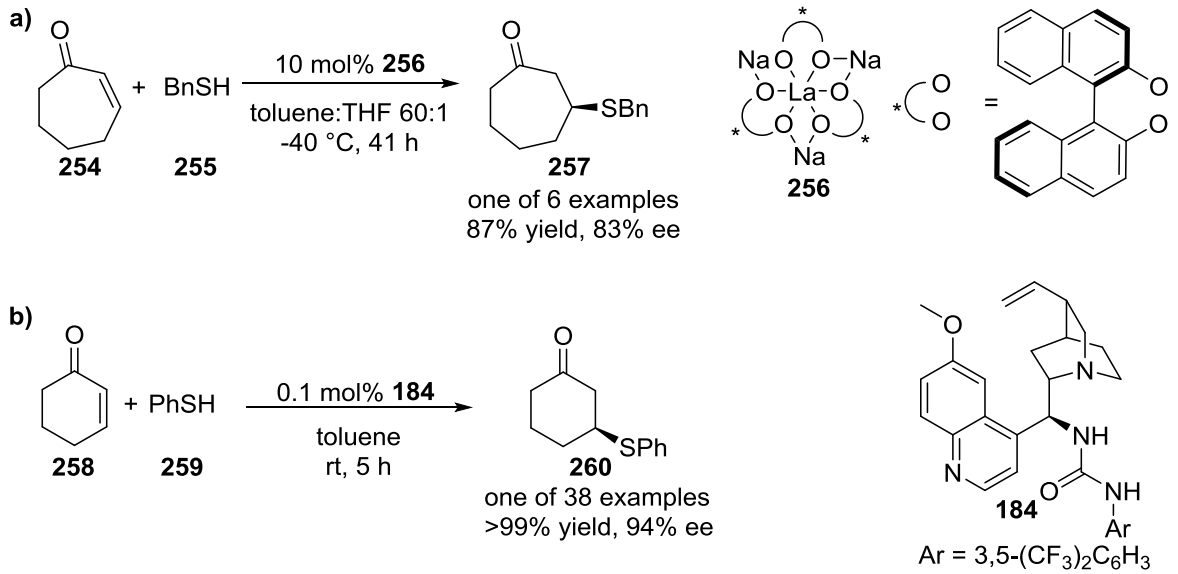
Scheme 48 Examples of chiral auxiliary controlled asymmetric SMA reactions. a) Wu's diastereoselective SMA of thioacetic acid to 249**; b) Tomioka's diastereoselective SMA to β-substituted α,β-unsaturated ester surrogates such as** 252 **requiring the use of stoichiometric Lewis acids.**

In the same year, Tomioka *et al.* demonstrated the highly diastereoselective SMA of thiophenol to β-substituted α,β-unsaturated ester surrogate **252** bearing a chiral oxazolidinone (Scheme 48b).[205] The reaction required stoichiometric magnesium salts as Lewis acid to proceed, presumably to activate and rigidify the electrophile through interactions with the two carbonyl moieties. The reaction proceeded rapidly at –78 °C with catalytic lithium thiophenolate to afford **253** with excellent levels of diastereocontrol.

These examples allowed the construction of β-mercaptoester moieties containing a stereogenic centre at either the α- or β- position. However, the use of stoichiometric quantities of chiral auxiliaries reduced the atom economy of the reaction and additional synthetic steps for their installation and removal were required. Therefore, the development of effective catalytic enantioselective variants would be desirable.

4.2.2 Catalytic Enantioselective SMA Reactions to Enones

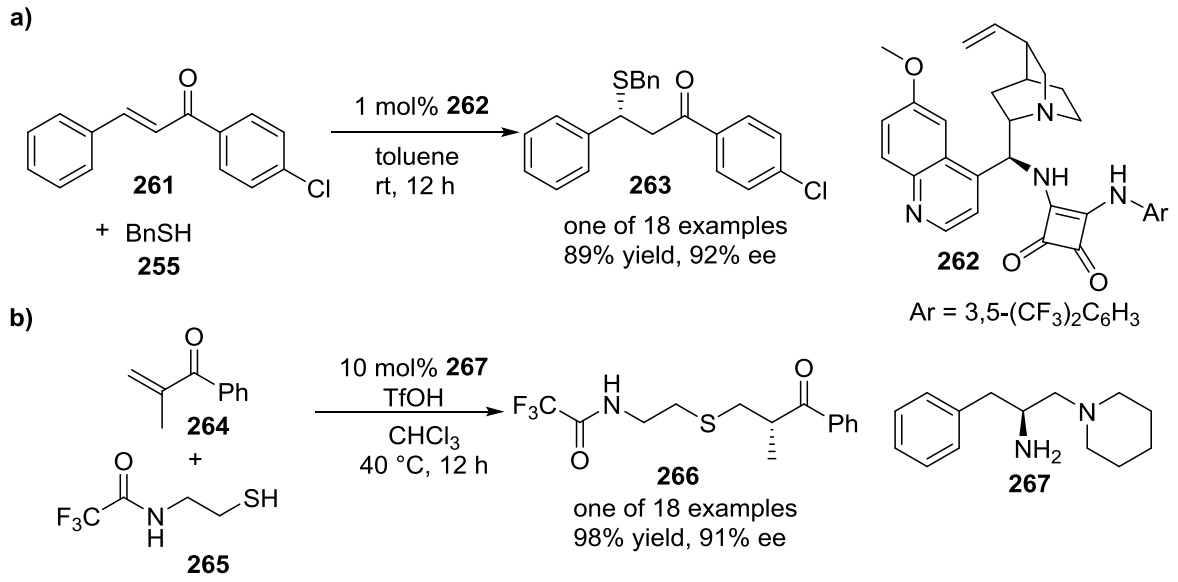
Following Wynberg and Hiemstra's seminal report of the cinchona alkaloid catalysed conjugate of aromatic thiols to cyclic enones (Scheme 2b), numerous reports have appeared in the literature for metal and organocatalytic SMA to α,β-unsaturated aldehydes and ketones. Shibasaki *et al.* demonstrated that chiral bimetallic complex **256** could catalyse the addition of benzyl and aromatic thiols to cyclic enones with moderate levels of enantiocontrol (Scheme 49a).[206] In 2010, Singh *et al.* published the highly enantioselective addition of aromatic thiols to a range of cyclic and acyclic enones using the cinchona alkaloid derived bifunctional organocatalyst **184** with loadings down to 0.1 mol% (Scheme 49b).[207]



Scheme 49 Selected examples of enantioselective conjugate additions of mercaptans to enones; a) Shibasaki's bimetallic complex in the conjugate addition of mercaptams to cyclic enones; b) Singh's organocatalytic addition of aromatic thiols to cyclic and acylic enones catalysed by 184.

In the same year, Chen and co-workers reported that the tertiary bifunctional organocatalyst **262** containing a squaramide moiety as the H-bond donor group was able to catalyse the reaction between mercaptans and enones with good to excellent levels of enantiocontrol (Scheme 50b).[208] In 2014, Cheng and co-workers published the sulfa-Michael addition of **265** to α-substituted α-β-unsaturated ketones catalysed by a primary amine catalyst **267** *via* iminium catalysis (Scheme 50b).[209] The enantiodetermining step

was believed to be the highly stereoselective protonation of the enamine intermediate from the protonated tertiary amine.



Scheme 50 a) Chen's squaramide catalysed SMA of alkyl and aromatic thiols to acyclic enones; b) Cheng's primary amine catalysed SMA to α-substituted vinyl ketones *via* iminium catalysis.

4.2.3 Enantioselective SMA to Activated α,β-Unsaturated Esters

The conjugate addition of mercaptans to α,β-unsaturated ester derivatives has been much less studied than the corresponding reaction to enone acceptors due to their reduced electrophilicity. Furthermore, the substrates are not amenable to activation *via* iminium catalysis as the amine catalyst cannot condense with the substrate. In a bid to address the lower reactivity associated with α,β-unsaturated esters, activated ester surrogates have been employed in the organocatalytic SMA (Figure 36). The use of activated esters such as imides,[62] oxazolidinones[210,211] or pyrazole esters[212] in the enantioselective SMA is commonplace.

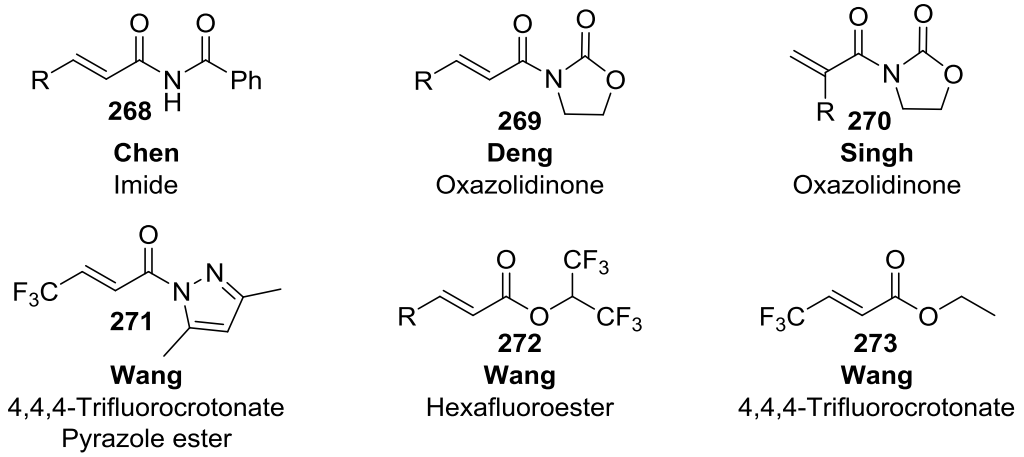


Figure 36 Examples of α-β-unsaturated ester surrogates used in the enantioselective SMA.

The ester surrogates increase the reactivity of the electrophile as they are inductively electron withdrawing and therefore enable the electrophiles to exhibit similar reactivity to that observed for enones. Furthermore, Takemoto *et al.* postulated that the presence of the extra carbonyl moiety when using oxazolidinones or imides as ester surrogates allowed additional H-bonding interactions with the H-bond donor group of the catalyst (Figure 37).[213] Wang successfully demonstrated the incorporation of fluorinated esters to increase reactivity of α,β-unsaturated esters.[214] In an alternative strategy, the highly electron withdrawing CF_3 moiety could be installed at the β-position of the unsaturated ester to augment the reactivity of the electrophile.[215] The conjugate addition to the 4,4,4-trifluorinated analogue of ethylcrotonate **273**, for example, allowed the construction of a stereogenic centre containing the biologically important trifluoromethyl group and the mercaptan moiety.[216]

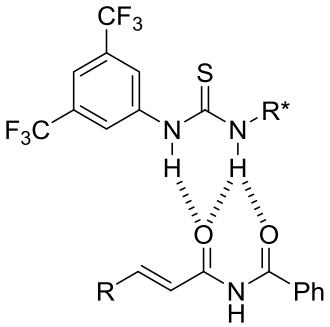
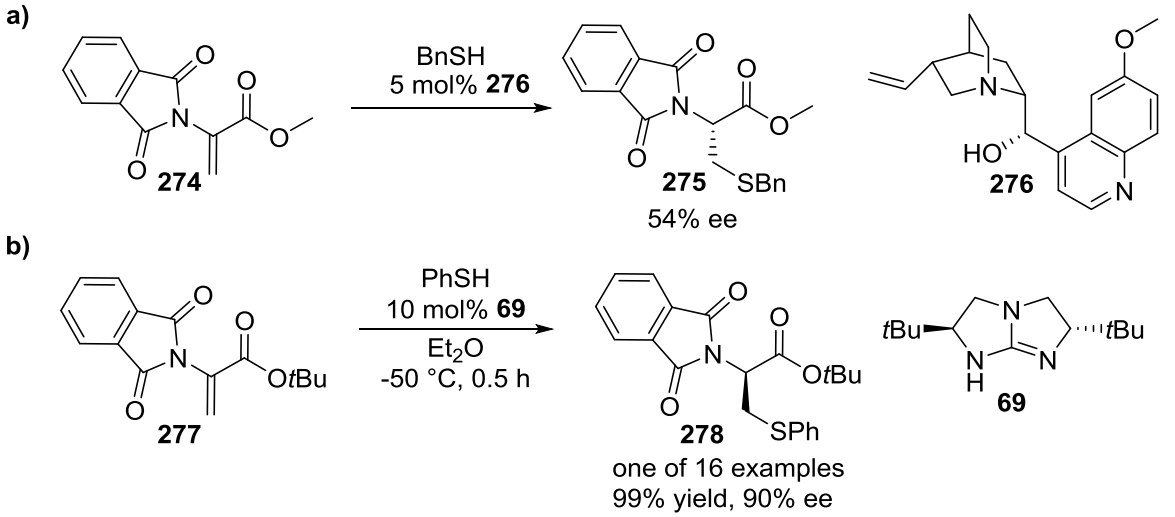


Figure 37 The presence of the extra carbonyl allows additional H-bonding interactions between the imide or oxazolidinone and the H-bond donor group of a bifunctional catalyst.

4.2.4 Chirality Derived from Enantioselective Protonation

The most efficient method for the creation of a tertiary α-stereocenter is the enantioselective protonation of a transient prochiral enolate using a catalytic chiral proton source.[217] In an early organocatalytic example, Pracejus and co-workers reported the enantioselective SMA of benzyl mercaptan to methyl 2-phthalimidoacrylate **274** using cinchona alkaloid catalyst **276** in 1977 (Scheme 51a).[218] No yields were disclosed and the enantioselectivity of the product **275** was only moderate (54% ee), but proof of concept was nevertheless established. Thirty years later, Tan *et al.* published an improvement to Pracejus' report with the use of a chiral guanidine **69** to catalyse the SMA enantioselective protonation sequence (Scheme 51b).[219] The authors found the *tert*-butyl ester to be critical for high enantioselectivity and the scope was extended to include a range of aromatic thiols and substitution around the phthalimide moiety.

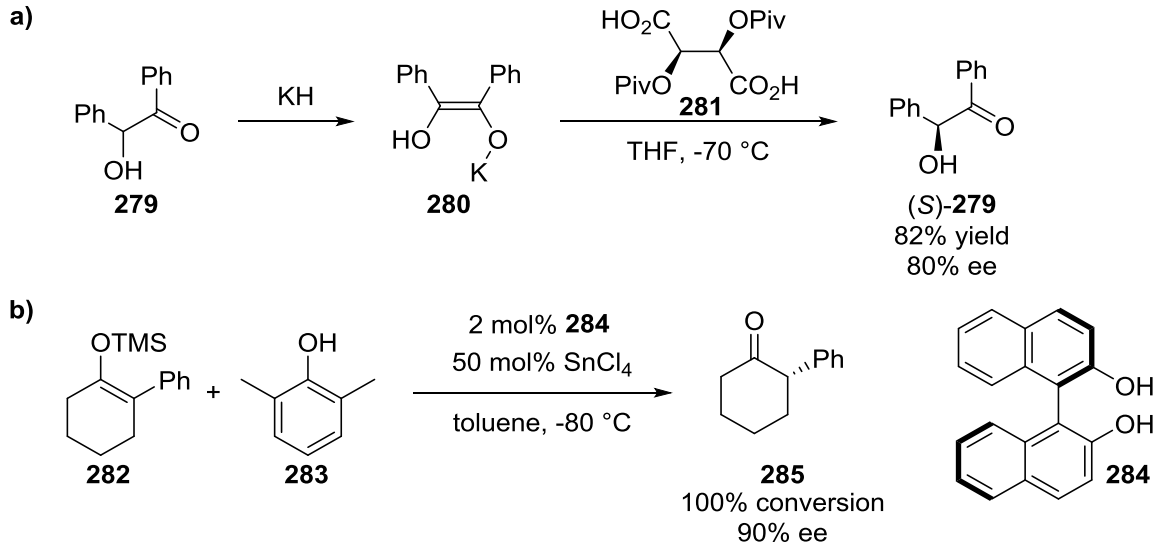


Scheme 51 Addition of aromatic and benzylic mercaptans to 2-phthalimidoacrylates.

The enantiodetermining step in these reactions is the protonation of the prochiral transient enolate formed after the initial conjugate addition of the thiolate anion to the α-substituted α,β-unsaturated ester. The protonation step is rapid and enantioselectivity arises under kinetic control due to preferential protonation of one of the prochiral faces of the enolate. The α-stereocenter can be prone to racemisation (by reforming the enolate) and thus

conditions for enantioselective protonation are usually quite subtle. The acidity of the proton source is therefore important and should be appropriately matched to the acidity of the substrate.

The SMA enantioselective protonation reactions shown in Scheme 51 are part of a wider class of enantioselective protonation reactions whereby the addition of the small hydrogen atom allows the construction of tertiary α-stereogenic centres. Early work into enantioselective protonation as a method to impart enantiocontrol includes investigations by Duhamel and co-workers who discovered that α-hydroxyketone **279** could be formed in up to 80% ee from the protonation of the enediolate **280** (Scheme 52a).[220] Yamamoto *et al.* developed a Lewis acid Brønsted acid complex for the enantioselective protonation of silyl enol ethers **282**, as preformed enolate equivalents (Scheme 52b).[221] Enantioselective protonation has been widely utilised as a strategy to install chirality in a molecule and has been comprehensively reviewed[222,223] and only selected notable contributions have been discussed here.



Scheme 52 Early examples of enantioselective protonation reactions.

4.3 Proof of Principle and Initial Catalyst Screen

4.3.1 Addition of 1-Propanethiol to Methyl Methacrylate

Due to the synthetic utility of β-mercaptoesters and the lack of a general strategy for their asymmetric synthesis *via* a catalytic enantioselective conjugate addition of mercaptans to simple α,β-unsaturated esters, we decided to invest considerable effort into the development of a practical solution. To probe the conjugate addition of thiols to unactivated α,β-unsaturated esters, we selected the smallest pro-nucleophile electrophile combination devoid of protecting groups that would allow the construction of a stereogenic centre α to an ester. 1-Propanethiol **286a** and methyl methacrylate **287a**[xiv] were thus chosen as our model reagents to optimise the sulfa-Michael addition to α-substituted α,β-unsaturated esters (Figure 38). We were delighted to observe the formation of the β-mercaptoester **288a** in quantitative yield using 10 mol% of **147** within just three hours and with an ee of 72%.

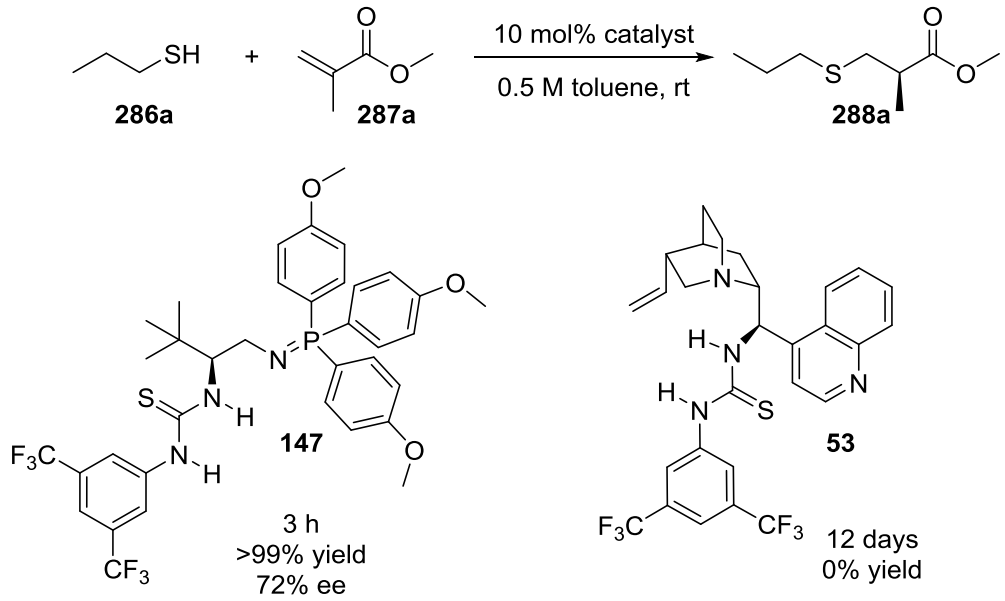


Figure 38 Sulfa-Michael addition of 1-propanethiol to methyl methacrylate using 147 **and comparison with cinchona alkaloid catalyst** 53**.**

[xiv] At the time of writing 5 kg of methyl methacrylate could be purchased for £65.40 from Sigma-Aldrich.

To allow for a comparison, the reaction was performed using cinchona alkaloid derived catalyst **53** and no product was observed even after an extended reaction time of 12 days. We were thus confident that we had discovered another reaction that required the use of organosuperbases to proceed.

4.3.2 Temperature and Screen of Solvents

The formation of enantioenriched products in this reaction arises from protonation of the pro-chiral transient enolate **289** formed after the initial attack of the sulfur nucleophile (Figure 39). We therefore expected the solvent choice to be paramount in controlling the levels of enantioselectivity.

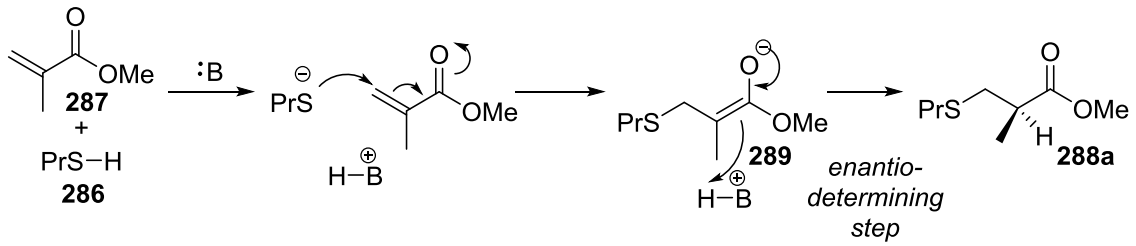
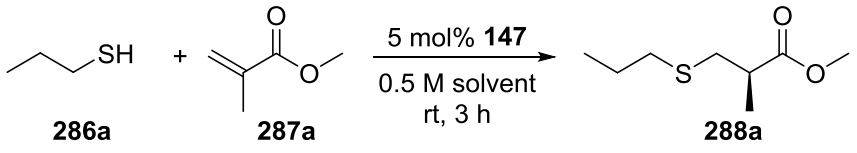


Figure 39 Representation of the stepwise mechanism of the SMA of 1-propanethiol to methyl methacrylate.

A screen of solvents was conducted using 5 mol% of catalyst **147** at rt and the reactions were quenched after 3 h by the addition of 1 M AcOH in CH_2Cl_2 (Table 11). The reactions were difficult to monitor by TLC analysis since the volatile 1-propanethiol **286a** (boiling point 68 °C) was used as the limiting reagent and therefore yields were taken as a measure of conversion. The enantiocontrol was found to be very solvent dependent and higher enantioselectivities in the formation of **288a** were observed with apolar solvents such as Et_2O (71% ee), benzene (70% ee) and hexane (73% ee) whereas the enantioselectivity was significantly lowered in a polar aprotic solvent such as DMF (19%). Chlorinated solvents also imparted lower levels of enantiocontrol (61% and 57% ee for CH_2Cl_2 and $CHCl_3$ respectively) and interestingly the rates of reaction were also lower. We postulated the lower enantioselectivity in chlorinated solvents to be due to trace HCl content. Whilst the

reaction proceeded quantitatively in MeOH, a polar protic solvent, the product **288a** was formed as a racemate, likely due to extensive protonation of the transient enolate from the methanolic solvent cage.



286a **287a** **288a**

Entry	Solvent	Yield / %	ee / %	Entry	Solvent	Yield / %	ee / %
1	MeOH	>99	0	7	$CHCl_3$	57	57
2	DMF	85	19	8	TBME	74	70
3	EtOAc	71	67	9	Toluene	>99	72
4	THF	80	65	10	Benzene	88	70
5	CH_2Cl_2	51	61	11	Cyclohexane	74	71
6	Et_2O	82	71	12	Hexane	88	73

Table 11 Screen of solvents in the SMA addition of 1-propanethiol (0.20 mmol) and methylmethacrylate (5.0 eq) catalysed by 5 mol% 147**.**

Since the screen of solvents did not lead to an improvement in the enantiocontrol in the formation of **288a**, a screen of temperatures was performed and surprisingly a remarkable *indifference* in the enantioselectivity of **288a** with respect to the reaction temperature was observed (Table 12). Whilst the rate diminished at –40 °C the enantioselectivity remained at 72% (Table 12, entry 1), with just a slight improvement to 74% ee at –20 °C and 0 °C (Table 12, entries 2 and 3). Conversely, heating the reaction up to 50 °C only marginally reduced the ee in the formation of **288a** to 68% (Table 12, entry 5). Dilution of the reaction to 0.05 M, whilst increasing the reaction time, did not significantly improve the ee (Table 12, entry 6).

Entry	Temp. / °C	Catalyst Loading / mol%	Concentration / M (toluene)	Time / h	Yield / %	ee / %
1	–40	5	0.5	24	88	72
2	–20	10	0.5	6	>99	74
3	0	10	0.5	6	>99	74
4	rt	10	0.5	3	>99	72
5	50	10	0.5	1	>99	68
6	rt	10	0.05	27	92	74

Table 12 Temperature screen for the SMA addition of 1-propanethiol 286a **and methylmethacrylate** 287a **catalysed by** 147**. Reactions were performed on 0.20 mmol scale of 1-propanethiol and 5 eq of methylmethacrylate.**

Disappointingly, we were unable to significantly enhance the enantioselectivity beyond our initial proof of principle value of 72%; although we noted that the invariance of the enantioselectivity with temperature could be exploited when performing the reaction on preparative scale (*vide infra*). It was also clear that the optimal catalyst for the ketimine nitro-Mannich reaction did not perform equally well in the SMA of α-substituted α,β-unsaturated esters and therefore catalyst optimisation studies were required.

4.3.3 Initial Screen of Catalysts

BIMP catalysts bearing a range of H-bond donor groups were synthesised and a brief survey of their efficacy was conducted in the SMA reaction of 1-propanethiol **286a** to methyl methacrylate **287a** (Figure 40). When the 3,5-$(CF_3)_2C_6H_3$ urea catalyst **290** was used, the ee was reduced from 72% to 57% ee. This reduction in enantioselectivity could probably be attributed to the less acidic H-bond donor groups not binding as effectively to the prochiral enolate. Catalyst **291** gave identical enantiocontrol to the 3,5-$(CF_3)_2C_6H_3$ thiourea **147**, presumably, as a result of the similar acidities of the thiourea hydrogens. The use of a catalyst with a single H-bond donor capability, in the form of **292** reduced the enantioselectivity to 37% and this could be rationalised from the catalyst only possessing single H-bond donor capabilities. The use of the sulfonamide derived catalyst **293** resulted

in lower yields and levels of enantiocontrol, again consistent with the ability of the catalyst to form only weak H-bonding interactions with the reagents. The effect of the H-bond donor group of the catalyst on the enantioselectivity imparted in the SMA reaction was very similar to that observed previously in the ketimine nitro-Mannich reaction (section 3.4.3).

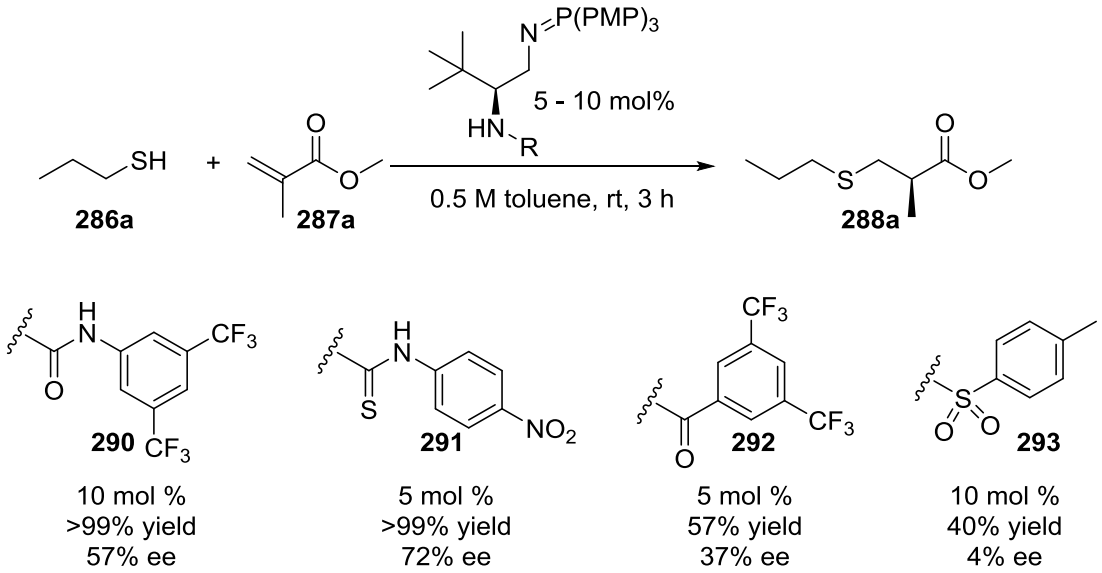
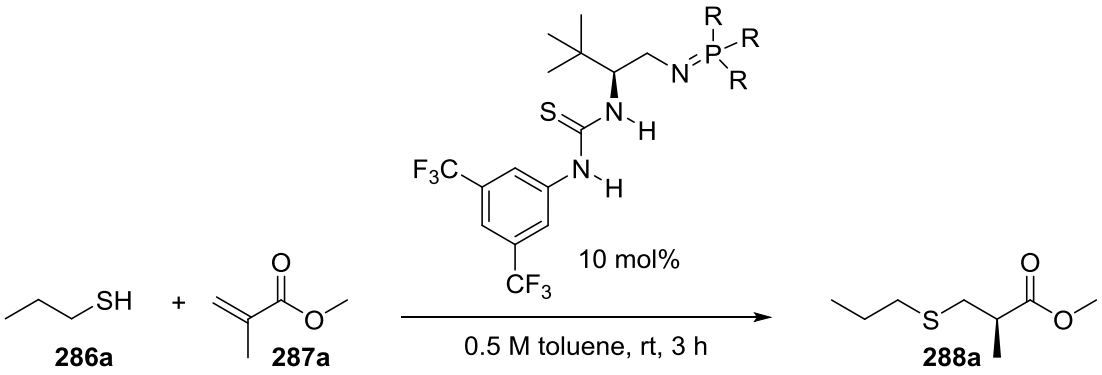


Figure 40 Screen of catalysts with variations to the hydrogen bond group on the sulfa-Michael addition of 1-propanethiol to methyl methacrylate.

Various trivalent phosphines were trialled to determine the steric and electronic effects of the iminophosphorane moiety on the yield and enantioselectivity of **288a** (Table 13). The PPh_3 derived catalyst **145** was slower than **147** in the formation of **288a** and the ee was slightly reduced, as was the *p*-Cl catalyst **229** (Table 13, entries 1 and 2). Similarly to the ketimine nitro-Mannich reaction, the conversion to **288a** after 3 hours was strongly influenced by the iminophosphorane moiety, suggesting that the extent of deprotonation of the pro-nucleophile was important. Increasing the number and varying the position of the methoxy substituents around the aromatic ring did not enhance the enantioselectivity (68 and 67 % ee respectively for the catalysts **232** and **233**, (Table 13, entries 3 and 4)) however the rate was maintained. Interestingly, the use of tri(^{n}butyl) phosphine to form catalyst **294** reduced the enantioselectivity, presumably due to greater conformational

flexibility of the chiral pocket associated with the alkyl phosphine moiety (Table 13, entry 5).



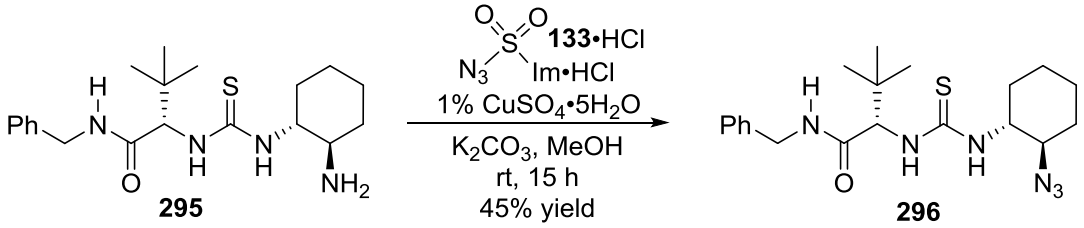
286a **287a** **288a**

Entry	Catalyst	PR_3	Yield / %	ee /%
1[a]	**145**	PPh_3	14	64
2	**229**	$P(pClC_6H_4)_3$	9	68
3	**232**	$P(m,p(OCH_3)_2C_6H_3)_3$	97	68
4	**233**	$P(m,m,p(OCH_3)_3C_6H_2)_3$	91	67
5	**294**	$P(^nBu)_3$	91	35

Table 13 Variation of the iminophosphorane moiety in the SMA to methyl methacrylate; [a] reaction was performed using 5 mol% catalyst.

4.4 Development of BIMP Catalysts Incorporating Amide-Thiourea H-Bond Donor Groups

The catalyst optimisation studies in section 4.3.3 revealed that a new catalyst design was necessary to enhance the enantioselectivity and thus we needed to expand our catalyst library. Whilst the 3,5-$(CF_3)_2C_6H_3$ thiourea moiety has been used extensively in organocatalysis as an extremely effective H-bond donor group other structural thioureas have also been explored. Jacobsen, for example, pioneered the amide thioureas as effective H-bond donor catalysts in a variety of asymmetric transformations (Scheme 6).



295 **296**

Scheme 53 Synthesis of 296 ***via*** **diazotransfer.**

Drawing inspiration from Jacobsen's cyclohexyl diamine derived organocatalysts, we synthesised the iminophosphorane analogue by initially transforming the primary amine **295** into the azide **296** (Scheme 53). The active catalyst **297** was then made *in situ* by treatment of **296** with tris(4-methoxyphenylphosphine) **146** and evaluated in the SMA between 1-propanethiol and methyl methacrylate (Figure 41). Disappointingly, whilst demonstrating excellent rate, the catalyst **297** afforded the product **288a** in just 9% ee. This result is in line with our previous work on the ketimine nitro-Mannich reaction that catalyst **211** derived from cyclohexyl diamine bearing the Schreiner type thiourea also gave poor enantioselectivities (section 3.4.2 and Figure 23). It was postulated therefore that the *trans*-1,2-diamine was perhaps antagonistic with the iminophosphorane moiety.

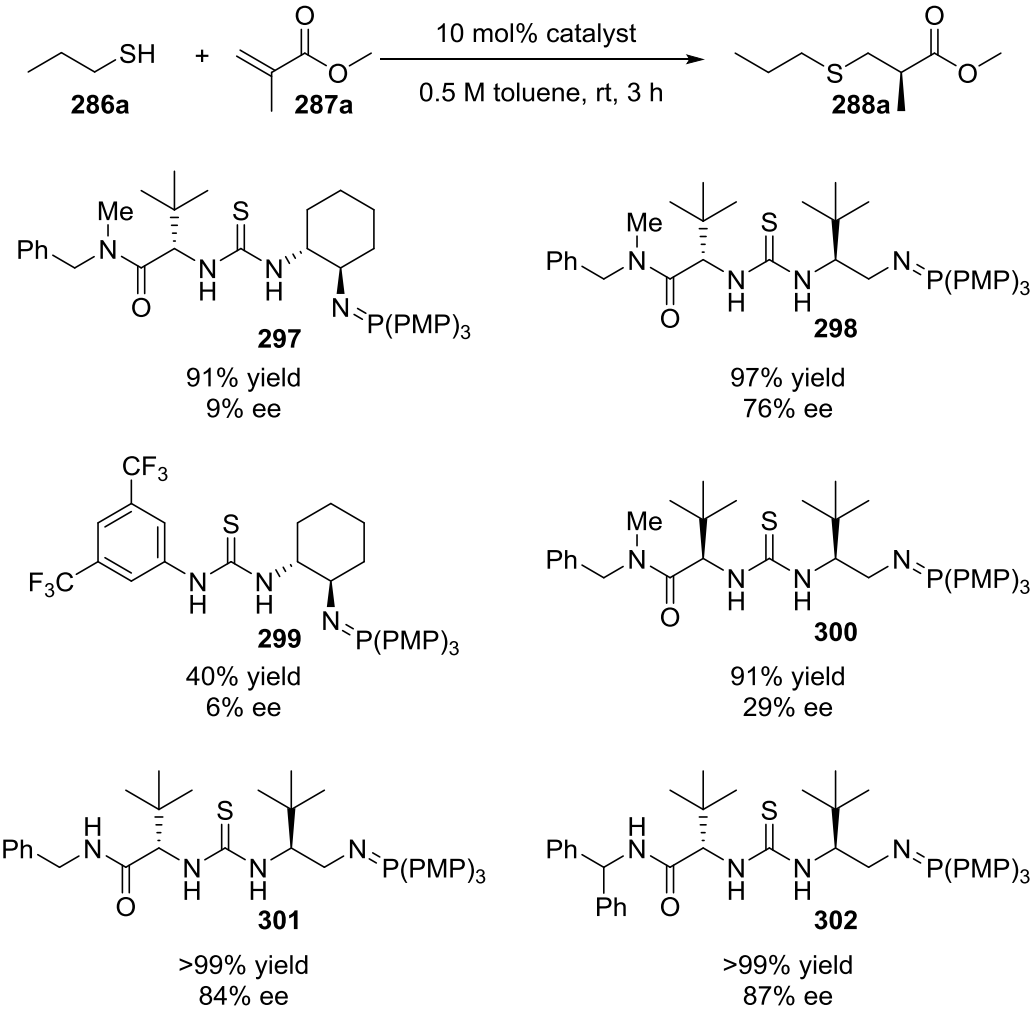
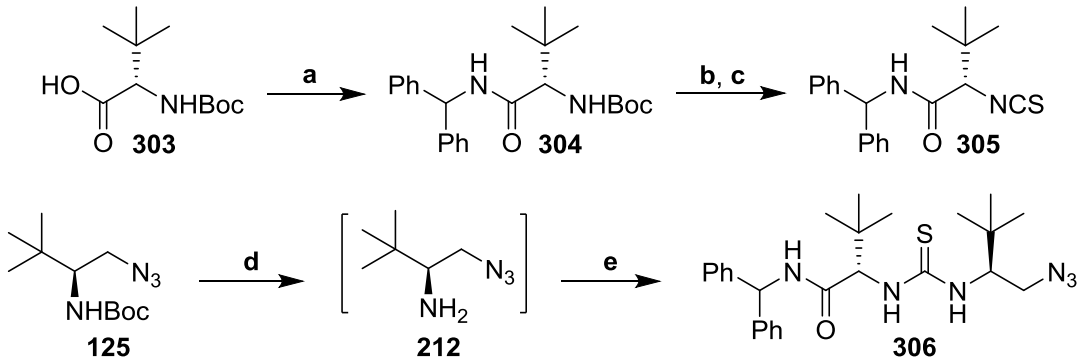


Figure 41 Evaluation of BIMP catalysts bearing an amide thiourea H-bond donor in the SMA to methyl methacrylate.

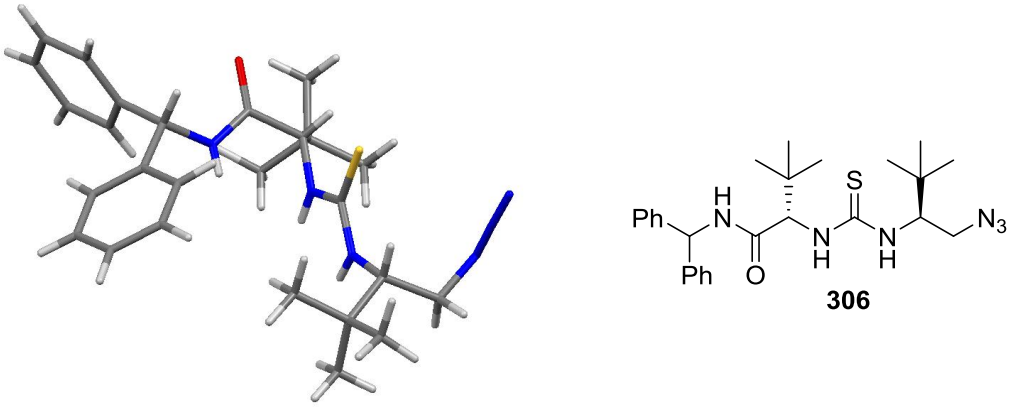
We hypothesised that the amide-thiourea moiety of catalyst **297** could be incorporated with the *tert*-leucine backbone that had been demonstrated to be optimal with the iminophosphorane group. Thus, catalyst **298** was synthesised and to our delight an enhancement in the enantioselectivity to 76% ee was observed. As a comparison, trans-1,2-diaminocyclohexane derived catalyst **299** was evaluated in the reaction and the enantiocontrol was just 6%. Interestingly, the yield (as a reflection of conversion) was also lower. The diastereomer of **298** was synthesised and evaluated but the enantioselectivity was reduced to 29% ee with catalyst **300**. Importantly, the same major enantiomer was formed and thus we concluded that the proximal stereocenter was dominating the stereocontrol in the formation of **288a**. Some fine-tuning of the amide group revealed the secondary amide to be beneficial, with catalyst **301** increasing the ee to 84%. Increasing the steric bulk of the amide moiety using catalyst **302**, possessing a benzhydryl group afforded the β-mercaptoester **288a** in 87% ee.



Scheme 54 Synthesis of thiourea amide H-bond donor azide 306**; a: Ph_2CHNH_2, DIPEA, EDCI, HOBt, CH_2Cl_2, 20 h, rt; b: 4 M HCl in dioxane, CH_2Cl_2, 4 h; c: Cl_2CS, aq $NaHCO_3$, CH_2Cl_2, 30 mins, 84% yield over 3 steps; d: TFA, then aq NaOH; e:** 305**, THF, 90% yield over two steps.**

The synthesis of the amide thiourea H-bond donor catalysts followed the strategy outlined in Scheme 54. According to a procedure developed by Jacobsen,[224] amide coupling of benzhydryl amine and *N*-Boc L-*tert* leucine, *N*-Boc deprotection of **304** and treatment of the amine with thiophosgene afforded the isothiocyanate **305** in 84% yield over three steps on gram scale. The isothiocyanate was of sufficient purity to be used without purification and could readily be stored for several months at –20 °C. Addition of the *N*-Boc protected

amino azide **125** to the isothiocyanate under our previously developed conditions afforded the azide **306** in 90% yield. The structure of **306** was confirmed by single crystal X-ray diffraction (Figure 42). The BIMP catalyst **302** could then be made *in situ* by reacting the azide with equimolar quantities of tris(4-methoxyphenylphosphine). The other BIMP catalysts **298**, **300** and **301** evaluated for efficacy in the SMA reaction between 1-propanethiol and methyl methacrylate (Figure 41) were synthesised in an analogous manner using the desired amine and the (*R*) or (*S*)-enantiomer of *N*-Boc *tert*-leucine **303**.



306

Figure 42 Single X-ray crystal structure of 306**.**

Having observed an improvement in the enantioselectivity in the formation of **288a** with the amide thiourea BIMP catalysts, optimisation of the reaction conditions was undertaken next. Performing the SMA reaction at lower temperature resulted in a slight decrease in the enantioselectivity to 82% at –20 °C in the formation of **288a** (Table 14, entry 3). Dilution of the reaction mixture to 0.05 M increased the enantioselectivity of **288a** to 91% ee albeit with a slightly extended reaction time concomitant with dilution (Table 14, entry 3). A solvent switch to Et_2O increased the enantioselectivity of the β-mercaptoester to 94% and the product could be formed in quantitative yields after 24 h (Table 14, entry 8).

Entry	Temp / °C	Catalyst Loading / mol%	Solvent	Concentration / M	Time / h	Yield / %	ee / %
1	rt	10	Toluene	0.5	3	>99	87
2	0	5	Toluene	0.5	5	>99	83
3	–20	5	Toluene	0.5	5	>99	82
4	50	5	Toluene	0.5	1	>99	86
5	rt	5	Toluene	0.05	6	74	91
6	rt	5	Toluene	0.01	24	14	91
7	rt	5	Et_2O	0.5	3	86	89
8	rt	5	Et_2O	0.05	24	97	94

Table 14 Optimisation table for the addition of 1-propanethiol to methyl methacrylate using catalyst 302**. Reactions were performed with 0.2 mmol of 1-propanethiol and 5 eq of methyl methacrylate and quenched by the addition of 1 M AcOH in CH_2Cl_2.**

The catalyst **302** was synthesised *in situ* by premixing equimolar quantities of the azide and tris(4-methoxyphenylphosphine). Several attempts were made to isolate the iminophosphorane catalyst but issues pertaining to the stability of the catalyst when isolated were encountered and as such the methodology was performed with the catalyst synthesised *in situ* for 24 h prior to the experiment (see section 5.3 for further discussion).

4.5 Substrate Scope of the Sulfa-Michael Addition Reaction to α-Substituted α,β-Unsaturated Esters

4.5.1 Screen of Methacrylic Esters and Alkyl Thiols

With optimised conditions established, the generality of the reaction was probed and variation of the ester moiety was the first point of investigation (Figure 43). The scope was expanded to include ethyl methacrylate with a marginal decrease in yield but maintained enantioselectivity in the formation of **288b**. The enantioselectivities in the formation of β-mercaptoesters **288c** and **288f** from isopropyl and *tert*-butyl methacrylate respectively were high, with a slight increase to 96% ee in the case of **288f**. The reaction with *tert*-butyl methacrylate proceeded slower and necessitated a 48 h reaction time, presumably due to

increased steric interactions associated with the bulky ester. The SMA reaction was also highly enantioselective when the ester was substituted to a benzyl or phenyl group (89 and 95% ee for the formation of **288d** and **288e** respectively).

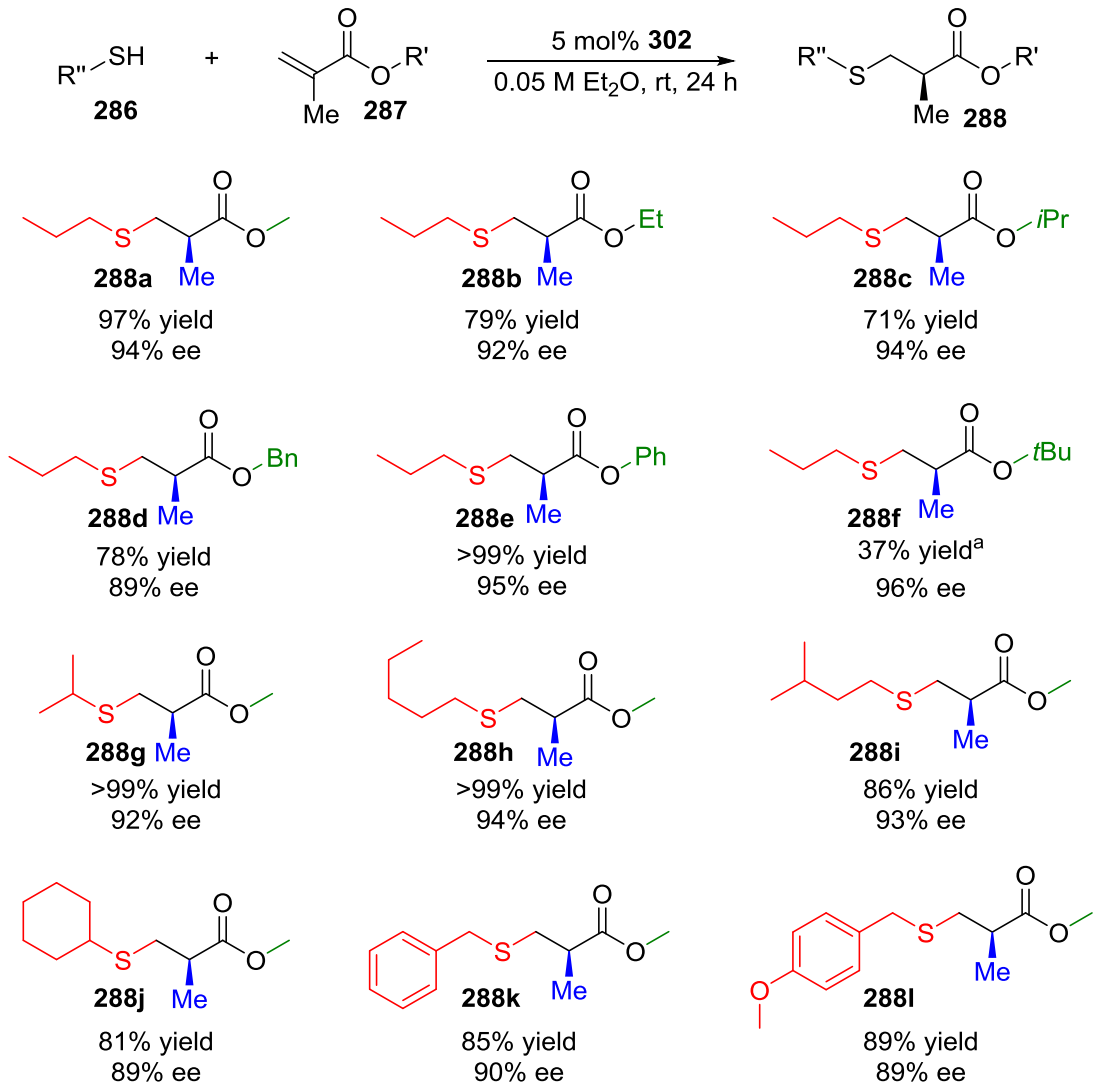
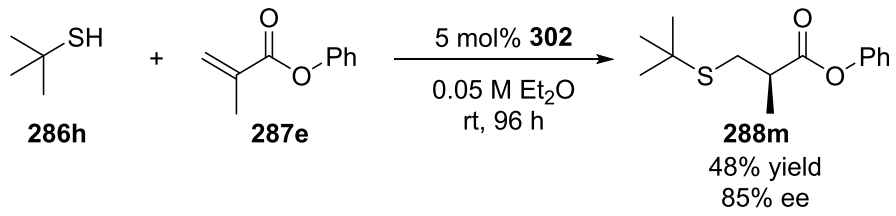


Figure 43 Substrate scope of the SMA with variations to the ester group and alkyl thiols; [a] the reaction was left for 48 h.

The scope with respect to the alkyl thiols in the addition to methyl methacrylate was subsequently investigated. Primary and secondary mercaptans performed well in the reaction with near quantitative yields after 24 h and with enantioselectivities in the range of 89 – 94%. The β-mercaptoester **288g** was formed quantitatively whereas the yield of **288j** was slightly reduced (81%), possibly as a result of increased repulsive steric interactions of the cyclohexyl moiety reducing the nucleophilicity. β-Mercaptoester products **288k** and

288l synthesised by the addition of benzyl and 4-methoxybenzyl mercaptans to methyl methacrylate **287a** were afforded with enantioselectivities of 90 and 89% respectively in good yields.



Scheme 55 Addition of *tert*-butyl mercaptan to phenyl methacrylate.

When we investigated the addition of *tert*-butyl mercaptan to methyl methacrylate no product was observed under the standard conditions.[xv] However it was noted that the addition of 1-propanethiol to phenyl methacrylate **287e** proceeded faster (by TLC) than the analogous reaction with methyl methacrylate (Figure 43). This was postulated to be due to the electron withdrawing effect of the phenyl substituent lowering the LUMO of the Michael acceptor relative to the methyl ester. Therefore, we reasoned that the use of phenyl methacrylate **287e** may yield the desired β-mercaptoester when using the tertiary mercaptan. Pleasingly, with an extended reaction time of 4 days, the desired product **288m** was isolated in 48% yield and 85% ee (Scheme 55).[xvi]

Having established that a range of alkyl and benzylic thiols could successfully be added to various methacrylate esters in quantitative yields and with up to 96% ee, we turned our investigation towards the addition of alkyl thiols to other α-substituted α,β-unsaturated esters.

4.5.2 Synthesis of α-Alkyl Substituted α,β-Unsaturated Esters

The synthesis of alkyl α-substituted α,β-unsaturated esters could be readily accomplished in three steps following literature procedures.[225] Initial hydrolysis of the mono-substituted

[xv] The reaction with 10 mol% BEMP to afford the racemate in 0.5 M toluene proceeded in *circa* 50% yield.
[xvi] The ee of **288m** could not be determined by HPLC or GC analysis but was determined on the corresponding sulfone. See Section 8.4.3.8 for details.

diethylmalonate **307** followed by treatment of the crude diacid **308** with *p*-formaldehyde and diethylamine in a decarboxylative aldol condensation afforded the α,β-unsaturated acids **309** in yields ranging from 19 – 76% (Figure 44).[xvii]

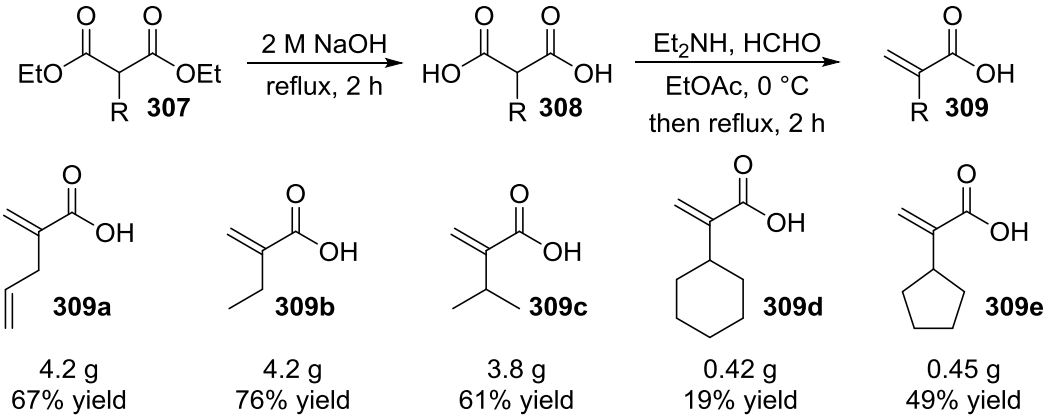


Figure 44 Synthesis of aliphatic α-substituted α,β-unsaturated acids 309 **from mono substituted diethyl malonate. Yields are given over the two steps.**

The methyl esters **287g – i** were synthesised by initial treatment of thionyl chloride with MeOH to generate HCl and then addition of the corresponding acid **309**. The reactions were refluxed for 2 h then purified by basification and extraction (Figure 45). The products were of sufficient purity to be used crude in the asymmetric sulfa-Michael addition reactions.[xviii]

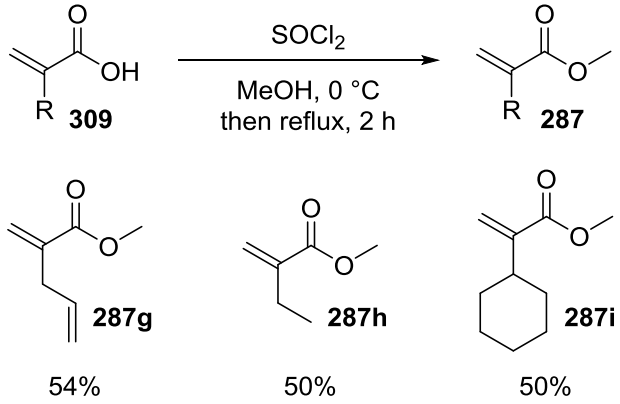


Figure 45 Synthesis of α-substituted α,β-unsaturated methyl esters.

[xvii] The mono-substituted diethyl malonates were either bought from commercial suppliers (ethyl diethylmalonate) or synthesised by the treatment of diethyl malonate with NaH and the corresponding alkyl bromide in DMF. When installing the cyclohexyl or cyclopentyl groups the reactions necessitated refluxing overnight.

[xviii] In some of the decarboxylative aldol condensation reactions, we observed the competing formation (typically less than 10%) of the decarboxylated product which proved inseparable either at the acid **309** or ester **287** stage. Slow addition of the base and *p*-formaldehyde at 0 °C in the aldol reaction was necessary to minimise the formation of the inseparable side product.

The phenolic esters were synthesised, by treatment of the α,β-unsaturated acids **309** with phenol, EDCI, DIPEA and catalytic DMAP, in yields ranging from 75 – 98% (Figure 46).

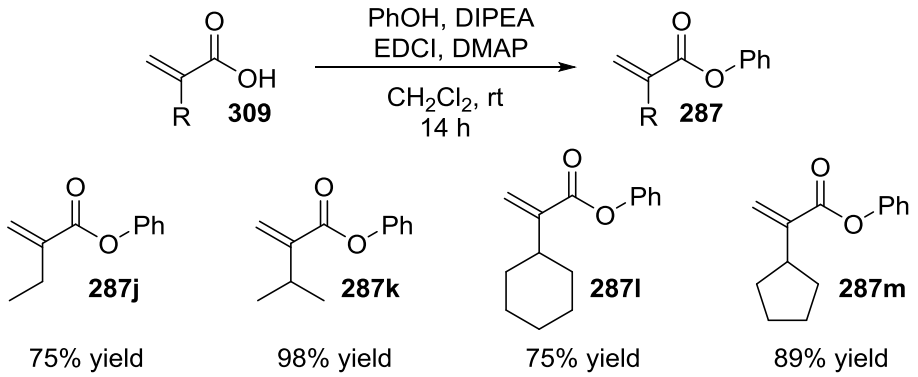
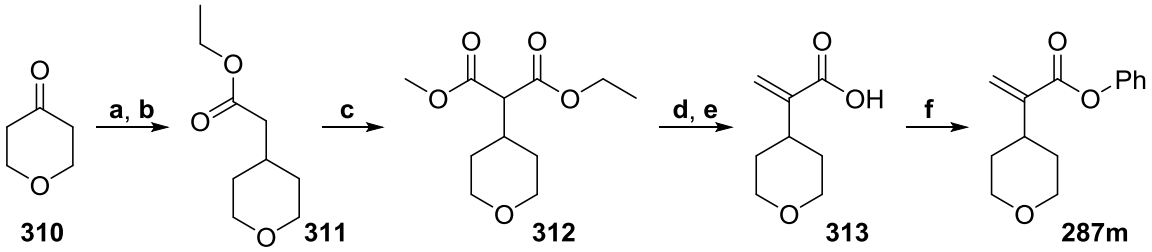


Figure 46 Synthesis α-substituted α,β-unsaturated phenolic esters.

To install a tetrahydropyran moiety at the α-position of an α,β-unsaturated ester we modified the synthesis slightly due to the commercial availability of tetrahydropyran-4-one **310** (Scheme 56). A two-step Horner-Wadsworth-Emmons reaction using **310** and hydrogenation of the double bond afforded the ester **311** in 85% yield over two steps.[226] Acylation to afford the monosubstituted malonate **312** by the dropwise addition of LiHMDS to a premixed solution of **311** and dimethylcarbonate was found to be optimal. A decarboxylative aldol condensation afforded **313** in 47% yield and subsequent esterification yielded the desired α-substituted α,β-unsaturated ester **287m** in 26% overall yield over 6 steps.



Scheme 56 Synthesis of 287m**; a: triethylphosphonoacetate, NaH, THF, rt, 6 h; b: H_2, Pd/C, MeOH, rt, 4 h, 85% over 2 steps; c: dimethylcarbonate, LiHMDS, THF, -78 to 0 °C, 14 h, 96%; d: 2 M NaOH, reflux, 2 h; e: Et_2NH, HCHO, EtOAc, 0 °C then reflux, 2 h, 47%; f: PhOH, DIPEA, EDCI, DMAP, CH_2Cl_2, rt, 14 h, 67%.**

4.5.3 Addition of 1-Propanethiol to Alkyl α-Substituted α,β-Unsaturated Esters

For simplicity, all the sulfa-Michael addition reactions to the range of α-substituted α,β-unsaturated esters were performed using 1-propanethiol on the assumption that the other

alkyl thiols would also be well-tolerated. The reaction was initially performed on commercially available dimethyl itaconate (dimethyl 2-methylidenebutanedioate) to afford the β-mercapto ester **288n** in 85% yield and 90% ee (Figure 47). This result gave us confidence that the reaction would be applicable to a wide range of substitutions at the α-position. The addition of 1-propanethiol to the allyl α-substituent also proceeded smoothly to afford **288o** in near quantitative yield (94% yield and 93% ee). However, the presence of an ethyl group at the α-position reduced the yield of **288p** significantly to 47% despite using 5 eq of the electrophile. A separate experiment extending the reaction time to 48 h had little effect on improving the yield. We showed in Figure 43 that the ee was minimally affected by using a different ester and therefore the phenolic ester was chosen to increase the electrophilicity of the substrate. This ester gave identical enantioselectivity (92% ee) in the formation of the β-mercaptoester **288q** but importantly with an improved yield of 85%. Similarly, when the reaction was performed with the cyclohexyl α-substituent **287i**, only a trace of product formation was observed. As a trial, the SMA reaction to **287i** was attempted substituting the solvent to TBME and refluxing for 24 h but the yield of the β-mercaptoester **288r** was only 39% after 24 h. We therefore elected to use the more active phenolic ester to afford the β-mercaptoester **288s** in 93% yield and 85% ee at rt. Analogously, the β-mercaptoester products bearing cyclopentyl **288t** (96% yield and 90% ee) and isopropyl **288u** moieties (98% yield, 85% ee) at the α-position necessitated the use of phenolic esters.[xix] Incorporating a saturated heterocycle at the α-position by synthesising **287n**, the enantioselectivity in the formation of β-mercaptoester **288v** was significantly reduced to 54% ee.

[xix] The addition of 1-propanethiol to the methyl esters of **309c** and **309e** was attempted under the methodology conditions but only trace product was observed. The reaction to afford the racemate using 10 mol% BEMP in 0.5 M toluene afforded in the products in moderate yields.

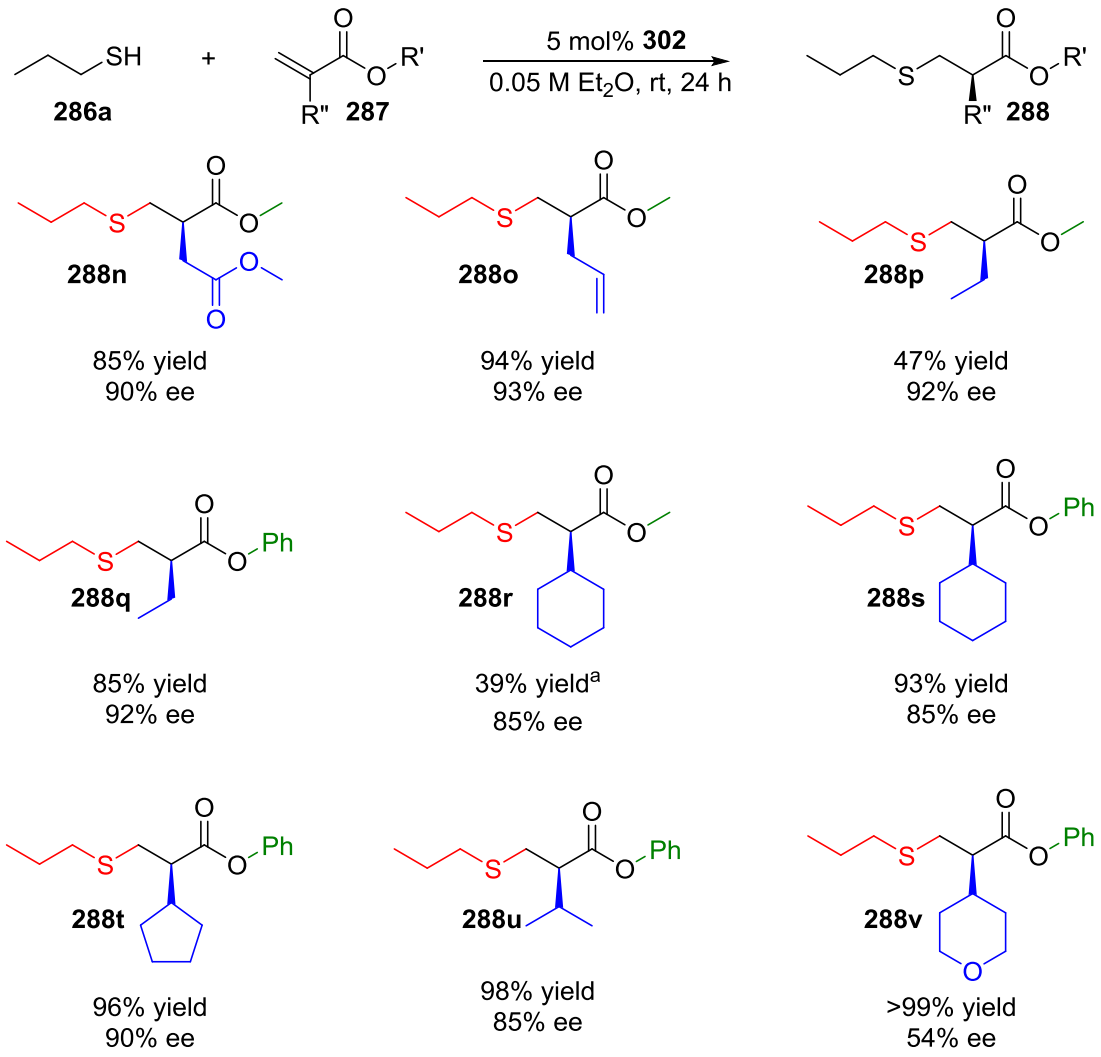
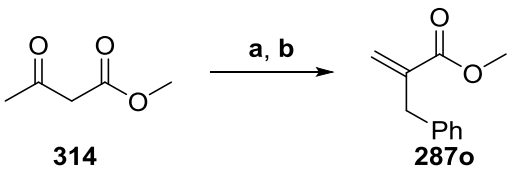


Figure 47 β-Mercaptoester products from the addition of 1-propanethiol to a range of alkyl α-substituted, α,β-unsaturated esters; [a] reaction was performed in 0.05 M TBME at 55 °C for 24 h.

4.5.4 Synthesis of α-Benzyl and α-Aryl Substituted, α,β-Unsaturated Esters

With a series of β-mercaptoesters bearing α-aliphatic substituents synthesised in good yields and enantioselectivities, the scope of the transformation was expanded to include α,β-unsaturated esters bearing α-aryl and α-benzyl substituents. The α-benzyl acrylate substrate **287o** was synthesised by alkylation of methyl acetoacetate with benzyl bromide and subsequent aldol condensation with *p*-formaldehyde in 57% yield over two steps (Scheme 57).[227]



Scheme 57 Synthesis of 287o **from methyl acetoacetate; a: ^{t}BuOK, BnBr, THF, 70 °C; b: LiHMDS, *p*-formaldehyde, THF, rt, 57% yield over two steps.**

Several electron rich or neutral aryl α-substituted α,β-unsaturated esters could be synthesised by the strategy outlined by Singh *et al.* in the synthesis of their α-substituted α,β-unsaturated oxazolidinones.[211] The *para*-methoxy α-substituent **317a** was synthesised by an initial Friedel-Crafts acylation of anisole to ethyl chlorooxoacetate with $AlCl_3$ to afford the oxoacetate. Alternatively, the oxoacetates **316** could be synthesised by lithium halogen exchange of the aromatic bromide and subsequent trapping with diethyloxalate (Figure 48).

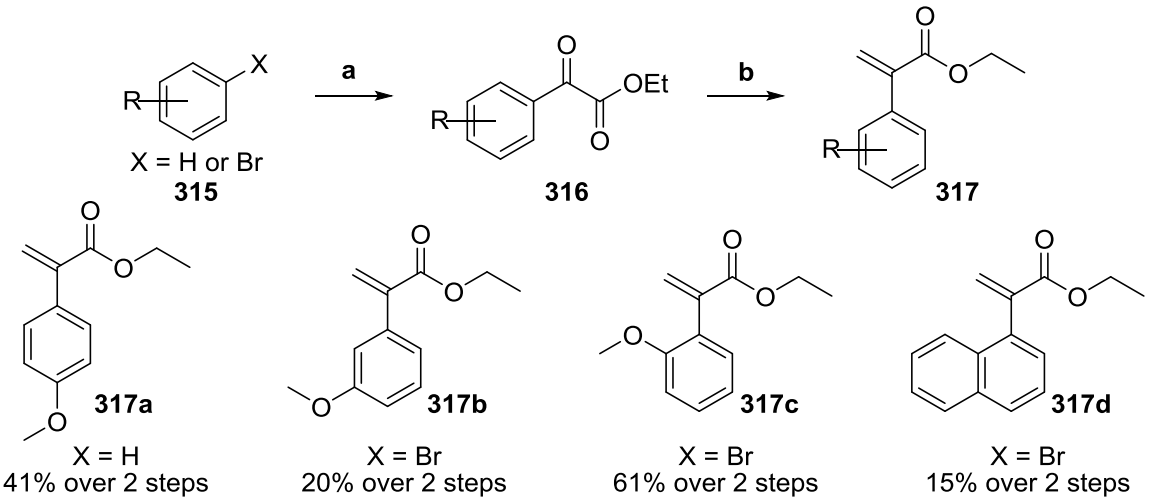


Figure 48 Synthesis of α-substituted α,β-unsaturated esters 317**; a: X = H: $AlCl_3$, $ClC(O)CO_2Et$, CH_2Cl_2, 0 °C; X = Br: ^{n}BuLi, diethyloxalate, THF, –78 °C to 0 °C; b: $MePPh_3Br$, ^{n}BuLi, THF, –78 °C.**

Transesterification to the methyl ester was accomplished by treatment of the ethyl ester **317** with MeOH and thionyl chloride under reflux for 24 h (Figure 49).[xx]

[xx] The transesterification reaction proceeded slower than esterification from the acid.

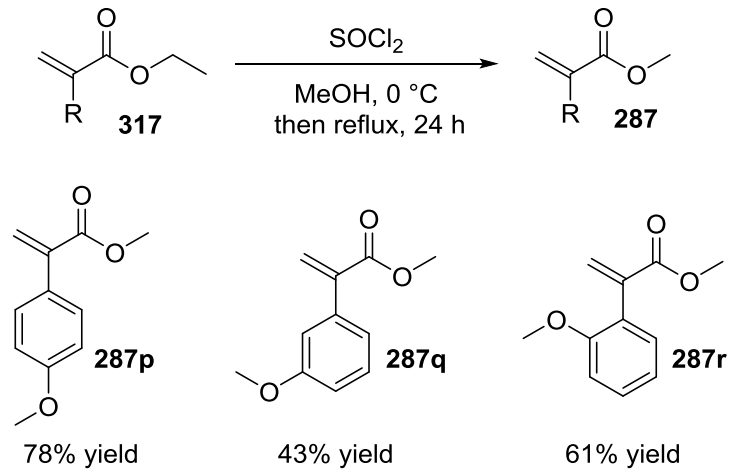
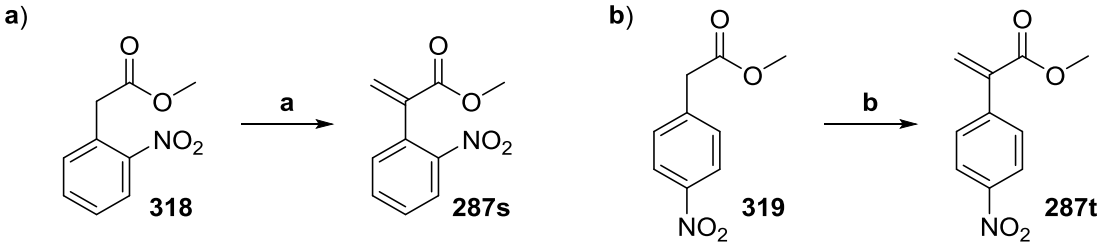


Figure 49 Preparation of methyl esters 287p - r**.**

According to a procedure by Felpin *et al.*, methyl 2-(2-nitrophenyl)acetate **318** was reacted in the presence of base and catalytic TBAI with *p*-formaldehyde to afford the SMA precursor **287s** in moderate yield (Scheme 58a).[228] Treatment of **319** with tetramethyldiaminomethane and acetic anhydride afforded the α-substituted α,β-unsaturated ester **287t** in 35% yield (Scheme 58b).



Scheme 58 Synthesis of *o*NO_2-phenyl α-substituent 287s **and *p*NO_2-phenyl α-substituent** 287t**; a: *p*-HCHO, K_2CO_3, TBAI, toluene, 53% yield; b: $Me_2NCH_2NMe_2$, Ac_2O, DMSO, 35% yield.**

The enantioselective SMA of 1-propanethiol to the range of electronically and sterically varied α-benzyl and α-aryl substituted α,β-unsaturated esters could be investigated following the synthesis of the electrophiles. Although the yields in the synthesis of the substrates were generally low to moderate, there was sufficient quantity of material to evaluate the conjugate addition reaction and as such little attempt was made to optimise these reactions.

4.5.5 Addition of 1-Propanethiol to α-Benzyl and α-Aryl Substituted α,β-Unsaturated Esters

The addition of 1-propanethiol to α-benzyl substituted ester **287o** proceeded smoothly to afford the product **288w** in quantitative yield and 86% ee, albeit with an increased reaction time of 48 h (Figure 50). The reaction to afford the β-mercaptoester **288x** with a phenyl group at the α-position resulted in a slightly diminished ee of 83% and incorporation of a methoxy group at the *p*-position of the aryl to yield **288y**, gave comparable levels of enantiocontrol. The enantioselectivity in the formation of **288z** was reduced to 75% ee; however when the *o*-OMe substituted aryl **287r** was used, the enantioselectivity of the SMA reaction increased to 94% ee for the formation of **288aa**. For comparison, when the ethyl analogue **317c** was trialled the yields and enantioselectivities of **288ab** were very similar (96% yield and 93 % ee). Increasing the steric bulk at the *ortho* position further by using the α-1-naphthyl substituted α,β-unsaturated ester **317d** lowered the enantiocontrol to 75% in the formation of β-mercaptoester **288ac**.[xxi] The reaction was applicable to the α-*ortho* nitro aryl substituted ester **287s** affording the product **288ad** in 98% yield and 84% ee. Extending the scope however, to the α-*para*-nitro aryl α,β-unsaturated ester **287t**, the addition product **288ae** was only obtained in modest 36% yield and 2% ee. We noted the presence of an intense pink coloured solution upon addition of the catalyst to the reaction and in the synthesis of the racemate using BEMP the colour was a deep blue.

[xxi] Conversion is given for this substrate as it proved impossible to separate the β-mercaptoester from the second equivalent of ester starting material. As the ee was only moderate, a repeat using one equivalent of electrophile was not performed.

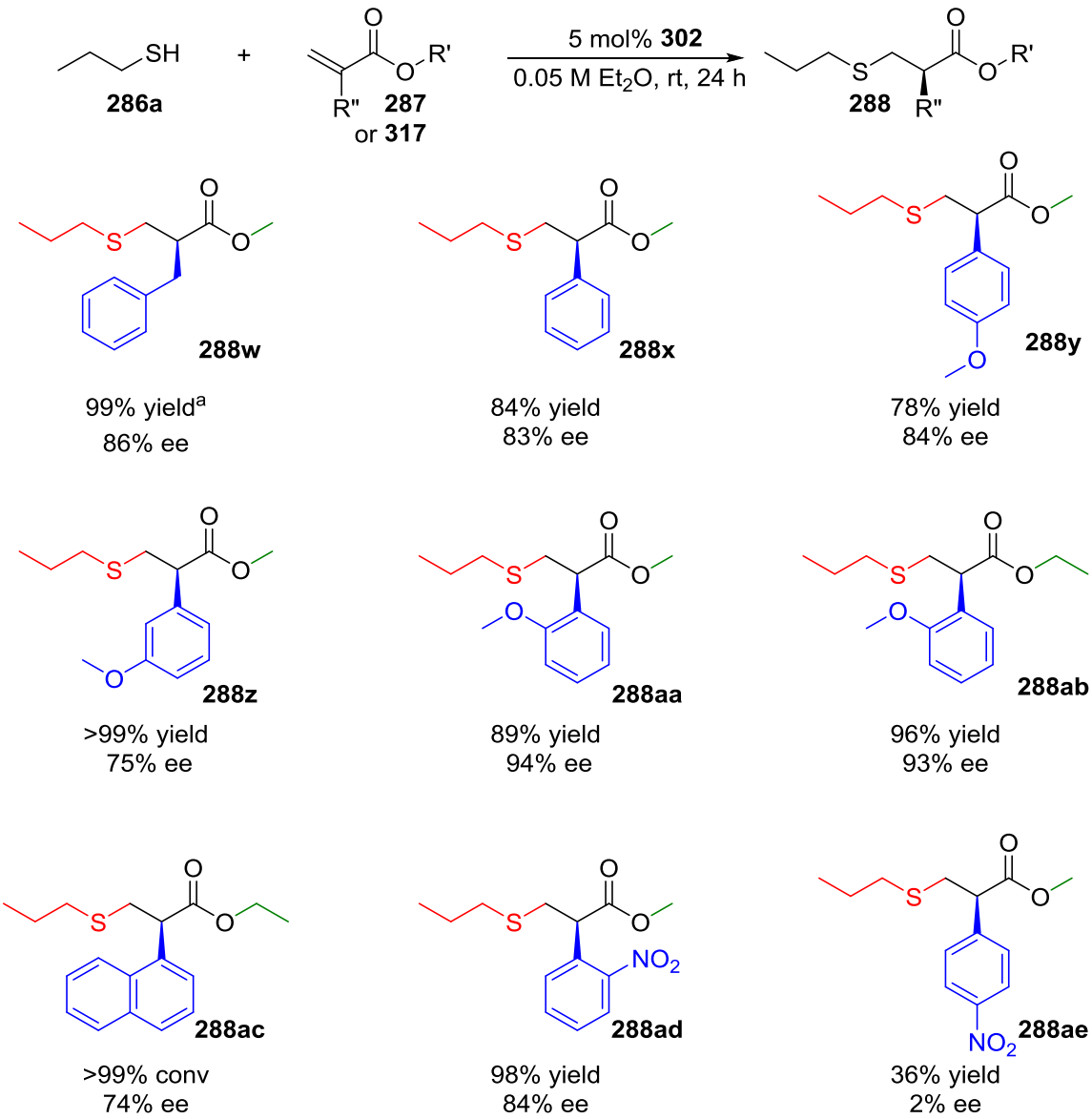
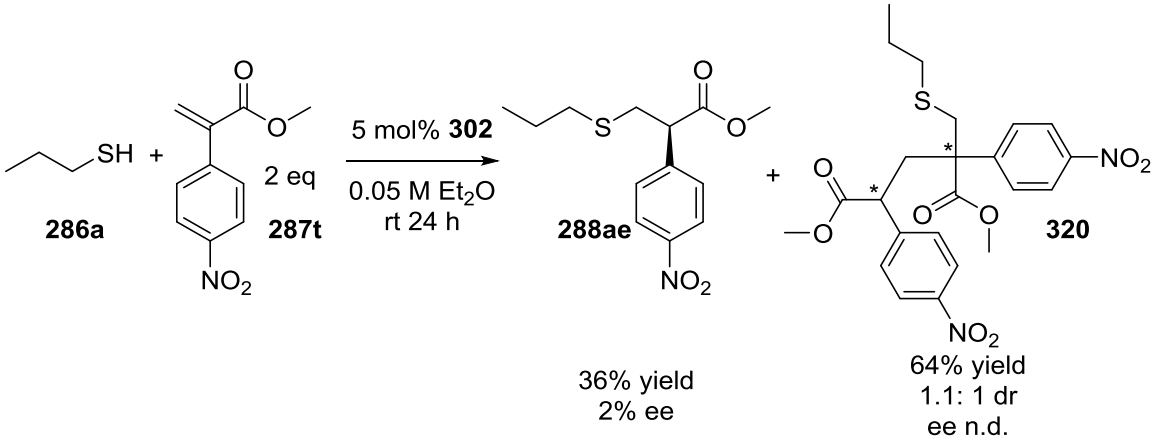


Figure 50 Addition of 1-propanethiol to α-benzyl and α-aryl substituted α,β-unsaturated esters.

The low yield associated with the synthesis of **288ae** was due to the competing formation of **320** as a result of the presence of excess electrophile (Scheme 59). Presumably, the β-mercaptoester is sufficiently acidic to undergo deprotonation and reprotonation at the α-position allowing racemisation of the product. The transient enolate can also react with excess **287t** to afford the double addition product **320** in 64% yield and as a 1.1:1 inseparable mixture of diastereomers. In the synthesis of the racemic β-mercaptoester **288ae**, where an excess of 1-propanethiol was used (as the avoidance of excess thiol reducing the enantioselectivity was not a concern) exclusive formation of the desired product **288ae** was observed. This indicated that the SMA reaction proceeded faster than

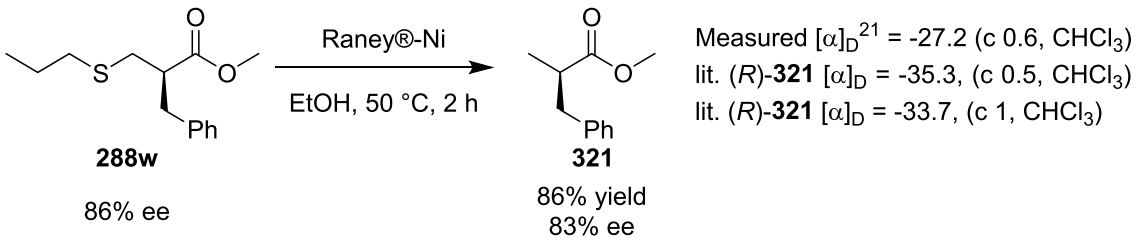
the second conjugate addition. The competing side reaction implied that the catalyst **302** was sufficiently basic to abstract the proton at the tertiary α-position to generate a new pro-nucleophile (see Section 7.5 for preliminary results).



Scheme 59 Addition of 1-propanethiol to 287t **and formation of unexpected side product** 320**.**

4.5.6 Determination of Absolute Configuration

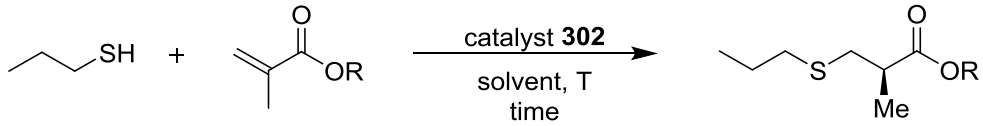
The absolute configuration was determined by treatment of **288w** with Raney®-nickel to afford **321** in good yield (Scheme 60). The enantioselectivity was marginally eroded to 83% from 86% but nevertheless allowed the specific optical rotation of **321** (83% ee) to be measured ($[\alpha]_D^{21}$ = -27.2 (*c* 0.6, $CHCl_3$)) and compared with those reported in the literature ((*R*)-**321** lit.[229] $[\alpha]_D$ = -35.3, (*c* 0.5, $CHCl_3$) and (*R*)-**321** lit.[230] $[\alpha]_D^{25}$ = -33.7, (*c* 1, $CHCl_3$)). The absolute stereochemical configuration of **288w** was thus determined to be (*R*) and the absolute configuration of the remainder of the β-mercaptoesters in the SMA methodology was assigned by analogy.



Scheme 60 Treatment of 228w **with Raney®-nickel to determine absolute stereochemical configuration.**

4.6 Preparative Synthesis of β-Mercaptoesters

With the substrate scope of the SMA reaction extensively investigated, we next pursued the synthesis of the β-mercaptoester moiety on a preparative scale to demonstrate practical utility. The same criteria used in the scale-up of the ketimine nitro-Mannich reaction were applied; namely that the procedure should be operationally simple, with no purification by chromatography and complete within one day. An enantiomeric excess greater than 90% was also desirable.



286a

287a, R = Me
287e, R = Ph

288a, R = Me
288e, R = Ph

Entry	Scale /mmol	R	Eq of 287	Temp / °C	Catalyst loading / mol%	Solvent	Time / h	(Conv.) Yield / %	ee / %
1	0.20	Me	5.0	rt	5	0.05 M Et_2O	24	97	94
2	0.20	Me	5.0	rt	5	0.5 M Et_2O	3	86	89
3	0.20	Me	5.0	rt	1	0.5 M toluene	3	96	86
4	50	Me	5.0	50	0.05	1.0 M toluene	60	78	83
5	20	Ph	1.2	50	0.1	0.5 M toluene	18	(>98)	80
6	20	Ph	1.2	50	0.1	0.1 M toluene	72	(11)	90
7	20	Ph	1.0	50	0.1	0.25 M toluene	24	(77), 62	86
8	10	Ph	1.0	50	0.1	0.25 M TBME	14	(76)	91
9	123	Ph	1.0	50	0.1	0.25 M TBME	12	(62)	91
10	20	Ph	1.2	55	0.05	0.3 M TBME	23	(96)	90
11	100	Ph	1.2	55	0.02	0.3 M TBME	22	(75)	-
12	100	Ph	1.2	55	0.01	0.3 M TBME	60	(54), 38	89
13	100	Ph	1.2	55	0.05	0.3 M TBME	22	(95), 84.5	90

Table 15 Optimisation of the preparative scale formation of 288a **and** 288e **using catalyst** 302**.**

We initially sought to scale up the formation of **288a** due to the readily available methyl methacrylate starting material (Table 15). In the optimised methodology, the reaction was performed at high dilution (0.05 M) to maximise the enantioselectivity (Table 15, entry 1) but this was deemed impractical for scale up. Increasing the concentration to 0.5 M caused

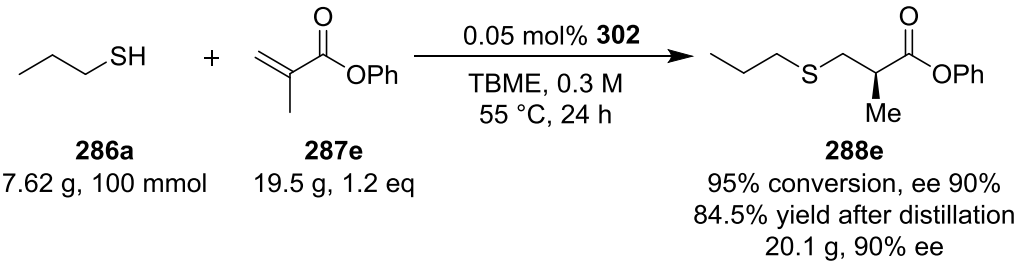
a reduction in the enantioselectivity to 89 and 86% ee respectively for Et_2O and toluene and the reaction with just 1 mol% catalyst was found to be complete within 3 h with an ee of 86% (Table 15, entries 2 and 3). Heating the reaction to 50 °C and performing the reaction on a 50 mmol scale afforded the β-mercaptoester **288a** in 78% isolated yield and 83% ee after 60 h using just 0.05 mol% catalyst **302** (Table 15, entry 4). We were unable to find a suitable compromise between the acceptable rate and enantioselectivity as an increase in the concentration, whilst increasing the rate, lowered the asymmetric induction (Table 15, entries 5 and 6). We realised therefore that the use of a slightly more active methacrylate ester was required and so continued the optimisation studies with phenyl methacrylate **287e** as the electrophile.[xxii]

With 0.1 mol% catalyst **302** and on a 20 mmol scale of **286a** the reaction using phenyl methacrylate was complete in 18 h and the product **288e** formed in 80% ee (Table 15, entry 5). Diluting the reaction from 0.5 M to 0.1 M in toluene increased the enantioselectivity of the product to 90% but the formation of **288e** was prohibitively reduced to only 11% conversion after 72 h (Table 15, entry 6). A solvent switch to TBME increased the enantioselectivity of the product **288e** to 91% at 0.25 M relative to the corresponding reaction in toluene (Table 15, entries 7 and 8). On a 20 mmol scale, with 0.05 mol% **302** the reaction was found to be complete within 23 h and **288e** formed in 90% ee (Table 15, entry 10). Subsequently lowering the catalyst loading to 0.02 and 0.01 mol% resulted in lower levels of conversion (75 and 54% respectively, Table 15, entries 11 and 12) and therefore 0.05 mol% was chosen as the optimal catalyst loading.

With the optimisation complete and with confidence that the reaction was reproducible the reaction was performed on a 100 mmol scale of 1-propanethiol with 0.05 mol% catalyst **302**. The catalyst was made *in situ* for 24 h prior to the reaction using just 24 mg of the

[xxii] See Section 8.4.2.1 for the synthesis of phenyl methacrylate.

azide **306** and 18 mg of tris(4-methoxyphenyl)phosphine **146** and then transferred to the reaction vessel. To minimise disturbance to the reaction an aliquot was only taken after 22 h and revealed a conversion of 95% by ^{1}H NMR and an ee of 90%. The reaction was quenched by the addition of a 1 M AcOH in CH_2Cl_2 solution and then the reaction mixture was concentrated. Distillation afforded 20.1 g of the product **288e** in 84.5% isolated yield. Difficulties in purification resulted in an erosion of the theoretical yield as co-distillates were obtained during the distillation. This presumably occurred through the formation of an azeotrope between excess phenyl methacrylate and the product **288e**.



Scheme 61 Preparative scale of β-mercapto ester 288e**.**

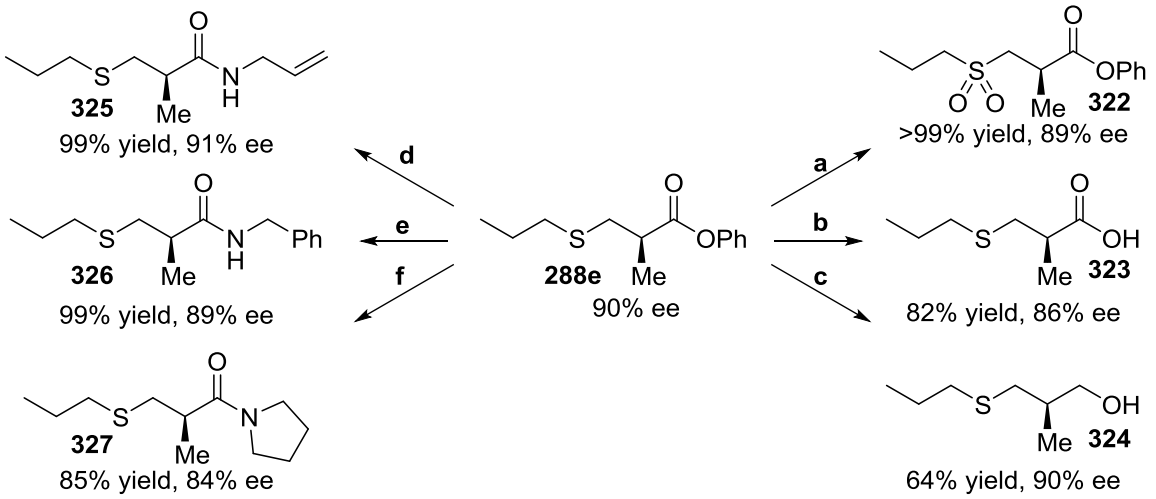
4.7 Synthetic Utility of β-Mercaptoesters

4.7.1 Derivatisation of 288e

To illustrate the synthetic utility of the β-mercaptoesters **288** we sought to derivatise the products obtained from the methodology. Due to the large quantities of material available, **288e** was initially used for this purpose (Scheme 62). Oxidation of the sulfide using hydrogen peroxide and trifluoroacetic acid afforded the sulfone **322** in quantitative yield in just 4 hours with no loss of enantioselectivity. Alternatively, the ester group could be hydrolysed to afford the acid **323** in good yield but with partial racemisation (82% yield and 86% ee).[xxiii] Reduction of **288e** to the alcohol proceeded with no loss of enantioselectivity to afford **324** in moderate yield. Treatment of **288e** with 3 eq of

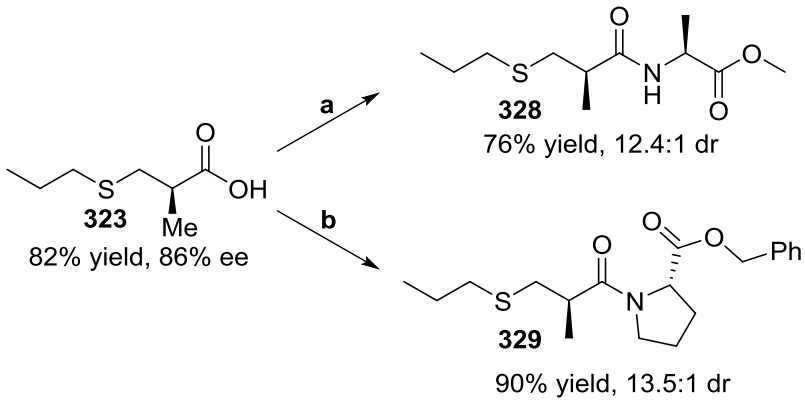
[xxiii] The enantioselectivity was determined by treating **323** with (trimethylsilyl)diazomethane to afford **288a** in 86% ee

allylamine as solvent at 0 °C afforded the secondary amide **325** in quantitative yield with maintained enantioselectivity. Analogously, the reaction with benzylamine proceeded smoothly to yield **326** in 89% ee. The synthesis of the tertiary amide **327** using pyrrolidine, under the same conditions however, resulted in partial racemisation to 84% ee.



Scheme 62 Derivatisation of 288e**; a: 30% H_2O_2, TFA, rt, 2 h; b: LiOH•H_2O, 2:1 THF: H_2O, rt, 2 h c: DIBAL-H, THF, –78 °C to 0 °C, 1 h; d: allylamine, 0 °C, 2 h; e: benzylamine, 0 °C, 12 h; f: pyrrolidine, 0 °C, 2 h.**

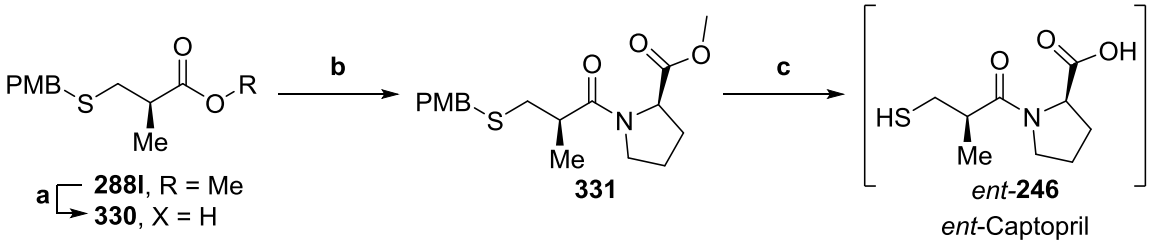
The carboxylic acid **323** could then be readily coupled to α-amino acids protected at the C-terminus to afford the amides **328** and **329** using L-alanine methyl ester hydrochloride and L-proline benzyl ester hydrochloride respectively in good yields (Scheme 63).



Scheme 63 Synthesis of amides 328 **and** 329**; a: L-alanine methyl ester hydrochloride, PyBOP, NEt_3, DMF, rt, 16 h; b: L-proline benzyl ester hydrochloride, PyBOP, NEt_3, DMF, rt, 16 h.**

4.7.2 Endeavours Towards Captopril

Lastly, we turned our attention towards the synthesis of Captopril **246** – a mercapto containing derivative of proline developed to treat hypertension as an angiotensin-converting enzyme (ACE) inhibitor (Scheme 64).[231]



Scheme 64 Derivatisation of 288l **towards Captopril; a: LiOH•H_2O, 1:1 THF: H_2O, rt, 16 h, 82% yield; b: D-proline methyl ester hydrochloride, PyBOP, NEt_3, DMF, rt, 16 h, 66% yield, dr 19:1; c: anisole, TFA, 60 °C, 2 h, then LiOH•H_2O, 1:1 THF: H_2O, rt, 16 h, trace product formation.**

The *para*-methoxybenzyl β-mercaptoester **288l** was initially hydrolysed by treatment of LiOH•H_2O to give the crude acid **330** in 82% yield. A PyBOP mediated amide coupling of the acid with D-proline methyl ester hydrochloride then afforded protected captopril **331** in good yield. Finally, a small scale, one pot global deprotection by initial removal of the PMB group with anisole and TFA and subsequent ester hydrolysis gave only trace amounts of ent-Captopril **246**. Unfortunately purification issues were encountered during work-up; likely associated with the high polarity and instability of the free mercapto moiety and we were unable to isolate a clean sample of **246**. Analysis of the crude reaction mixture by ^{1}H NMR and LRMS showed the formation of the product but due to time constraints and limited quantities of material available the synthesis has not been repeated. Further work to optimise the synthesis of Captopril *via* the SMA reaction to α-substituted α,β-unsaturated esters is still ongoing.[xxiv]

[xxiv] An earlier route towards ent-Captopril followed a similar strategy starting from benzylmercaptan and methyl methacrylate. Amide coupling with D-proline benzyl ester and global deprotection of the benzyl groups using Na/NH_3 resulted in extensive epimerisation of the α-stereocentre of **246**.

4.8 Mechanistic Work and Origins of Enantioselectivity

In a preliminary investigation into the mechanism of the sulfa-Michael addition to α-substituted α,β-unsaturated esters we performed a kinetic isotope study; specifically comparing the rates of addition of 1-propanethiol and d_1-1-propanethiol to methylmethacrylate by ^{1}H NMR (Figure 51).[xxv]

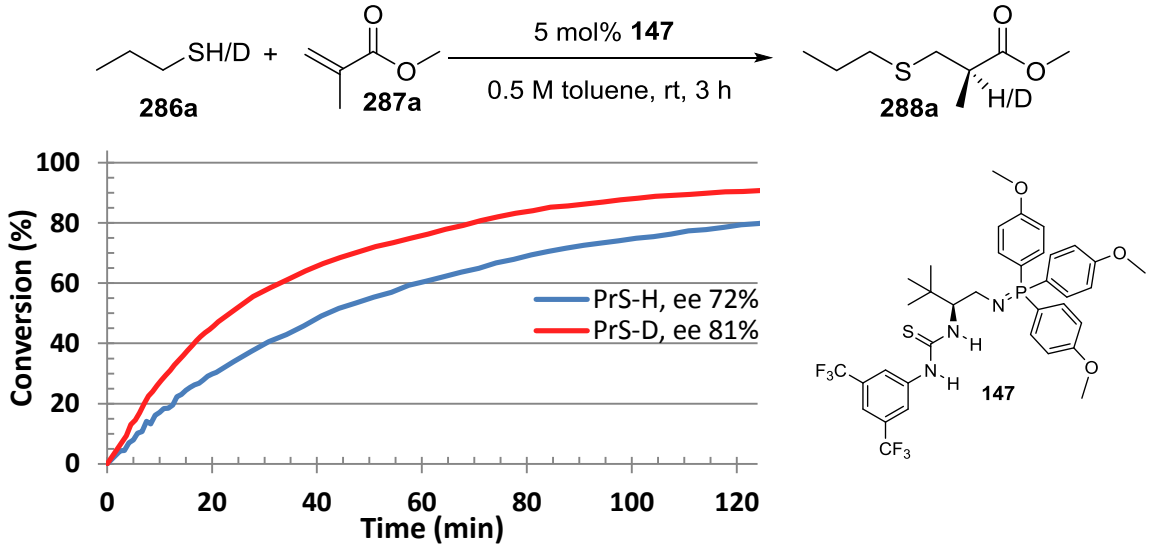


Figure 51 Comparison of the rate of reaction between PrSH and PrSD (87% D incorporation) in the SMA reaction. Reaction was performed on 0.20 mmol of scale of PrSH, 2.0 eq of methylmethacrylate, 5 mol% 147 **in 0.40 mL d_8-toluene with allyl ether as internal standard. ^{1}H NMR spectra were collected every 50 s with the first spectrum collected after 170 and 210 s respectively for d_1-**288a **and** 288a**. The deuterated product d_1-**288a **was formed with 79% D incorporation. The KIE ratio was found by comparing the gradients for the two curves over the initial 10 minutes, with the error from maximum and minimum gradients given over the first 10 minutes.**

The initial rate of reaction was found to be greater with the deuterated mercaptan (k_H/k_D = 0.59 ± 0.14) and with an enhanced enantioselectivity (81% versus 72% ee) than the protonated mercaptan. The observed inverse kinetic isotope effect indicated that the rate determining step did not involve the transfer of a proton or deuterium which would be expected in a normal KIE. In a reaction where the RDS involves the transfer of a proton a normal KIE ($k_H/k_D > 1$) would be observed due to the lower zero point energy (ZPE) for X-D than X-H (Figure 52a). The lower ZPE for X-D relative to X-H arises from the greater reduced mass of X-D since ZPE $\propto \mu^{-1/2}$.

[xxv] The deuterated thiol was prepared with 87% D incorporation by treating 1-propanethiol with D_2O, and drying with $MgSO_4$. For consistency 1-propanethiol was treated with H_2O in an analogous manner to allow comparison between the results.

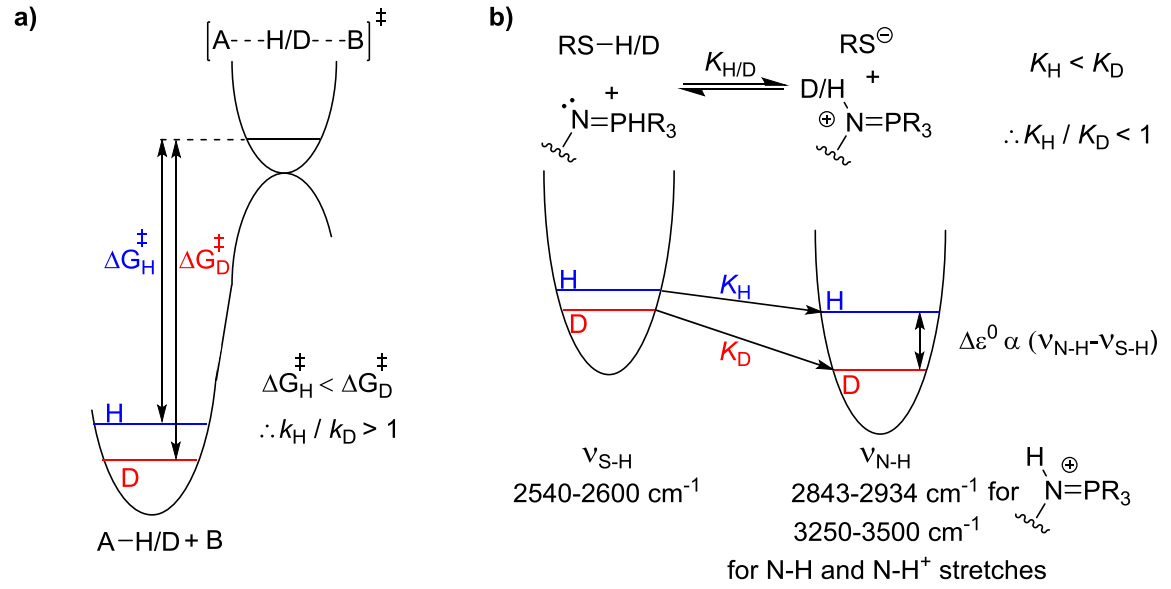


Figure 52 a) Energy level diagram for a normal KIE; b) illustration of a thermodynamic isotope effect showing that deuterium preferentially resides to the site corresponding to the highest stretching frequency (i.e. the strongest bond). ZPE energy level diagrams adapted from Parkin,[232] νS-H (2540-2600 cm^{-1}) and νN-H (3250-3500 cm^{-1}) values from IR tables.[233] IR shifts for H-R'N=PR$_3^+$ measured for 110a**•HCl and** 110b**•HCl.**

One explanation for the observed inverse KIE is that the rate determining step in the SMA reaction is the nucleophilic attack of the thiolate to methyl methacrylate. The observed inverse KIE arises due an equilibrium isotope effect in the initial acid base equilibrium. Parkin, in a study on the reductive elimination of methane or d_4-methane from $[Me_2Si(C_5Me_4)_2]W(Me)H$, noted that the observed rate of reaction was proportional to the deprotonation equilibrium constant K_1.[232] The deuterium atom will preferentially reside on the highest frequency oscillator (i.e. the strongest bond). Since the N-H bond is stronger than the S-H bond (Figure 52b) then the concentration of the thiolate in the case of the deuterated thiol will be greater as $K_{1(D)} > K_{1(H)}$.

$$k_{obs} = \frac{k_1 k_2}{k'_1 + k_2}, \text{ if } k_2 \ll k'_1 \text{ then } k_{obs} \cong K_1 k_2$$

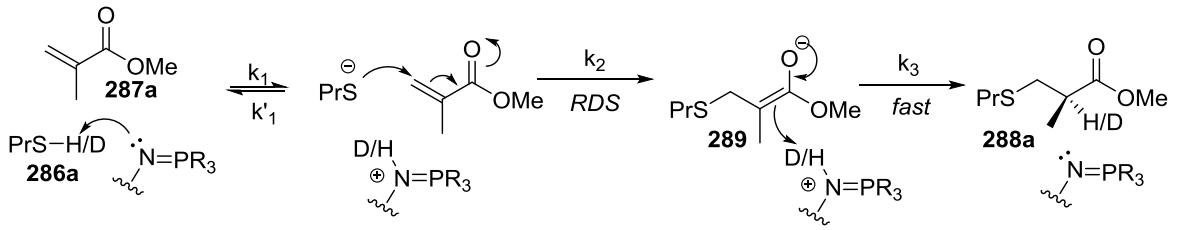
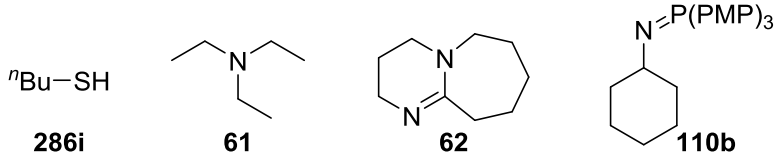


Figure 53 Proposed mechanism of the SMA of 1-propanethiol to methylmethacrylate.

The nucleophilic attack by the thiolate to methyl methacrylate is a bimolecular process and the rate of reaction will therefore be dependent on the concentration of the active nucleophile (R-S$^-$). If the initial acid/base equilibrium is fast and reversible then the rate of the SMA reaction is dependent on the equilibrium constant, K_1 (Figure 53). The rate of reaction being dependent on the concentration of the thiolate anion is consistent with the observation that the cinchona derived tertiary amine catalysts such as **53** are ineffective in promoting this reaction (Figure 38). The pK_a value of ^{n}BuSH **286i** is 17.0 in DMSO which is 8 units greater than the pK_{BH+} value of triethylamine **61** in the same solvent (Figure 54). Therefore, in the fast and reversible initial deprotonation of the alkyl thiol by the Brønsted basic moiety of the catalyst **53** the equilibrium will lie much further towards the starting materials and hence there is less active pro-nucleophile. Correspondingly, the reaction does not proceed with the tertiary amine bifunctional organocatalyst. On the other hand, the BIMP catalysts, which contain a superbase with a pK_{BH+} value of 25.0 in MeCN (and by extrapolation can probably be estimated at around 13 to 14 in DMSO by comparison to DBU **62**) deprotonate the mercaptan to a greater extent. Therefore the effective concentration of the thiolate anion is greater and thereby the rate of reaction is increased.[xxvi] The Kinetic Isotope Effect study and consideration of thermodynamic pK_a values support our working model that the pK_{BH+} value of the catalyst influences the rate of reaction.



	286i	**61**	**62**	**110b**
DMSO	17.0	9.0	13.9	-
MeCN	-	18.8	24.33	25.0

Figure 54 pK_a value of ^{n}BuSH in DMSO[234] and comparison with the pK_{BH+} values of triethylamine, DBU and a triaryliminophosphorane in DMSO and MeCN (Chapter 2).

[xxvi] Caution must be exercised when comparing pK_a values across different solvents and furthermore the pK_{BH+} value of catalyst **147** or **302** containing a H-bond donor group is likely to differ slightly from the achiral iminophosphorane **110b**. Additional considerations such as the effect of the counterion should also be taken into account. The rates of deprotonation may also need to be considered.

Whilst the kinetic isotope effect studies suggested that the turnover limiting step in this reaction was C-S bond formation, the enantiodetermining step however was protonation of the transient enolate. In our working model, protonation to the *si* face of the enolate occurred by fast and irreversible abstraction of a proton from the iminophosphorane salt of the catalyst. The higher enantioselectivity observed in the installation of the deuterium may possibly be due to the larger differences in the ZPE values of TS_S and TS_R for the deuterium analogue as a result of the lower ZPE of the deuterated system (Figure 55). An alternative explanation is that since the C-N and N-D bonds are slightly shorter than the corresponding C-H and N-H bonds due to their lower ZPE the enantiodetermining step with ^{n}PrSD proceeded *via* a tighter transition state than the analogous reaction with ^{n}PrSH. The tighter transition state amplified the repulsive steric interactions with the catalyst and therefore increased the energetic discrimination between the two diastereomeric transition states, TS_S and TS_R, and hence resulting in greater enantioselectivity for the deuterated analogue.

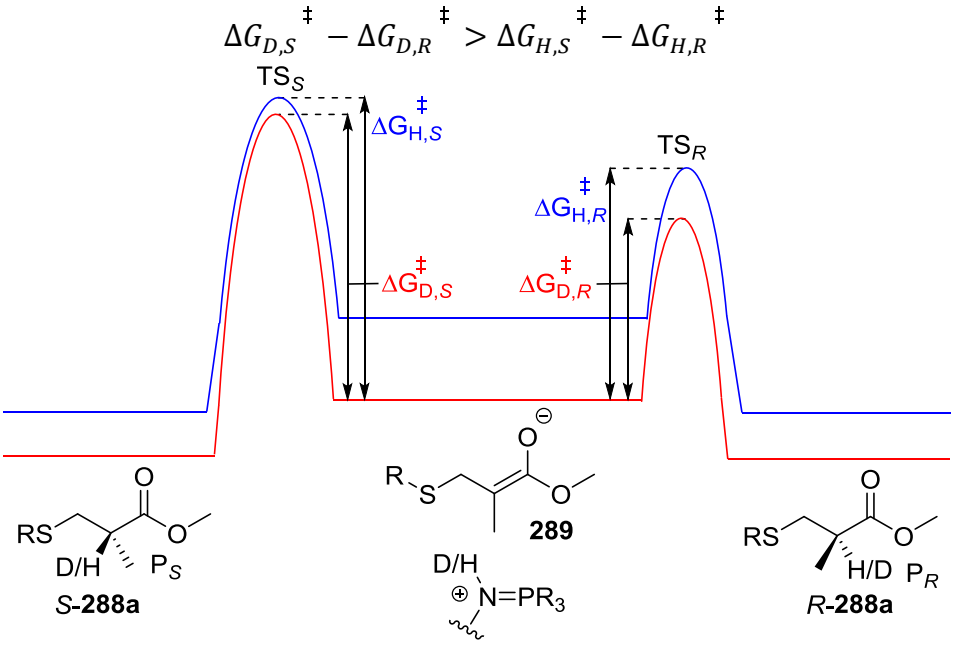


Figure 55 Possible reaction energy profile diagram for the enantioselective protonation of the transient enolate during the SMA reaction. Horizontal energy levels represent ZPE values for the deuterated system in red and proton in blue.

The deuterated product was formed with 79% deuterium incorporation from an initial 87% deuterated propanethiol. The 10% loss of D incorporation coincides with the number of acidic thiourea protons present in the catalyst. This is suggestive of possible additional proton exchanges that should be taken into account. An extension of the KIE investigation should use catalyst **302**, optimal in the SMA methodology, to see whether the alternative thiourea exhibits the same KIE.

Interestingly, when Tan *et al.* performed a kinetic isotope study on the addition of aromatic thiols to methyl 2-phthalimidoacrylate **277** catalysed by a chiral guanidine **69** (Scheme 51b) they noticed a positive KIE indicating that the rate determining step involved proton transfer.[219]

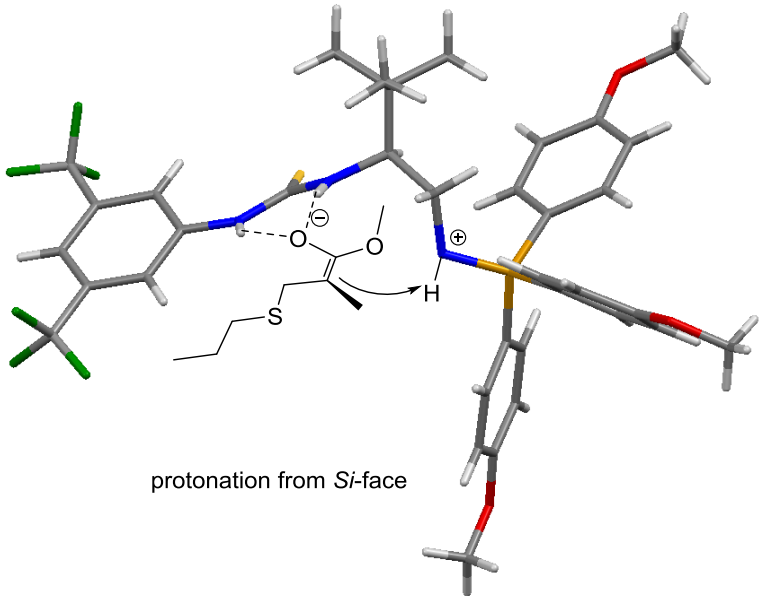


Figure 56 Proposed transition state for the SMA of 1-propanethiol to methyl methacrylate catalysed by 147**. The three dimensional structure of the catalyst was obtained from single X-ray crystal data.**

In a working model to explain the observed enantioselectivity, the negatively charged oxygen atom of the transient *E*-enolate is bound by the two thiourea protons of catalyst **147** and protonation occurs preferentially from the S*i*-face. The proton is abstracted from the protonated iminophosphorane salt formed from the deprotonation of 1-propanethiol (Figure 56). Presumably the transition state in the SMA reaction using catalyst **302** that

incorporates the additional stereocenter and the amide benzhydryl amide moiety is similar to that shown in Figure 56. The enhanced enantioselectivity observed with **302** may arise from the bulky amide group blocking the top face of the enolate and hence prevent protonation from the *Re*-face. The presence of the second stereogenic centre of the catalyst and the amide moiety may also increase the conformational rigidity of the catalyst relative to the 3,5-$(CF_3)_2C_6H_3$ thiourea analogue. Low enantioselectivities observed with polar protic and aprotic solvents are consistent with the necessary formation of a tight ion pair between the catalyst and the substrates. Furthermore, the increased enantiocontrol in the formation of β-mercaptoesters observed upon dilution of the reaction, due to minimal competing protonation of the transient enolate from neighbouring thiol molecules is supportive of the working model.

4.9 Conclusion

We have successfully developed the first catalytic enantioselective general addition of a range of alkyl and benzyl mercaptans to simple α-substituted α,β-unsaturated esters. The reaction necessitated the incorporation of an alternative H-bond donor group into the catalyst to afford the β-mercaptoesters in good yields and enantioselectivities. A new type of H-bond donor BIMP catalyst possessing two stereocenters from two separate chiral building blocks, highly efficacious in the SMA to α-substituted α,β-unsaturated esters, was added to the catalyst library. The performance of the catalysts was exemplified by performing the reaction on a preparative 100 mmol scale with loadings of 0.05 mol% and the β-mercaptoester products were derivatised to illustrate the synthetic utility of the enantioenriched products. Preliminary studies were also undertaken in a bid to propose a coherent mechanistic pathway and a working model for the observed enantioselectivity; comprehensive computational and kinetic analyses would however be required to fully elucidate the mechanism.

5 Structure and Properties of BIMP Catalysts

5.1 Overview

As described in Chapter 2, the BIMP catalysts were isolated and fully characterised and the atom connectivity of the structures was confirmed by single X-ray crystallography. The NMR spectra of the iminophosphorane catalysts were often broad at room temperature and therefore suggestive of dynamic behaviour. We therefore decided to instigate preliminary investigations into their properties and this chapter highlights some of the interesting features encountered. Understanding the three dimensional structures and aggregate states adopted by the BIMP catalysts may aid the design of future iminophosphorane catalysts.

5.2 BIMP Catalysts Possessing 3,5-$(CF_3)_2C_6H_3$-Substituted Thioureas

The appearances of the NMR spectra of various BIMP catalysts were very solvent dependent indicating the presence of rotamers or aggregation. A representative example of this phenomenon is given in Figure 57. In $CDCl_3$ and MeOH the signals of **230** are broad, and no thiourea protons are observable. In benzene, however, the NMR shows the presence of several species and the peaks are well resolved, including multiple thiourea signals.

Studies on tertiary amine bifunctional catalysts bearing a thiourea demonstrated that aggregation was intrinsic to these systems. Soós and co-workers studied the structural conformations *via* NMR of cyclohexyl diamine-derived thiourea organocatalysts such as **42** and concluded the thiourea or urea moiety was primarily responsible for the aggregation.[235] Related work by the same authors showed that with cinchona alkaloid derived bifunctional thiourea organocatalysts such as **53** additional edge-face CH/π aromatic interactions from the quinoline heterocycle also led to aggregation.[236]

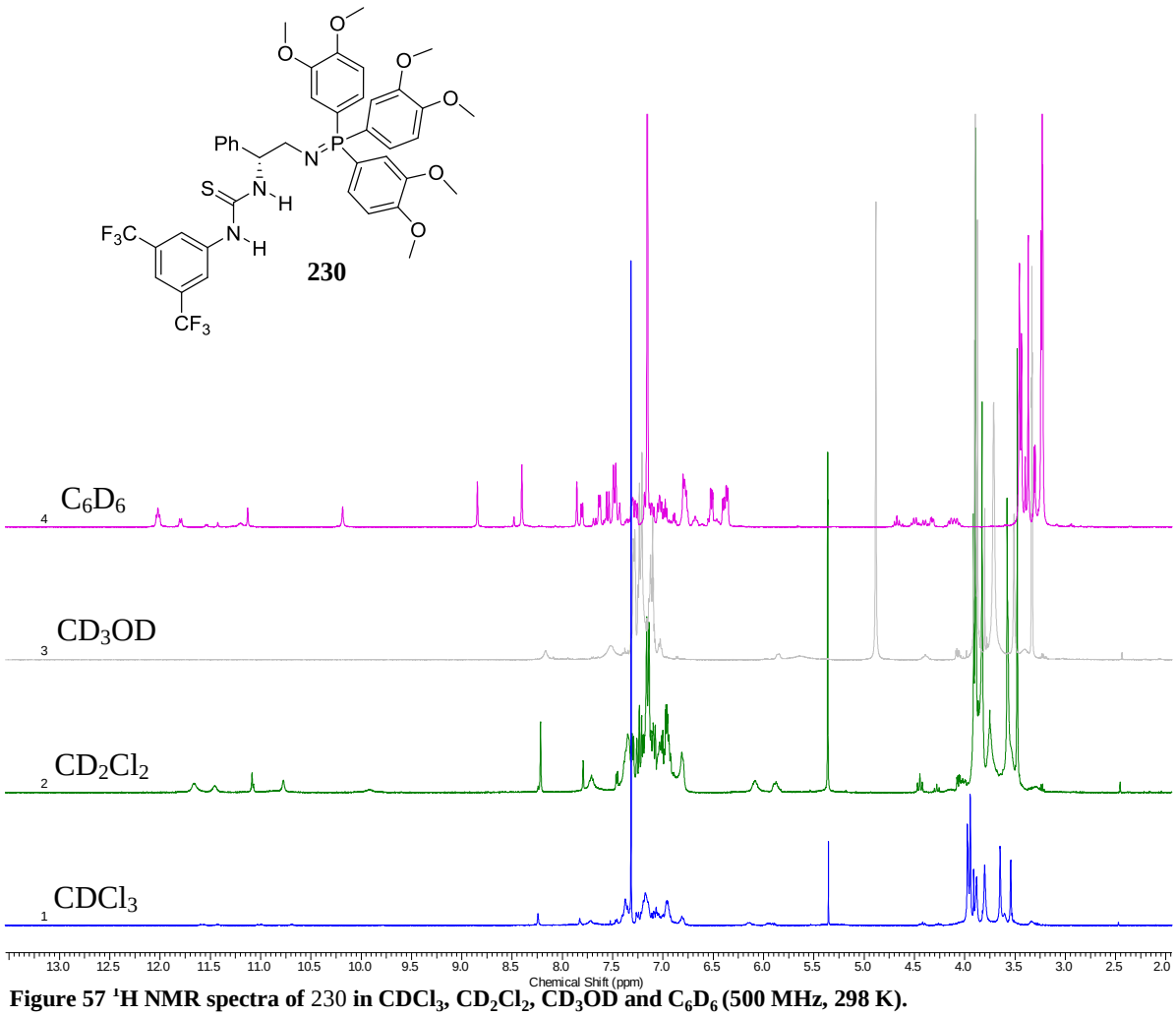


Figure 57 ^{1}H NMR spectra of 230 **in $CDCl_3$, CD_2Cl_2, CD_3OD and C_6D_6 (500 MHz, 298 K).**

During the characterisation of **147** at room temperature, we noticed the ^{1}H NMR spectrum to be broad and the individual resonances were poorly resolved (Figure 58). In particular, both the CH at the stereogenic centre and the diastereotopic CH_2 adjacent to the iminophosphorane were very broad. The N-H thiourea protons were also not observable. The ^{31}P NMR spectrum of **147** was also found to be broad in both $CDCl_3$ (29.8 ppm) and CD_3CN (33.3 ppm) at room temperature (Figure 59). The spectrum also indicated the presence of trace triphenylphosphine oxide at 27.6 ppm. The ^{13}C NMR was similarly broad with poor peak resolution; the thiourea carbon (C=S) at 181.7 ppm was particularly unresolved. Taken together, these observations are indicative of dynamic behaviour of the catalysts in solution, such as aggregation.

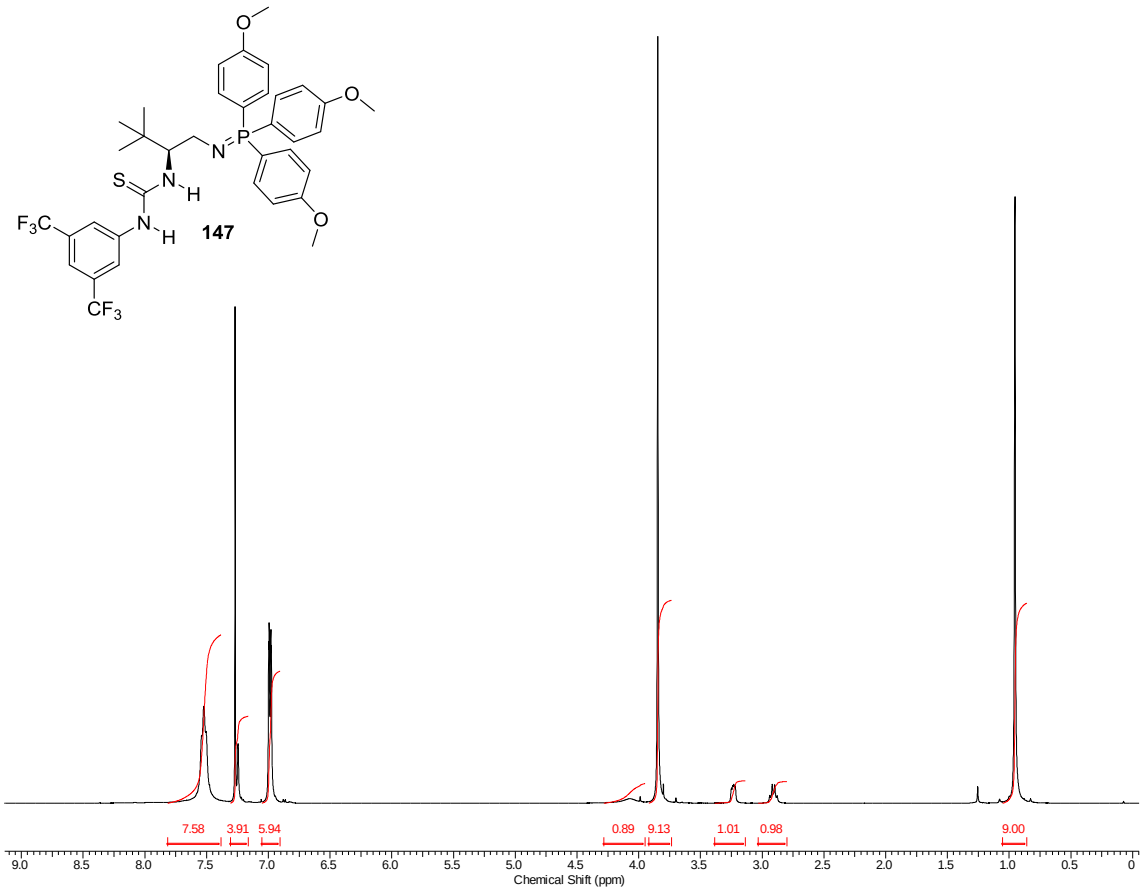


Figure 58 ^{1}H NMR spectrum of 147 **in $CDCl_3$ (500 MHz at 298K).**

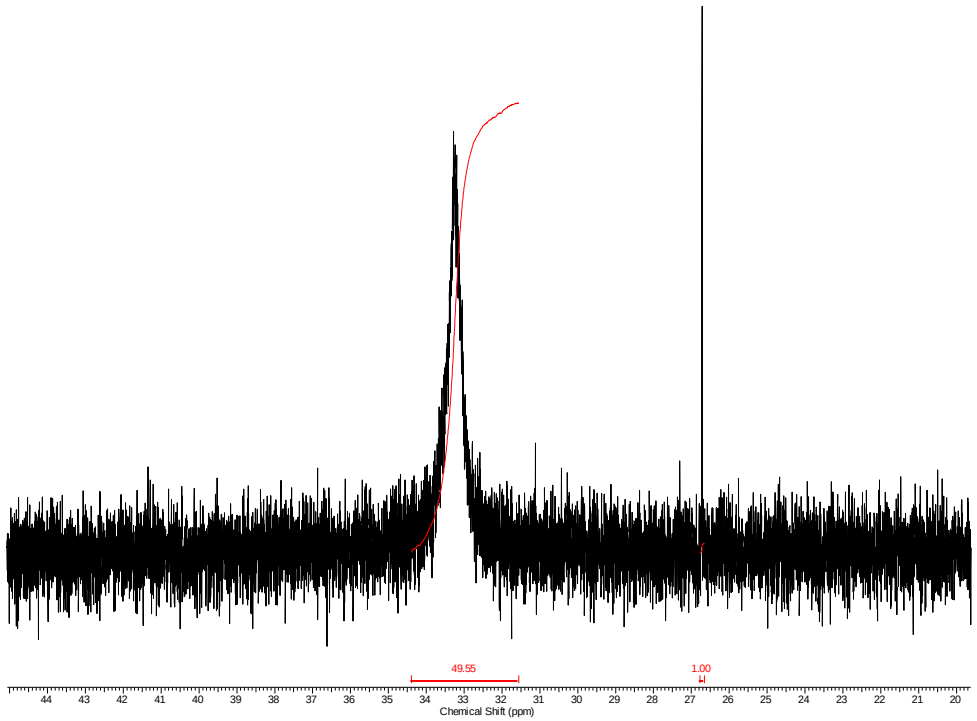


Figure 59 ^{31}P NMR of 147 **in CD_3CN (202 MHz, 298 K).**

5.2.1 ^{1}H and ^{31}P VT NMR Experiments on 147

A series of variable temperature (VT) NMR experiments were performed to investigate the observed room temperature broadness in the NMR spectra. At 238 K (–35 °C), in the region of slow exchange, two sharp singlets at 34.6 and 30.5 ppm were observed in the ^{31}P NMR spectrum (Figure 60). As the temperature was increased to 280 K, both peaks broadened, but the peak at 30.5 ppm was especially broad. At 298 K a single broad peak at 33.3 ppm was observed representing the merged average of the two signals.

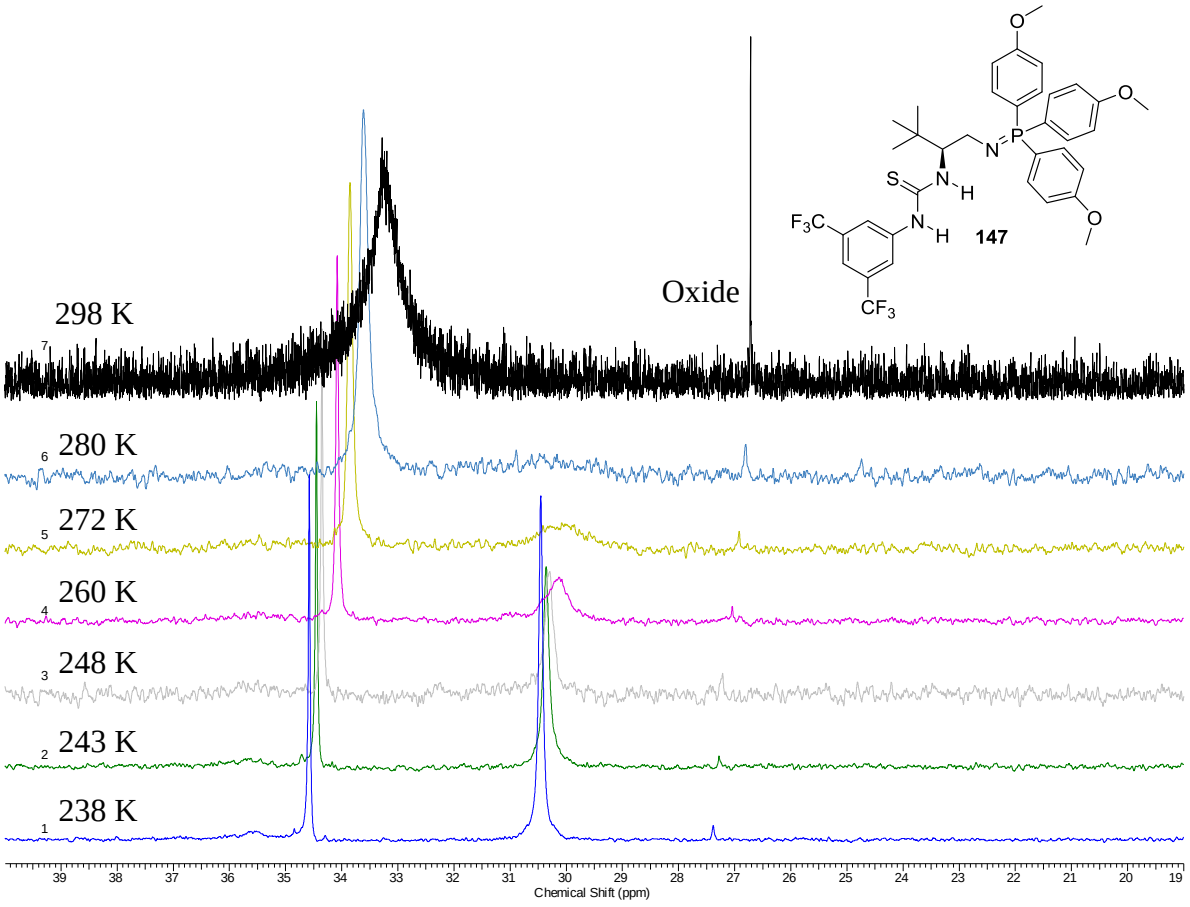


Figure 60 ^{31}P VT NMR of 147 (20 mg, CD_3CN).

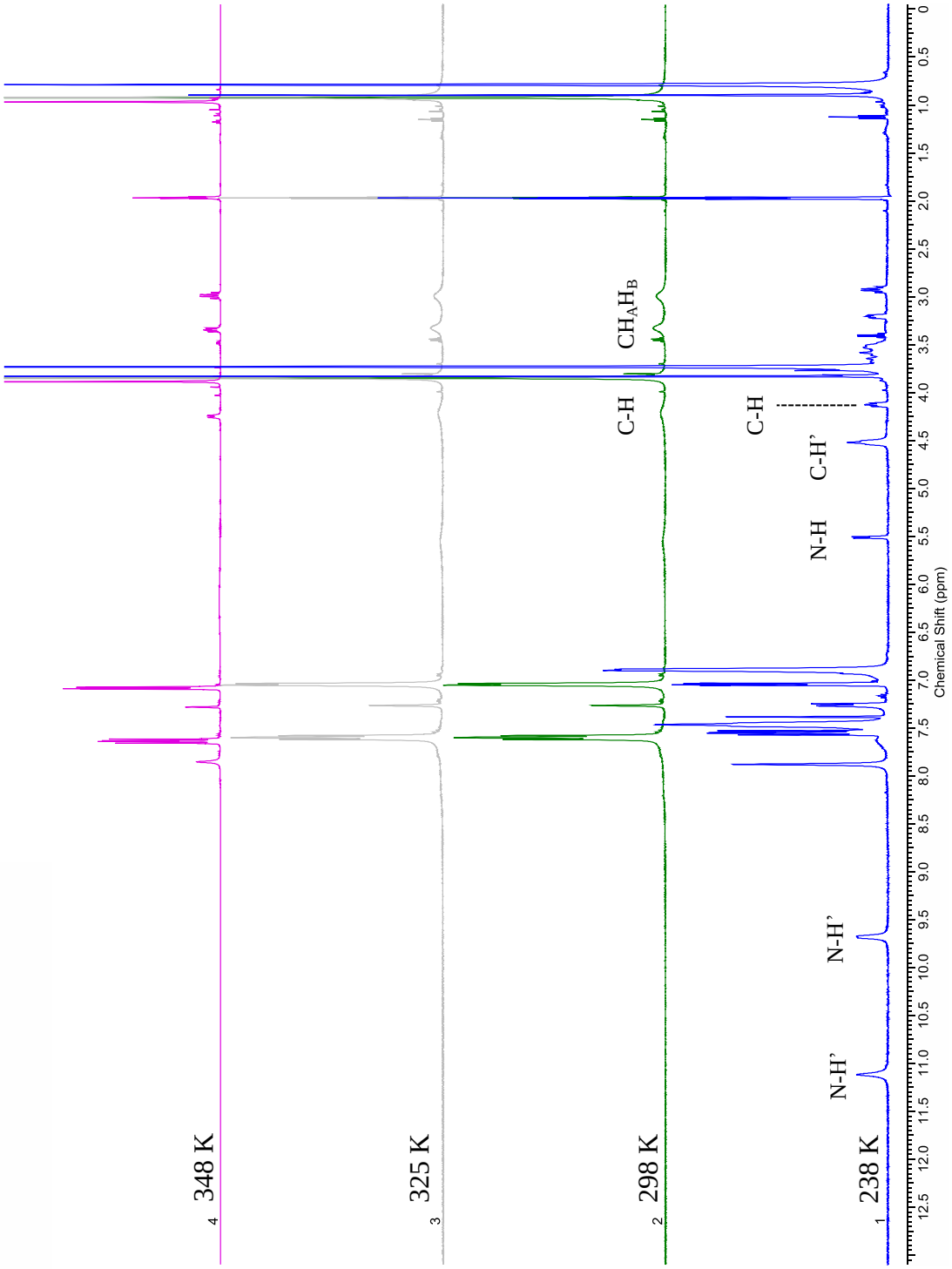


Figure 61 ^{1}H VT NMR spectra for 147 **in CD_3CN (500 MHz, 20 mg of** 147 **in 0.5 mL CD_3CN, 0.05 M).**

The ^{1}H NMR spectrum at 348 K, in the region of fast exchange, was sharp and showed the presence of only one species (Figure 61). The thiourea protons were, however, not observable. Conversely, a low temperature spectrum of the catalyst **147** at 238 K showed two species were present indicated by two sets of *tert*-butyl signals as well as two CH

groups at 4.20 and 4.60 ppm belonging to the proton at the stereogenic centre. At this temperature the thiourea protons were observable for the first time at 9.6 and 11.1 ppm. These VT experiments were measured on a sample made from 20 mg of **147** in 0.5 mL of CD_3CN (0.054 M solution). An analogous experiment was performed using 2 mg of **147** (0.0054 M solution) and the relative amounts of the two species was inversed (1:2.1 vs 2.4:1 respectively as indicated from the integration of the ^{31}P signals at 34.6 and 30.5).

5.2.2 Investigating the Structures of 147 at 238 K

A NOESY experiment showed the two species were in exchange with one another at 238 K (Figure 62). Cross-peaks were observed for the proton signals at 4.2 and 4.6 ppm belonging to the CH at the stereogenic centre; since the C-H bond is not labile to exchange this is indicative that the two species are interconverting. The thiourea protons at 9.6 and 11.1 ppm also show cross-peaks and this could be due to their close spatial proximity as well as exchange between the labile N-H thioureas. In addition, further cross-peaks were observable between these two thiourea protons with another thiourea proton at 5.5 ppm. However, the presence of the fourth thiourea proton was not observable which would be consistent with the integration of the two species.

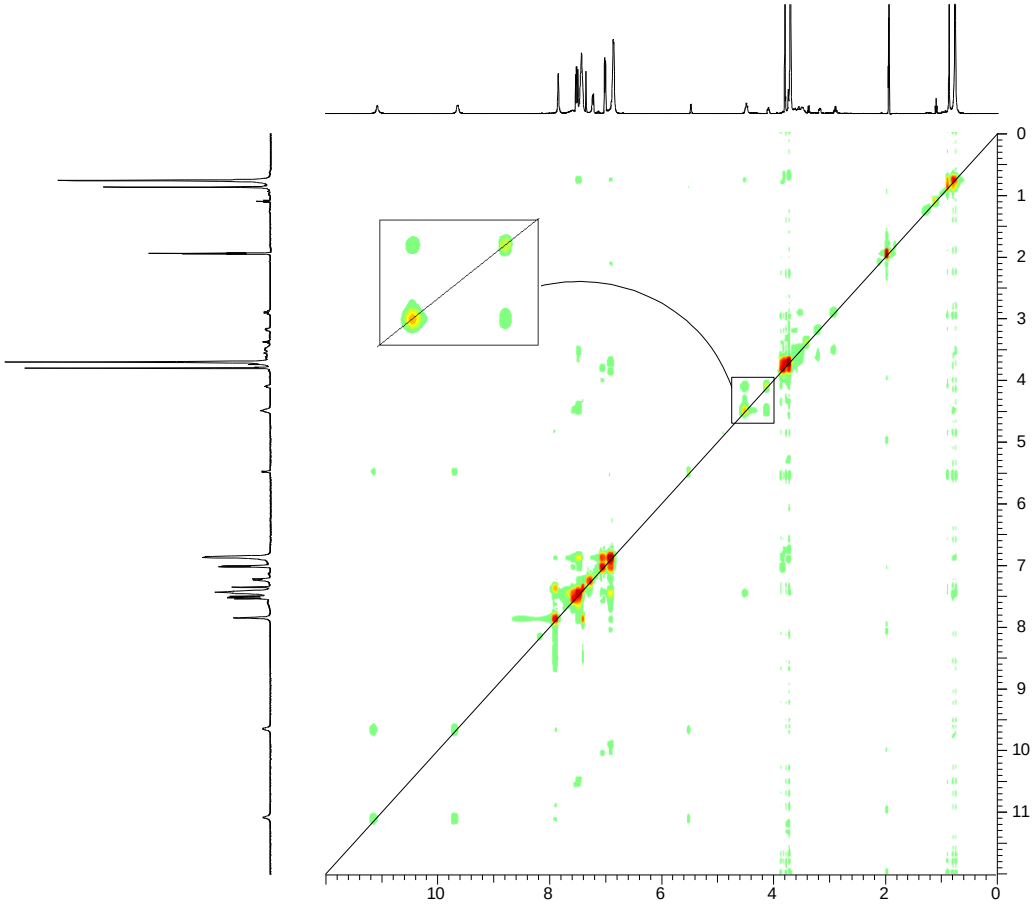


Figure 62 500 MHz ^{1}H NOESY experiment of 147 **at 238 K in CD_3CN.**

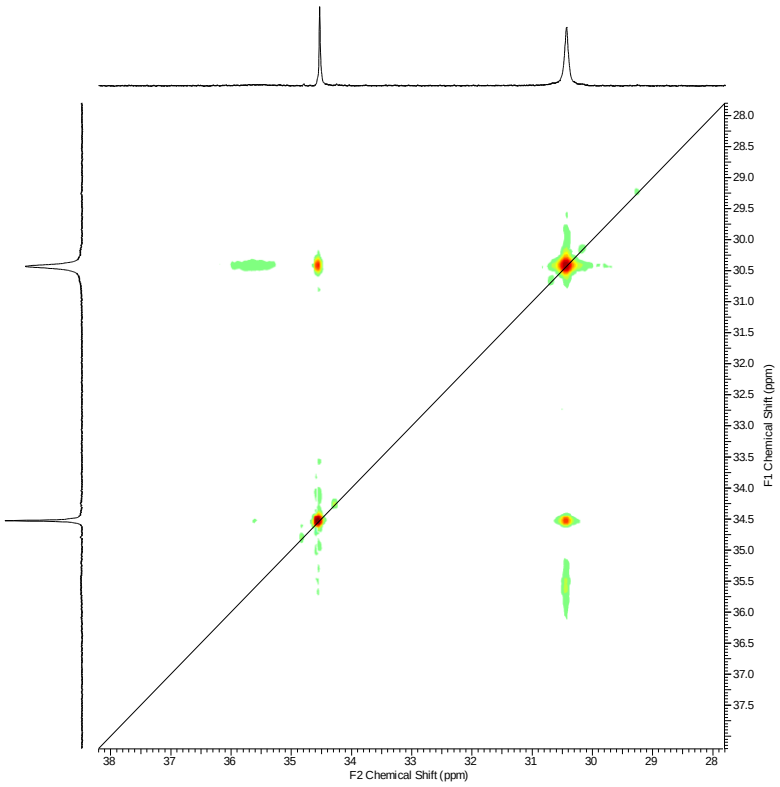


Figure 63 ^{31}P-^{31}P {^{1}H} 2D EXSY spectrum of 147 **at 238 K.**

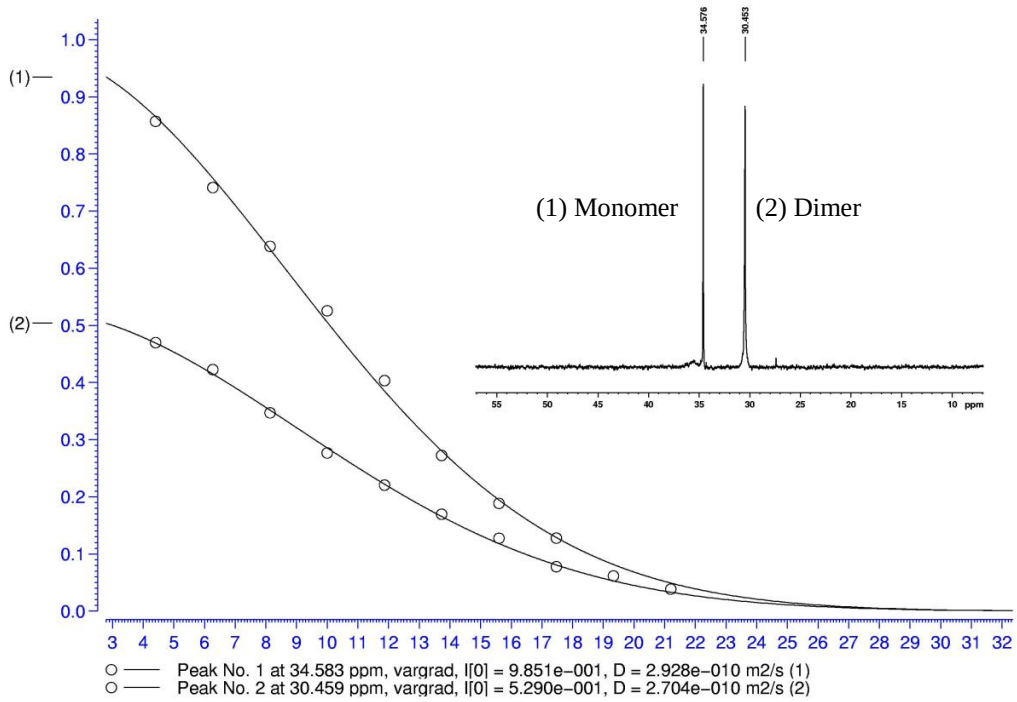


Figure 64 ^{31}P DOSY NMR experiment at 238 K using 20 mg of 147 **in CD_3CN showing the different diffusion coefficients of the two species.**

Performing a similar experiment targeting the ^{31}P nucleus in a 2D EXSY experiment showed that the two major phosphorous species were also in dynamic exchange (Figure 63). These results in conjunction with the dilution experiment suggest that the two ^{31}P NMR signals correspond to the monomer and dimer.

A ^{31}P DOSY (Diffusion-Ordered Spectroscopy) NMR experiment showed that the two phosphorous signals had different diffusion coefficients indicating that the two species had different molecular weights (Figure 64).[xxvii] We can conclude therefore that at low temperature in CD_3CN there is an observable mixture of two interconverting species which are proposed to be the monomeric and dimeric forms of **147**. Based on the values of the diffusion coefficients the ^{31}P NMR signal at 34.6 ppm corresponds to the phosphorous nucleus of the monomer and the shift at 30.5 ppm to that of the dimer.

$$[A] + [A] \overset{K}{\rightleftharpoons} [2A]$$

[xxvii] Quantitative DOSY NMR experiments allow the diffusion coefficients to be calculated. The DOSY experiment shown above however only qualitatively shows the two signals to have different diffusion coefficients as a reference signal was not measured. Further experiments would be required to determine the exact diffusion coefficients.

Presumably at room temperature this equilibrium is also present; however the ratio of the two species will differ due to the effect of temperature on the position of equilibrium as a result of entropic considerations.

5.2.3 Possible Structures of the Monomer and Dimer

A closer inspection of the single X-ray crystal structure of **147** revealed a dimeric structure (Figure 65). The dimer is C2 symmetric with the two thiourea protons of one molecule oriented towards the nitrogen of the iminophosphorane of the other with bond lengths of 2.15 – 2.19 Å, consistent with the formation of strong hydrogen bonds. The two thiourea protons observed in the 238 K ^{1}H NMR spectrum at 9.6 and 11.1 ppm correspond to the thiourea of the dimer. Moreover, the high chemical shifts of the N-H thioureas are consistent with the presence of strong H-bonds. Although the solution and solid state conformations of a molecule may differ, the structure of the catalyst dimer in solution may adopt a similar structure to that observed in the solid state.

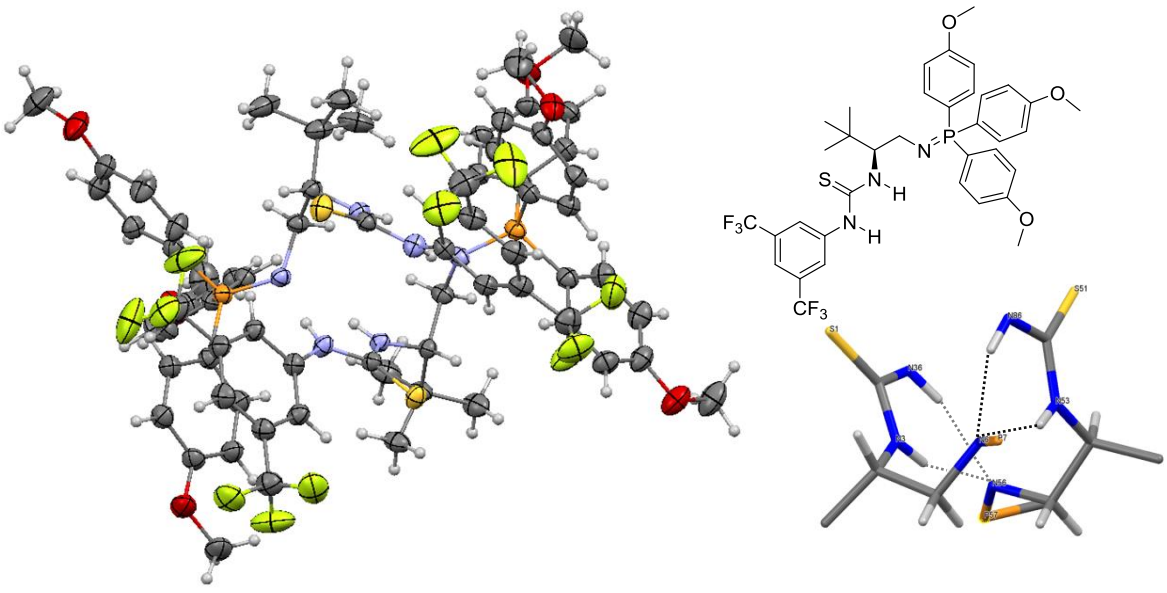


Figure 65 ORTEP diagram of 147 **depicting the dimer. Hydrogen bonding between thiourea protons and the iminophosphorane is shown in the stick model.**

Only one of the monomer thiourea protons is observable at 5.5 ppm as a doublet (J = 6.6 Hz) and this corresponds to the NH adjacent to the aliphatic CH (Figure 61). The other thiourea proton of the monomer is too broad to be observed, possibly as a result of intramolecular fast exchange with the basic nitrogen of the iminophosphorane. Preliminary calculations performed on **145**, derived from triphenylphosphine **98** suggest a rapid equilibrium between the monomer and dimer and that the monomer may preferentially reside as the isomer with the acidic thiourea proton residing on the iminophosphorane (Figure 66).

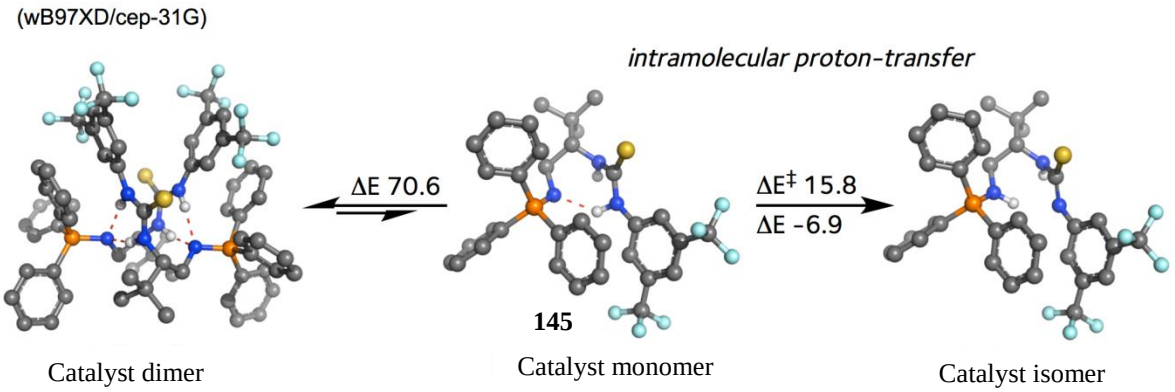


Figure 66 Preliminary calculations on bifunctional iminophosphorane equilibria. Calculations performed by Prof. Rob Paton and co-workers, unpublished results.

It seems reasonable that if the structure of the dimer in solution is similar to that observed in the solid state it is catalytically inactive as the *N*-lone pair of the iminophosphorane is strongly interacting with the thiourea moiety. The monomer/dimer equilibrium presumably occurs during a reaction and must be taken into account when determining the reaction kinetics.

During our kinetic studies on the ketimine nitro-Mannich reaction we observed some unexpected rate profiles that could be explained by considering the monomer/dimer equilibrium present with the BIMP catalysts (Figure 67 and section 3.4.4). The ^{1}H NMR kinetic experiments whilst demonstrating that the tris(4-methoxyphenylphosphine) derived iminophosphorane **147** is faster than the triphenylphosphine derived catalyst **145** only

show a marginal difference in the rates of reaction. The monomer/dimer equilibrium appears to inhibit the rate of reaction in the ketimine nitro-Mannich reaction for the tris(4-methoxyphenylphosphine) derived catalyst **147**.

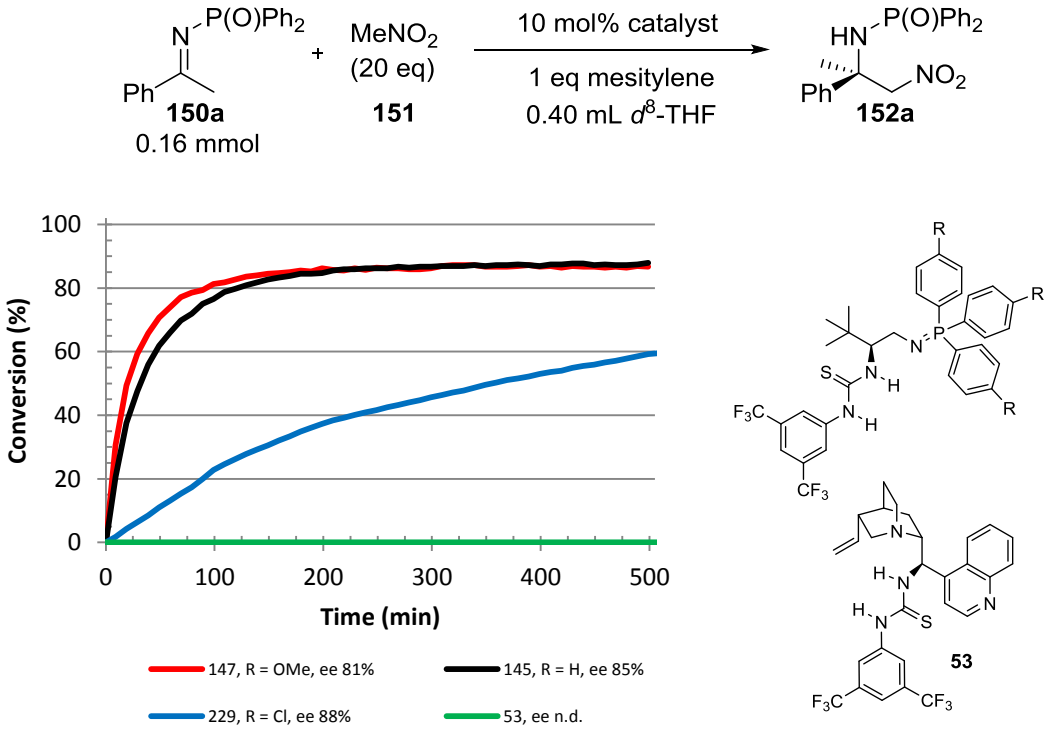
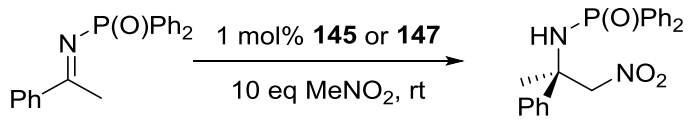


Figure 67 Rate of the ketimine nitro-Mannich reaction as a function of the iminophosphorane substituents (Chapter 3, section 3.4.4).

When the catalyst loadings were lowered to 1 mol% the difference in rates between the two catalysts was, however, much more pronounced (Table 16). The conversion in the formation of **152a** using catalyst **145**, derived from triphenylphosphine was 75% after 5 days at rt (Table 16, entry 1) whereas the conversion with catalyst **147** was 98% after 21 h (Table 16, entry 2). The larger discrepancy between the rates of reaction between catalysts **145** and **147** at 1 mol% catalyst loading presumably arises from **147** existing predominantly as the catalytically active monomer at lower concentrations. At 10 mol% catalyst loading more of the inactive dimer form of **147** is present. To confirm this working model, full kinetic studies would need to be undertaken with various iminophosphorane catalysts in the ketimine nitro-Mannich reaction.



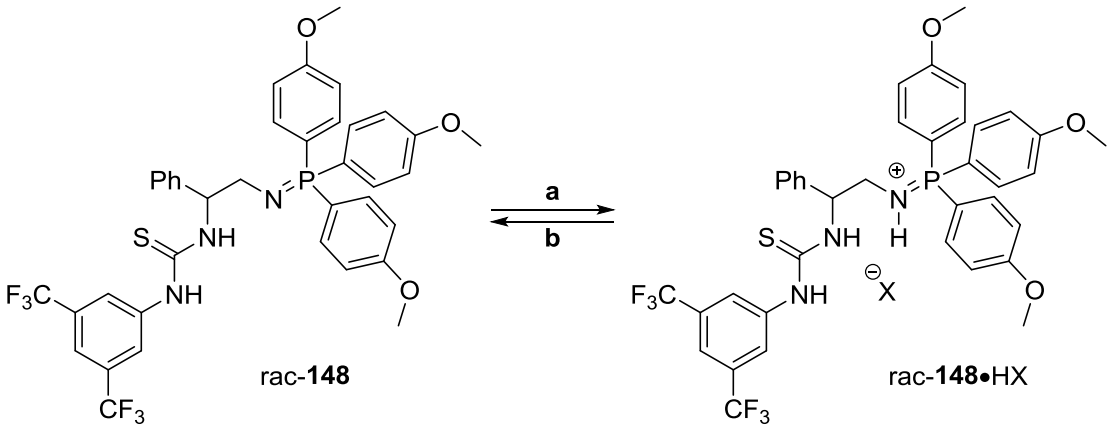
150a **152a**

Entry	Catalyst	Time /h	Conversion /%
1	**145**	120	75
2	**147**	21	98

Table 16 Comparison of the rate of the ketimine nitro-Mannich reaction at 1 mol% catalyst loading using catalysts 145 **and** 147**. Conversion determined by ^{1}H NMR.**

5.2.4 Stability of BIMP Catalysts to Aqueous Conditions

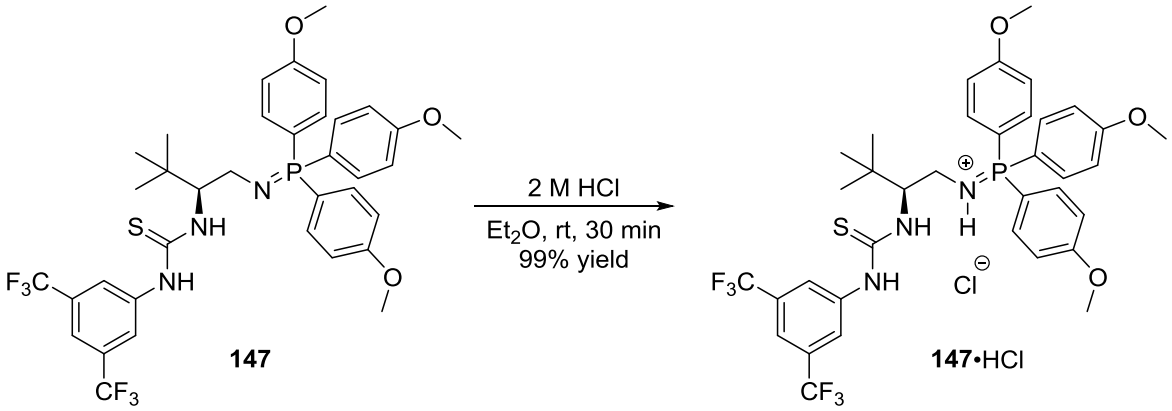
Whilst catalyst self-aggregation may diminish the catalytic activity we believed that it contributed to the remarkable stability of the catalysts. The BIMP catalysts bearing electron deficient aryl thioureas could be readily precipitated from diethyl ether and stored in the freezer for several months. The tris(4-methoxyphenylphosphine) derived iminophosphoranes were more crystalline than those derived from triphenylphosphine and this may possibly be due to stronger H-bonds formed in the dimer.



Scheme 65 Aqueous stability test of rac-148**; a) CH_2Cl_2, H_2O, rt, 2 min, then $MgSO_4$; b) PS-BEMP, CH_2Cl_2, rt, 1 h, 94% yield over two steps.**

Furthermore, treatment of rac-**148** with a mixture of water and CH_2Cl_2 at room temperature for two minutes and subsequent removal of the water afforded an ionic salt with the counterion most probably the hydroxide or sulfate anion (Scheme 65). After partitioning the two layers, excess H_2O was removed by drying the organic layer with anhydrous $MgSO_4$. No attempts were made to identify the counter ion and in hindsight, excess water

should have been removed by using toluene to form an azeotrope. Neutralisation by treatment of the intermediate with PS-BEMP, a polymer supported organosuperbase, returned rac-**148** in near quantitative yield. This remarkable hydrolytic stability of the BIMP catalyst is likely due in part to the presence of the acidic thiourea moiety enabling the formation of strong H-bonds with the iminophosphorane moiety.



Scheme 66 Synthesis of 147**•HCl.**

Although attempted purification of the iminophosphoranes in neutral form by flash column chromatography was unsuccessful, we found the hydrochloride salt of **147**, synthesised in quantitative yield by the addition of anhydrous HCl in Et_2O to **147**, could be purified by flash column chromatography (Scheme 66). The ^{1}H NMR spectrum of **147•**HCl at room temperature was sharply resolved and furthermore the two thiourea protons and the proton of the iminophosphorane were all visible (Figure 68).

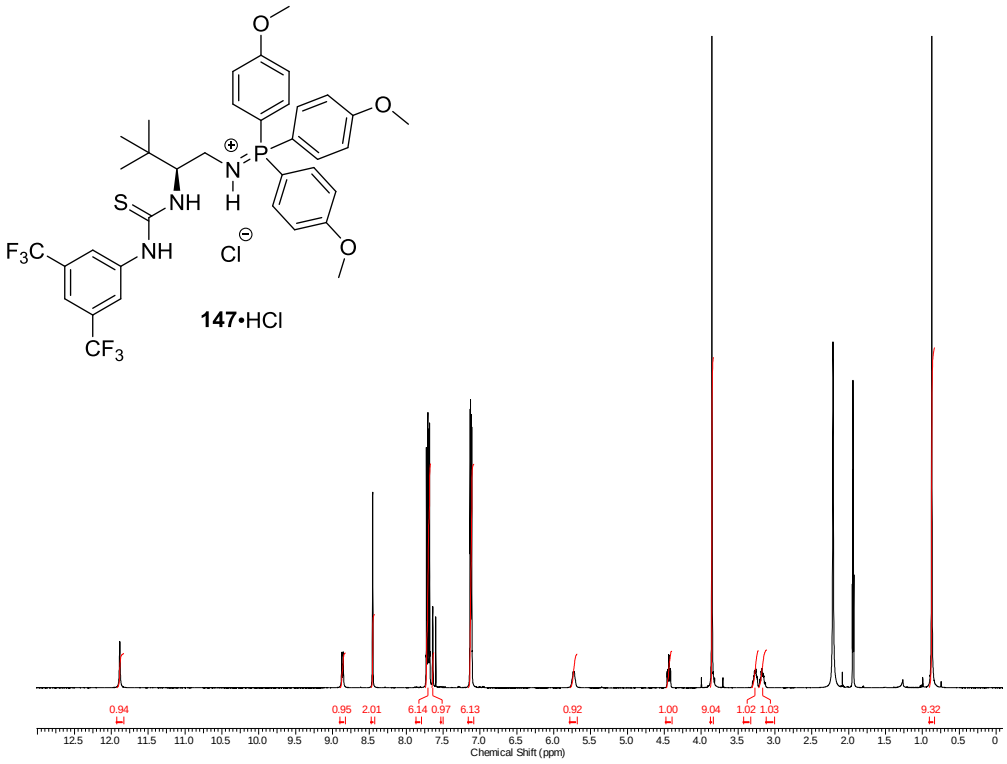
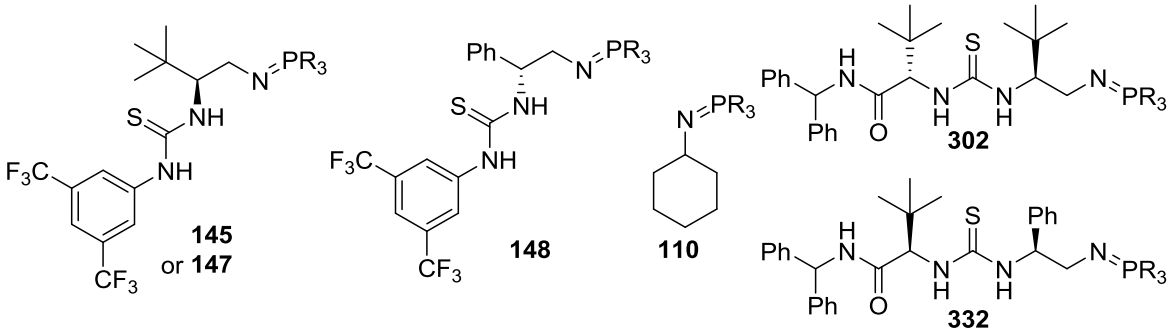


Figure 68 500 MHz ^{1}H NMR spectrum of 147•HCl (CD_3CN, 298 K).

5.3 BIMP Catalysts Incorporating the Amide Thiourea Moiety as the H-Bond Donor Group

It proved significantly more challenging to purify the iminophosphorane catalysts incorporating the amide thiourea H-bond donor group such as **302** used in the sulfa-Michael addition of thiols to α-substituted α,β-unsaturated esters (section 4.4 and Table 17). The iminophosphoranes were much less crystalline and did not readily precipitate in pentane. Furthermore, their stability relative to catalysts incorporating the 3,5-$(CF_3)_2C_6H_3$-substituted thiourea was diminished. Moreover, we noted that reactions performed using these BIMP catalysts in general proceeded faster (by TLC analysis) than those containing the 3,5-$(CF_3)_2C_6H_3$ thiourea moiety. We attribute both of these observations to the presence of the alternative, non-acidic thiourea moiety which results in less electrostatic and H-bonding interactions between the iminophosphorane and thiourea moieties. Consequently the stability of the catalysts that did not contain the acidic thiourea

moiety was reduced but conversely, the rates of reaction increased. Presumably this occurs due to a reduction in the monomer/dimer aggregations and therefore more active catalyst is present in a reaction and hence the rate of reaction increases.



Entry	R =	Iminophosphorane	^{31}P NMR /ppm (solvent)	Δδ (ppm)
1	Ph	**145**	21.9 ($CDCl_3$)	-
2	PMP	**147**	29.8 ($CDCl_3$)	-
3	PMP	**147**	33.3 (CD_3CN)	+3.6
4	PMP	**147**•HCl	36.9 (CD_3CN)	
5	PMP	**148**	27.4 ($CDCl_3$)	-
6	Ph	**110a**	9.4 (CD_3CN)	+26.2
7	Ph	**110a**•HCl	35.6 (CD_3CN)	
8	PMP	**110b**	8.9 (CD_3CN)	+25.2
9	PMP	**110b**•HCl	34.1 (CD_3CN)	
10	PMP	**302**	17.6 ($CDCl_3$)	-
11	PMP	**332**	11.4 ($CDCl_3$)	-

Table 17 ^{31}P NMR chemical shifts of various iminophosphoranes.

Further circumstantial evidence for the presence of different catalyst resting states came from analysis of the ^{31}P NMR shifts of various iminophosphoranes and their salts (Table 17). The ^{31}P NMR shift of the triphenylphosphine derived BIMP **145** was around 8 units lower than the tris(4-methoxyphenylphosphine) derived BIMP **147** (Table 17, Entries 1 & 2). This is in sharp contrast to the chemical shifts of the achiral iminophosphoranes **110a** and **110b** which have similar chemical shifts at 9.4 and 8.9 ppm in CD_3CN respectively (Table 17, Entries 6 & 8). The presence of the H-bond donor group is clearly having a large effect on the chemical shift and thus the nature of the

iminophosphorane. Augmenting the basicity of the iminophosphorane (by using a more electron rich phosphine) in the case of **147** significantly increases the chemical shift when the 3,5-$(CF_3)_2C_6H_3$-thiourea motif is present. These results suggest that the iminophosphorane moiety may to a large extent be protonated by the acidic thiourea moiety and that the thiourea is strongly interacting with the Brønsted basic part of the catalyst.

The ^{31}P NMR of **147** is similar to that obtained for **147**•HCl and **110b**•HCl (Table 17, Entries 4 & 9). The ^{31}P NMR chemical shift of the D-phenylglycine derived iminophosphorane **148** was two units lower than **147**, possibly due to the electron withdrawing effects of the phenyl ring relative to the *tert*-butyl group (Table 17, entry 5). Conversely the chemical shifts of the iminophosphoranes bearing amide-thiourea H-bond donor groups were lower (17.6 and 11.4 ppm for **302** and **332** respectively) and we attribute this to the presence of the less acidic thiourea and hence less strong H-bonding interactions between the iminophosphorane and the thiourea protons.

5.4 Conclusion

The aforementioned experiments and observations indicate that the BIMP catalysts undergo interesting self-aggregation in solution and the solid state – a phenomenon intrinsic to bifunctional organocatalysts.[235-237] These experiments, however give no indication to the conformation adopted by the catalyst in the transition state – kinetics and NMR studies of the catalysts during the course of a reaction would be beneficial to this end. We have demonstrated that iminophosphoranes that do not bear a H-bond donor group are highly catalytically active and reaction rates are impaired by the presence of the acidic thiourea moiety. We believe this to be as a result of an equilibrium between the monomeric and dimeric forms of the catalyst. The NMR studies and preliminary calculations suggest

that the monomeric form of catalysts bearing the 3,5-$(CF_3)_2C_6H_3$ thiourea may exist as the zwitterion and that the thiourea anion acts as the Brønsted base in the catalytic cycle. Further work to establish the correlation between the acidity of the thiourea moiety and the interactions of the thiourea protons with the iminophosphorane would aid the understanding of the active catalyst species.

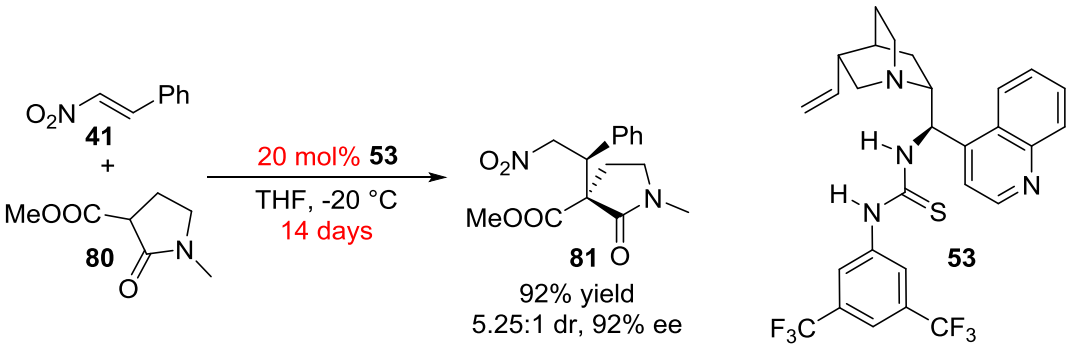
A series of experiments to determine whether any non-linear effects are present could provide further evidence for the presence of aggregates and whether the catalysts act as the monomer or as a higher order aggregate.

The BIMP catalysts incorporating the amide-thiourea H-bond donor group, although less stable, were nevertheless sufficiently stable under the reaction conditions to be used *in situ* with loadings as low as 0.05 mol%. One of the purported advantages of organocatalysis is ready catalyst recycling and whilst the amide-thiourea BIMP catalysts do not appear to be stable enough to be recycled they can be employed with exceptionally low catalyst loadings, thereby negating the requirement for catalyst recycling. In this regard, work conducted within the group has led to the development of solid supported bifunctional iminophosphorane catalysts, bearing the 3,5-$(CF_3)_2C_6H_3$ thiourea moiety, that demonstrate good reactivity, recyclability and applications in flow chemistry.[238,239]

6 Rate Enhancements in Michael Additions of β-Amido Esters to Nitro-Olefins

6.1 Introduction

The efficacy of the BIMP catalysts in the ketimine nitro-Mannich reaction (Chapter 3) and the sulfa-Michael addition of alkyl thiols to α,β-unsaturated esters (Chapter 4) was demonstrated, thus fulfilling the main aims outlined in Chapter 1. Examples of the two methodologies were illustrated on preparative scale with catalyst loadings as low as 0.05 mol% on decagram scale. A further objective of this thesis was to address the long reaction times typically required in many tertiary amine catalysed reactions and categorically illustrate the superiority of the BIMP catalysts in terms of turnover number (TON) and turnover frequency (TOF). To this end, literature examples of tertiary amine catalysed reactions that required long reaction times were selected as the platform upon which to demonstrate the increased catalytic activity of the BIMP catalysts. In particular, we chose reactions that had previously been developed in the Dixon group such as the conjugate addition between cyclic β-amido ester **80** and nitrostyrene **41** using 20 mol% of **53** (Scheme 67).[xxviii] Two weeks were required to afford the product **81** in good yield at –20 °C and we believed this challenging reaction provided an opportunity to exemplify the superior reactivity of BIMP catalysts relative to tertiary amine catalysts.



Scheme 67 Jakubec and Dixon's addition of cyclic β-amido ester 80 **to nitrostyrene catalysed by** 53 **requiring a two week reaction time at –20 °C.**

[xxviii] The work disclosed in this chapter was performed in collaboration with Dr. Pavol Jakubec.

The addition of a pro-nucleophile to an electron deficient carbon-carbon or carbon-heteroatom double bond requires activation of the pro-nucleophile **334** by deprotonation (Figure 69). The conjugate base of the pro-nucleophile is then poised to react with the electrophile **335**. The kinetic rate law equations for organocatalytic reactions are often complex; but in a simplistic model, the addition of a nucleophile to an electrophile is a bimolecular process. The rate of reaction is therefore dependent on the concentration of the conjugate base of the pro-nucleophile **334'** which is linked to thermodynamic pK_a values of the pro-nucleophile and the pK_{BH+} of the catalyst **333**.

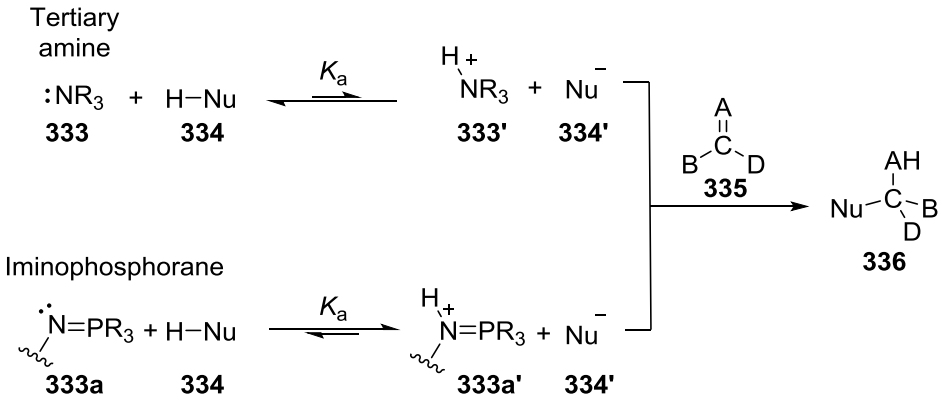
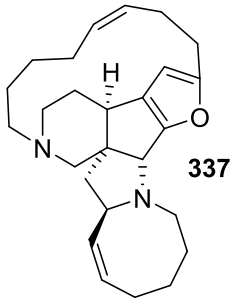


Figure 69 Schematic of a reaction between a pro-nucleophile (H-Nu) and an electrophile (B(C=A)D) containing an electron deficient carbon-carbon or carbon-heteroatom double bond. The rate of reaction is dependent on the concentration of the conjugate base of the pro-nucleophile which in turn is dependent on the basicity strength of the catalyst. This equilibrium is represented by K_a.

A more Brønsted basic catalyst will shift the acid/base equilibrium towards the conjugate base of the pro-nucleophile, thereby increasing the concentration of the active nucleophile and consequently, enhance the rate of reaction. In accordance with the argument outlined above, for an organocatalytic reaction proceeding *via* the general mechanism shown in Figure 69, the BIMP catalysts possessing a Brønsted base that is 6 orders of magnitude stronger than triethyl amine (Chapter 2) should outperform tertiary amine bifunctional organocatalysts.



337

Figure 70 Nakadomarin A; the Dixon group has published 4 total syntheses of this complex marine natural product utilising the tertiary amine bifunctional organocatalysed conjugate addition of β-amido esters to nitro-olefins as the key steps.

To exemplify this working model, we selected challenging asymmetric nitro-olefin Michael addition reactions, previously encountered by the Dixon group as key steps in four total syntheses of nakadomarin A, a complex marine natural product possessing anticancer properties. Long reaction times (2 – 8 days) and high loadings (10 – 30 mol%) of cinchona-derived bifunctional organocatalysts were required in the Michael addition reactions. These reactions are therefore examples where the pro-nucleophile/electrophile combination is approaching the reactivity threshold to asymmetric union under tertiary amine Brønsted base bifunctional organocatalysis. Although the reactions proceed to give heavily functionalised single enantiomer entities reducing the catalyst loadings and shortening reaction times would be greatly advantageous when performing the syntheses on preparative scale. In academia but especially in industry, rapid reactions under mild conditions are desirable. The challenge in asymmetric synthesis, therefore is to design efficient catalysts that can operate with low catalyst loadings and with good rates (i.e. maximising TON and TOF of a catalyst). Demonstrating that organocatalysts are complimentary to metal and enzymatic catalysts in reactions performed on industrial scale would represent significant progress to the field.

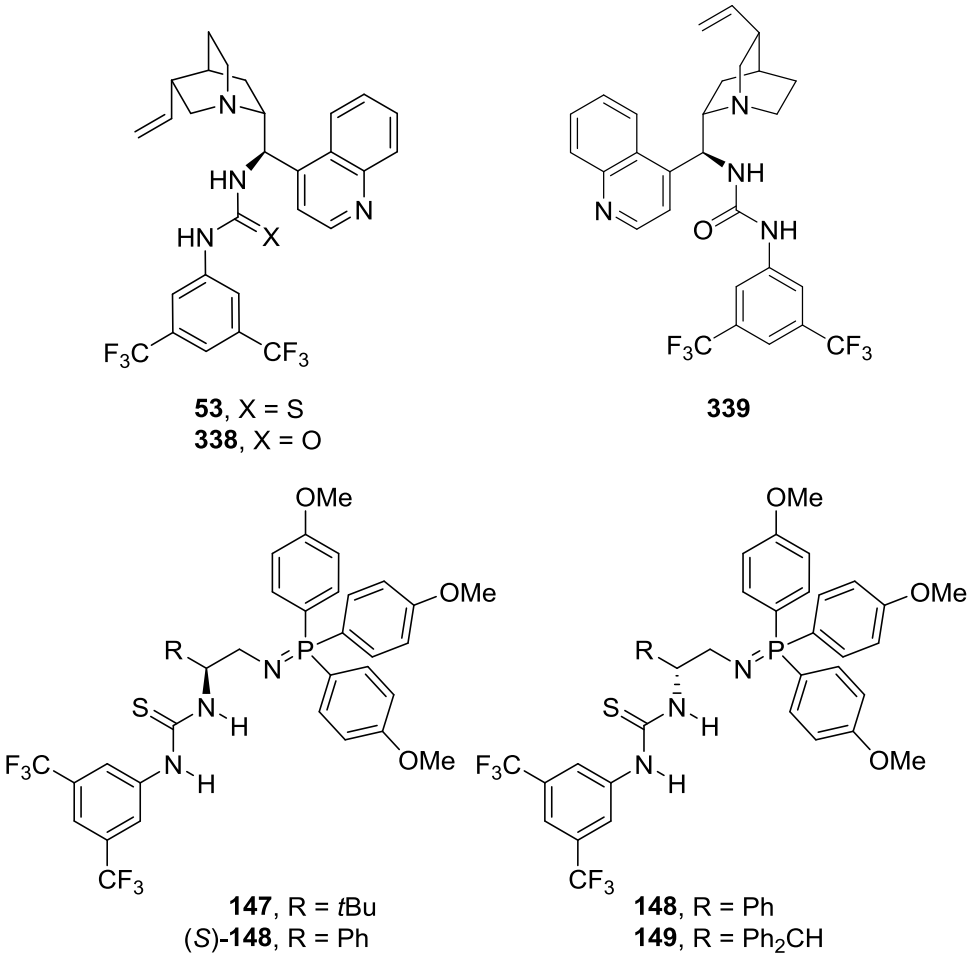
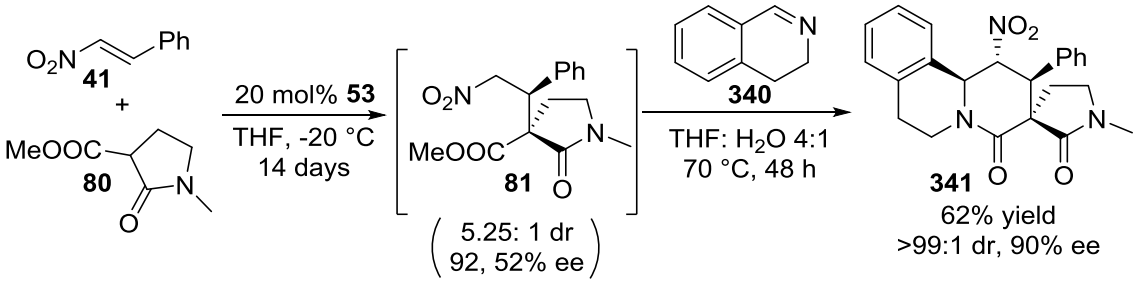


Figure 71 Structures of cinchona alkaloid derived bifunctional (thio)urea and BIMP catalysts used in the Michael addition reactions to nitro-olefins described in this chapter.

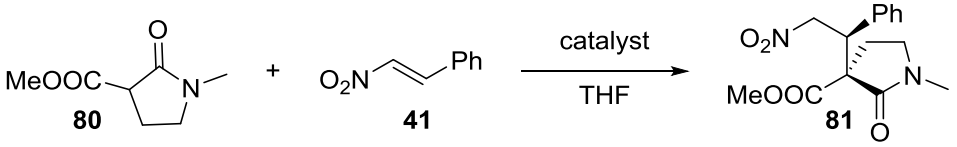
6.2 Enantio- and Diastereoselective Michael Additions of Cyclic β-Amido Esters to Nitrostyrene

In 2008, Jakubec and Dixon reported that the bifunctional thiourea cinchona-derived organocatalyst **53** catalysed the addition of pyrrolidinone **80** to nitrostyrene albeit with high catalyst loadings (20 mol%) and a two week reaction time (Scheme 68).[109] The primary focus of their paper however, was to illustrate the nitro-Mannich lactamisation cascade between **81** and related structures and a variety of imines such as **340** to afford polycyclic compounds such as **341** in good yields and diastereoselectivities. This challenging Michael addition reaction presented us with an ideal opportunity to test our hypothesis that the increased basicity of the BIMP catalysts relative to their tertiary amine counterparts would result in a shorter reaction time.



Scheme 68 One-pot Michael addition of pyrrolidinone 80 **to nitrostyrene and nitro-Mannich lactamisation cascade. The enantio- and diastereoselectivity of the Michael adduct** 81 **were determined subsequently (Table 18, Entry 1).**

For comparison, under otherwise identical conditions, the Michael addition was performed using catalyst **147**. To our delight the reaction was found to be complete in just 15 min at –20 °C with comparable dr and slightly diminished enantioselectivity (Table 18, Entry 2). Therefore, the reaction with BIMP catalyst **147** proceeded 1300 times faster than the tertiary amine Brønsted base catalyst **53**.[xxix]



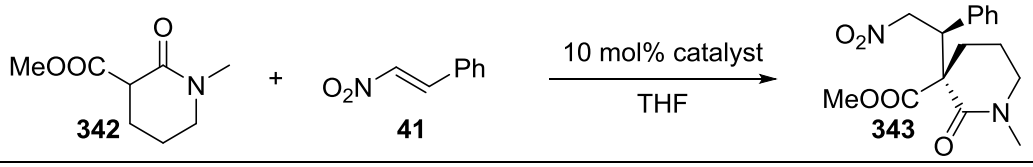
Entry	Catalyst	Temp. / °C	Loading / mol%	Time / h	Yield / %	dr	Ee / % maj., *min.*
1	**53**	–20	20	336	92	5.25 : 1	92, *52*
2	**147**	–20	20	0.25	97	6.0 : 1	84, *39*
3	**147**	–30	10	4	96	6.0 : 1	88, *48*
4	**147**	–40	10	9	75	6.9 : 1	90, *46*
5	**147**	–40	10	12	95	8.3 : 1	91, *52*
6	**149**	–20	20	2	95	7.3 : 1	92, *22*

Table 18 Performance comparison between a tertiary amine bifunctional catalyst 53 and BIMP catalysts 147 **and** 149 **in the enantio and diastereoselective addition of pyrrolidinone to nitrostyrene. The absolute and relative stereochemistry of** 81 **was determined by comparing the data reported in the literature by Dixon and Jakubec.[109]**

The enantioselectivity could be increased in excess of 90% by performing the reaction at lower temperature (Table 18, Entries 3 – 5). Interestingly, significantly longer reaction times were required at –40 °C than at –20 °C and this may be due to competing formation of catalyst aggregates at low temperature (see Section 5.2 for further discussion). When the

[xxix] The rate enhancement was verified in a repeat experiment by P.J.. The reaction was complete within 12 – 15 minutes (the time required for analysis by TLC) and the rate enhancement is therefore a conservative estimate.

enantiomeric catalyst **149** incorporating a benzhydryl group at the stereogenic centre was used at –20 °C the enantioselectivity in the formation of **81** could be increased to 92%, although a two hour reaction time was required (Table 18, Entry 6). Catalyst **149** appears to exhibit greater selectivity than **147** in this reaction although the reaction times are slightly increased.



Entry	Catalyst	Temp. / °C	Catalyst Loading / mol%	Time / h	Yield / %	dr	ee / %
1	**53**	rt	10	336	0[a]	-	-
2	**147**	rt	10	2.5	67	1.7:1	82
3	**147**	–20	10	10	98	2.8: 1	92
4	**149**	–20	10	22	78	4.0: 1	91

Table 19 Addition of 342 **to nitrostyrene catalysed by BIMP catalysts** 147 **and** 149**. Reactions were performed on 0.2 mmol of** 342 **and 1.2 eq of nitrostyrene; [a] denotes reaction performed in d_8-THF and conversion is reported against mesitylene as internal standard.**

The scope of the Michael addition of cyclic β-amido esters to nitro-olefins was extended to include the 6-membered ring analogue **342** derived from piperidinone as a pro-nucleophile (Table 19).[xxx] The reaction employing this pro-nucleophile proceeded more slowly and with slightly reduced levels of diastereocontrol but maintained enantioselectivity in the formation of **343** (Table 19, entries 2 – 4). Interestingly, the tertiary amine catalyst **53** was unable to catalyse the reaction even after two weeks at room temperature.

[xxx] The absolute stereochemistry of the tertiary centre was assigned by analogy to **81**. NOESY and nOe experiments on **343** were inconclusive in determining the relative stereochemistry and therefore the relative stereochemistry was tentatively determined by comparison of a single X-ray crystal structure of the Michael adduct formed by treatment of 3-furyl nitro-olefin and valerolactone derived-1,3-diester (Dr. Pavol Jakubec, *unpublished results)*. Initial derivatisation of **343** by reduction of the nitro group using Raney-nickel® and subsequent lactamisation was unsuccessful, Further work to derivatise **343** by performing a nitro-Mannich lactamisation cascade should allow for the determination of relative stereochemistry.

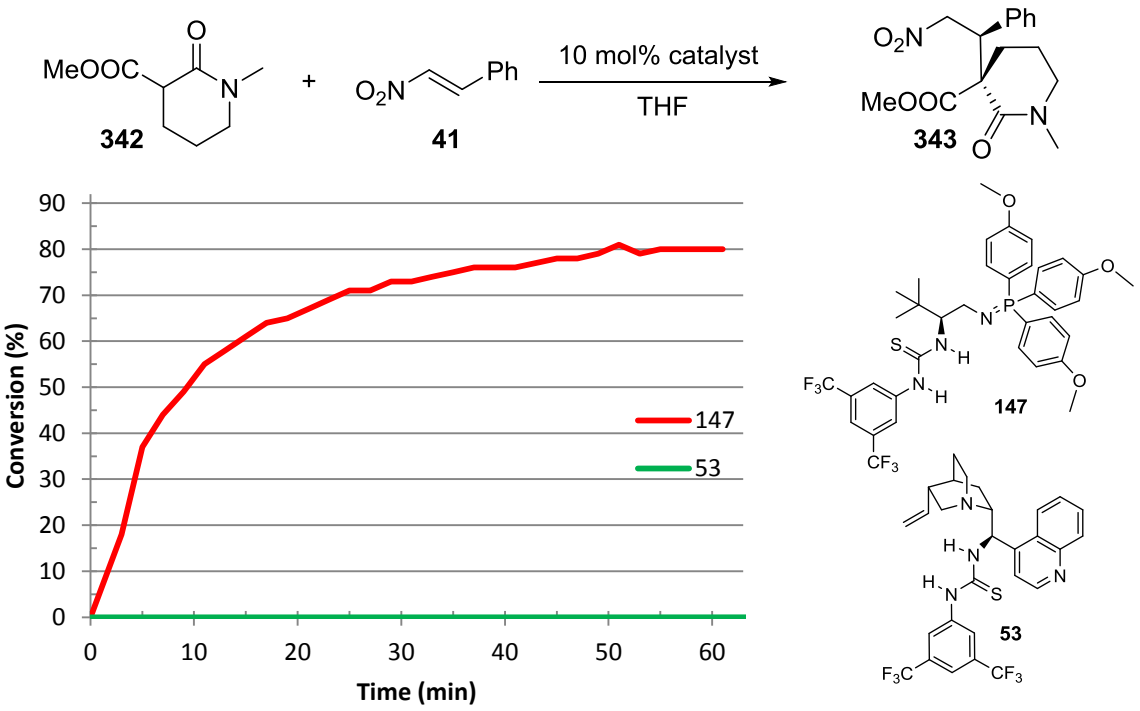


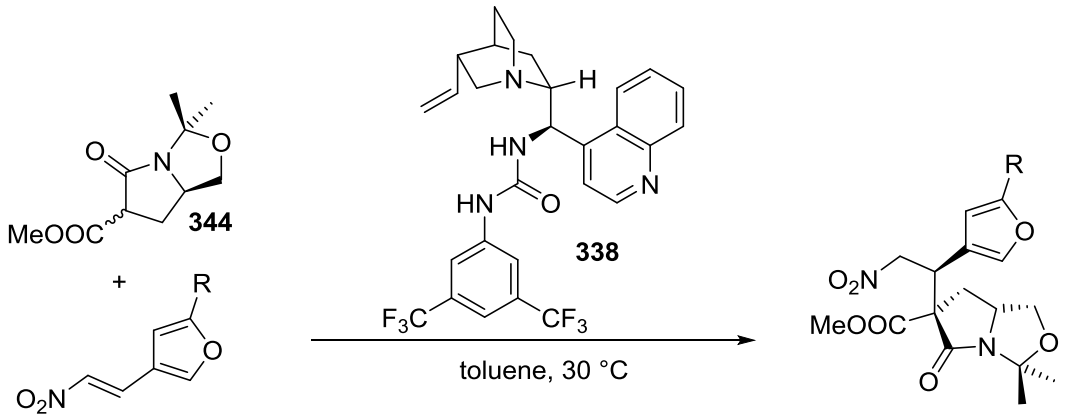
Figure 72 Comparison of the rates of the Michael addition reactions between piperidinone 342 **and nitrostyrene when using** 147 **and** 53 **as catalysts. Reactions were performed with 0.2 mmol** 342 **and 1.2 eq nitrostyrene with 10 mol% catalyst in 0.3 M d_8-THF. ^{1}H NMR spectra were recorded every two minutes and product conversion measured by integrating the $C\underline{H}_A H_B NO_2$ signal of both diastereomers against the $C\underline{H}_3$ signal of mesitylene as internal standard.**

To graphically illustrate the difference in rates between tertiary amine bifunctional catalysts and bifunctional iminophosphorane catalysts in the addition of **342** to nitrostyrene conversion to the product **343** was measured by ^{1}H NMR as a function of time (Figure 72). The reaction with 10 mol% **147** proceeds smoothly to 80% conversion within just one hour at room temperature, however no product was observable by ^{1}H NMR when the tertiary amine catalyst **53** was used even after an extended reaction time of 2 weeks.

6.3 Application of BIMP Catalysts to Natural Product Synthesis

Following the successful application of BIMP catalysts to the enantio- and diastereoselective conjugate addition of β-amido esters to nitro-olefins, we sought to enhance the rates of the Michael addition reactions found in the Dixon syntheses' of nakadomarin A **337** (Figure 70). Two routes, featuring late stage alkyne and alkene ring closing metathesis (RCM) reactions, relied on the cinchona-derived bifunctional urea **338**

catalysed conjugate addition between the enantiopure 5,5-bicycle **344** and a substituted nitro-olefin **345** or **347** (Scheme 69).[240,241] High yields of the products **346** and **348**, as single diastereomers, were obtained after purification by chromatography and trituration. The Michael addition reactions between the 5,5 bicycle **344** and the nitro-olefins **345** and **347** were found to require two to three day reaction times with catalyst loadings of 10 – 30 mol%. The use of large quantities of catalyst and relatively long reaction times were justifiable as the Michael addition reaction readily allowed the construction of the synthetically advanced intermediates **346** and **348** and controls the stereochemistry of the quaternary carbon of nakadomarin A. However, enhancing the rates of reaction using the BIMP catalysts would increase the practical elegance of the total syntheses.



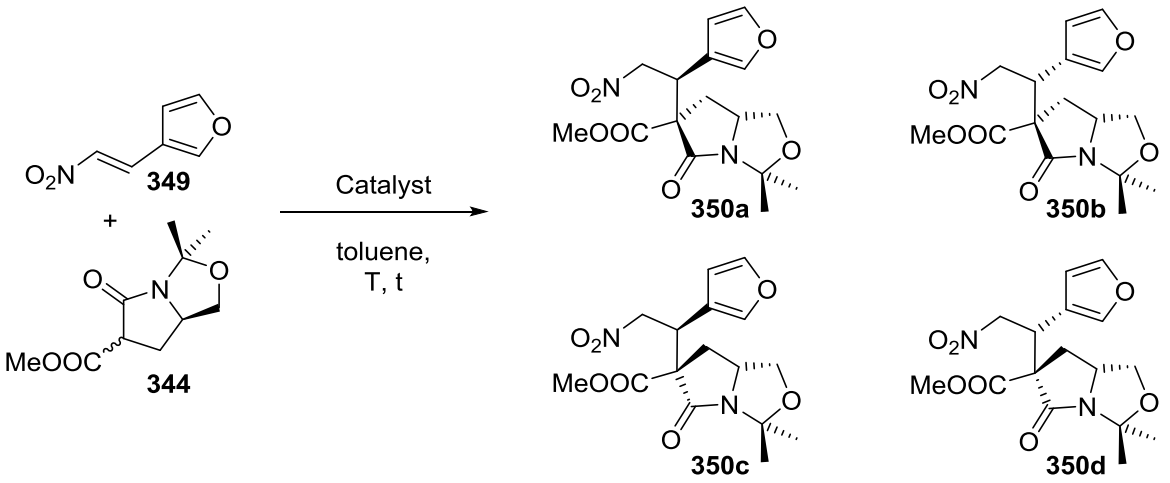
345, R = $CH_2CH_2CCCH_3$
347, R = $CH_2CH_2CHCH_2$
349, R = H

346, R = $CH_2CH_2CCCH_3$, 10% **338**, 52 h, 81% yield
348, R = $CH_2CH_2CHCH_2$, 30% **338**, 72 h, 72% yield
350, R = H, 10% **338**, 48 h, 80% yield

Scheme 69 Conjugate addition between 5,5-bicycle 344 **and substituted furan nitro-olefins catalysed by** 338**. Yields are reported for the Michael adducts as single diastereomers obtained after flash column chromatography and trituration.**

Kyle, Jakubec and Dixon optimised the diastereoselective Michael addition of bicycle **344** to nitro-olefins using **349** as a model electrophile.[240] The authors reported that the conjugate addition required 48 h to reach completion with 10 mol% of the bifunctional urea catalyst **338** to afford the product **350** with a crude d.r. of 15:1:0:0 (Table 20, entry 1). The nitro adduct **350** could then be isolated as a single diastereomer in 80% yield

following purification by flash column chromatography and trituration. However, when the reaction was performed using the pseudo-enantiomer catalyst **339**, derived from cinchonidine, reaction times increased to 5 days and the crude diastereoselectivity was found to be 4:12:1:1 (Table 20, entry 2). The catalyst and substrate were therefore deemed to be 'mismatched'. The authors proposed that the urea moiety of the catalyst activated the nitro-olefin through H-bonding interactions and the stereochemistry of the tertiary stereogenic centre was governed by the three dimensional structure of the catalyst. The stereochemistry of the quaternary carbon was controlled by the three dimensional structure of the pro-nucleophile with one face being more accessible.

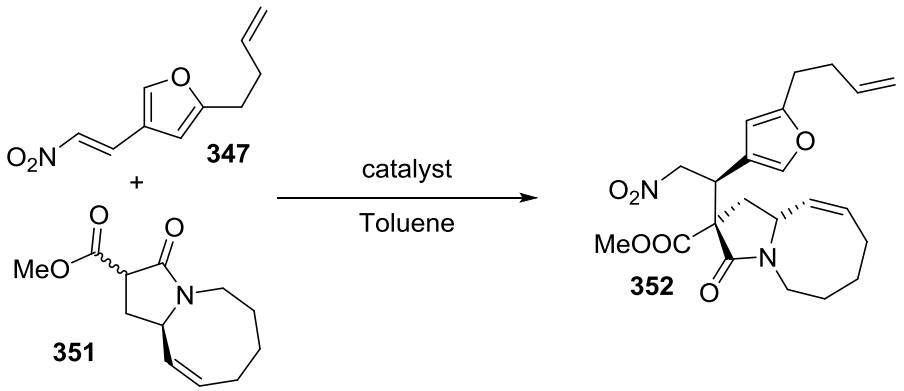


Entry	Catalyst	Temp. / °C	Loading / mol%	Time / h	Crude dr a:b:c:d	Yield / % (conv.)	dr
1	**338**	30	10	48	15:1:0:0	80	single[240]
2	**339**	30	10	120	4:12:1:1	61	6:19:1:1[240]
3	**148**	30	10	0.08	86:13:1:0	60, (80)	single
4	(*S*)-**148**	30	10	0.17	47:49:4:0	(86)	-
5	**148**	0	10	0.5	89:9:1:0	61, (78)	99:1
6	**149**	0	10	0.5	98:2:0:0	75, (92)	single
7	**149**	0	1	1.3	98:2:0:0	68	single

Table 20 Screen of catalysts in the addition of 5,5-bicycle 344 **to the model furan nitro-olefin** 349 **demonstrating the rate enhancements of BIMP catalyst relative to tertiary amine catalysts.**

The reactions when attempted with the BIMP catalysts proceeded significantly faster (5 minutes versus 48 h, (Table 20, entries 1 and 3)). Similar catalyst substrate 'matching'

and ‘mismatching’ that had been observed by Kyle, Jakubec and Dixon was encountered with the BIMP catalysts using both enantiomers of the phenylglycine derived catalysts (Table 20, entries 3 and 4). The inherent diastereocontrol when using the L-phenylglycine derived catalyst **148** was lower than the cinchona derived catalyst **338** (Table 20, entries 1 and 3). Due to the much greater reactivity of **148** relative to **338**, the lower diastereocontrol imparted by **148** could be alleviated by performing the reaction at lower temperature. Indeed, lowering the temperature to 0 °C increased the diastereocontrol in the formation of **350** to 89:9:1, with a marginal increase in reaction time to 30 minutes. Using catalyst **149**, incorporating a benzhydryl group at the stereogenic centre, increased the diastereocontrol of the crude reaction mixture to 98:2 with the desired diastereomer **350a** isolated in 75% yield after purification. Pleasingly, when the reaction was performed using just 1 mol% of **149**, the reaction was complete in 80 minutes with no loss of diastereocontrol. Presumably, by extension of Kyle, Jakubec and Dixon’s optimisation of the Michael addition reactions, the BIMP catalysed Michael additions reactions to nitro-olefins **345** and **347** would also be significantly faster and similarly high levels of diastereocontrol obtainable.



Entry	Catalyst	Temp. / °C	Catalyst Loading / mol%	Time / h	Yield / %	dr
1	**338**	30	15	192	57	91:9[160]
2	**148**	30	15	0.75	57	3.5:1
3	**148**	rt	10	2	59	4.5:1
4	**149**	rt	10	3.5	79	79:11:10

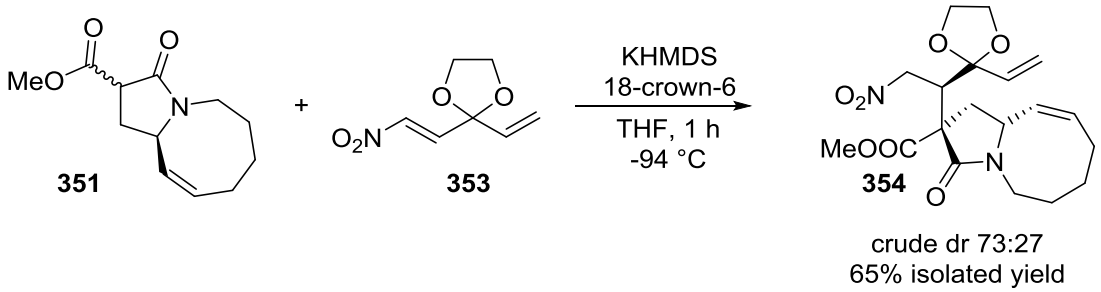
Table 21 Diastereoselective Michael addition between 8,5-pronucleophile 351 **and** 347**. Entry 3 was performed on 0.14 mmol scale of** 351 **and 1.1 eq of nitro-olefin in 0.33 M toluene. Yields are given of the purified product as a mixture of diastereomers after flash column chromatography.**

We next focussed on the diastereoselective Michael addition between the 8,5-bicyclic pro-nucleophile **351** and the furan nitro-olefin **347** that was key to the Dixon first generation synthesis of nakadomarin A (Table 21, Entry 1).[160] The reaction, whilst affording the addition product **352** in good levels of diastereocontrol, required 8 days to reach completion with 15 mol% catalyst at 30 °C. Under otherwise identical conditions, catalyst **148** was trialled and the reaction was complete within just 45 min with similar yields; albeit with lower levels of diastereoselectivity (Table 21, Entry 2). Performing the reaction at room temperature improved the diastereoselectivity marginally to 4.5:1 (Table 21, Entry 3). The catalyst containing the benzhydryl moiety at the stereogenic centre **149** was more selective and afforded the product in 79% yield with a dr of 79:11:10.[xxxi]

Lastly, we investigated the performance of the BIMP catalysts in the synthesis of manzamine A. In a similar strategy to that adopted in the first generation synthesis of nakadomarin A, Jakubec and Dixon described the Michael addition between the 8,5-

[xxxi] The enhanced yield was due to the presence of a 3rd diastereomer which had not been removed by flash column chromatography.

pronucleophile **351** and nitro-olefin **353** (Scheme 70).[242] Moderate levels of diastereocontrol (2.7:1) were achieved in the formation of **354** by using stoichiometric KHMDS and 18-crown-6 at –94 °C to form the 'naked' enolate of **351**. The authors attempted the Michael addition using tertiary amine bifunctional organocatalysts but no product was observable and they reasoned that the low electrophilicity of **353** was due to high steric hindrance of the adjacent acetal and vinyl groups.



Scheme 70 Jakubec and Dixon's diastereoselective Michael addition between 351 **and** 353 **towards the synthesis of manzamine A.**

We therefore attempted the Michael addition using the BIMP catalyst system in a bid to achieve the formation of **354** under catalytic conditions. Unfortunately, no trace of product was observable by ^{1}H NMR when 20 mol% of **147** and **148** were used even after extended reaction times of 72 h. This supports the report that this Michael addition required preformation of the enolate and subsequent quenching with the electrophile.

6.4 Conclusion

This chapter sought to demonstrate the superior performance of the BIMP catalysts relative to tertiary amine bifunctional organocatalysts in terms of turnover number (TON) and turnover frequency (TOF). Rate enhancements by a factor of up to 1300 were observed with reaction times reduced from two weeks to 15 minutes thereby fulfilling another objective of the thesis. In addition, the rate enhancements of the BIMP catalysts relative to tertiary amine catalysts were also illustrated in the key steps of the reported syntheses of nakadomarin A. The augmented basicity of the iminophosphorane catalysts was shown to

be responsible for the observed rate enhancements of BIMP catalysts relative to tertiary amine analogues. From an industrial perspective, the rate enhancements are attractive and presumably similar increases in reaction rates would be observed with the BIMP catalyst system in other organocatalytic reactions involving low acidity pro-nucleophiles and/or low energy electrophiles. The BIMP catalysts, possessing an organosuperbase, shift the pro-nucleophile/nucleophile acid/base equilibrium towards the active nucleophile, thereby increasing its concentration and consequently significantly enhancing the rate of reaction.

7 New Reactivity as a Springboard for Catalyst Development

7.1 Overview

This chapter is a depiction of some of the forays into new reactivity that we explored during the course of the DPhil. Not all of the reactions have been optimised for rate and enantioselectivity but with sufficient optimisation with respect to the reaction conditions and the catalyst enantiocontrol greater than 90% ee should be achieved. The opportunity was taken to design and evaluate new catalysts when a reaction of fundamental and practical importance (due to the products formed) was discovered. As such, this chapter is a smorgasbord of reactivity studies and new catalyst designs. A new catalyst design was systematically checked against our previously developed reactions to provide an indicator of performance.

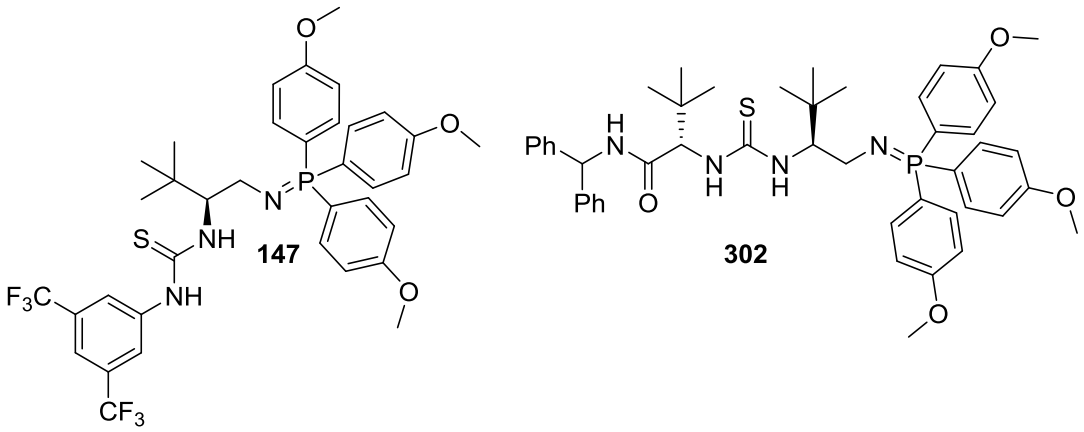
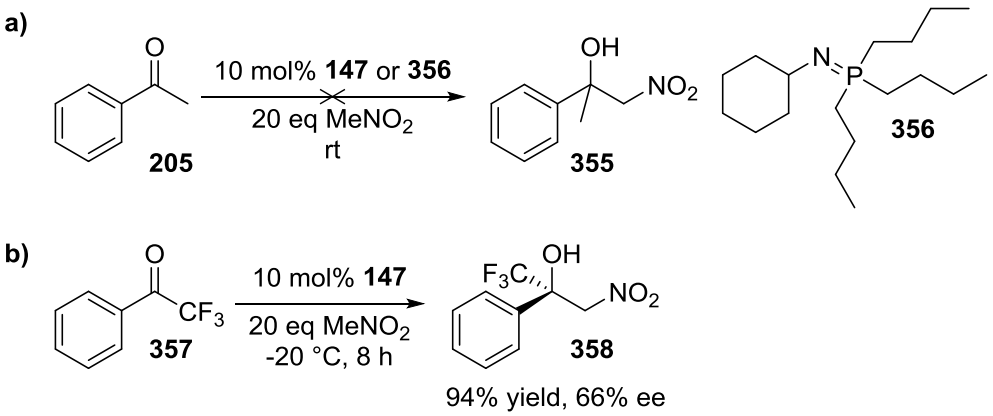


Figure 73 Structure of BIMP catalysts used in the screen of reactivity studies.

7.2 Addition of Nitromethane to Ketones: the Henry Reaction

The ketimine nitro-Mannich reaction described in Chapter 3 between *N*-DPP ketimines and nitromethane allowed the construction of amines bearing a fully substituted carbon. The analogous reaction to afford tertiary alcohols, the Henry reaction, involves the addition of nitroalkanes to ketones.[155] However, due to the lower electrophilicity of ketones relative to

imines[189,190] and the lack of possibility for a protecting group on the oxygen atom (due to its divalency) to aid enantiofacial discrimination, we postulated that this reaction would be very challenging. Indeed, when catalyst **147** was trialled in the addition of nitromethane to acetophenone **205** no product was observed. The use of a more basic iminophosphorane **356**, devoid of a H-bond donor group was no more successful (Scheme 71a). Interestingly there are no reports in the literature of the addition of nitromethane to acetophenone. Jacobsen and co-workers successfully demonstrated the organocatalytic enantioselective addition of TMSCN (an alternative one carbon pro-nucleophile) to acetophenone.[243] Organocatalytic Henry reactions to ketones require activated ketones such as α-ketoesters[244,245] or α-ketophosphonates[246,247] to proceed and these functionalities may also aid binding of the substrates to the catalysts to enhance the enantioselectivity.



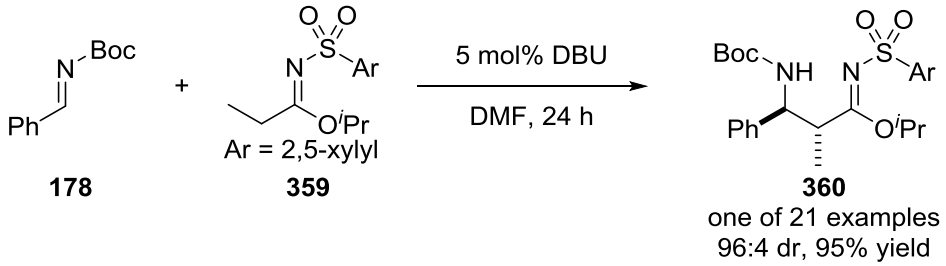
Scheme 71 a) Attempted Henry reaction of nitromethane to acetophenone; b) Henry reaction of 2,2,2-trifluoroacetophenone catalysed by 147**.**

The Henry reaction on 2,2,2-trifluoroacetophenone **357** was subsequently attempted, which due to the presence of the CF_3 moiety is significantly more electrophilic than acetophenone **205** but, nevertheless allows the construction of a chiral tertiary alcohol. Using catalyst **147** and nitromethane **151** as solvent at –20 °C, the formation of the Henry adduct **358** proceeded smoothly in an unoptimised 66% ee in just 8 h. The addition of nitromethane to **357** has been described previously with both metal[248] and organocatalysts[249-251] with excellent levels of enantiocontrol. Despite the reaction proceeding faster with BIMP

catalyst **147** than the examples described in the literature we decided against optimising the reaction further.

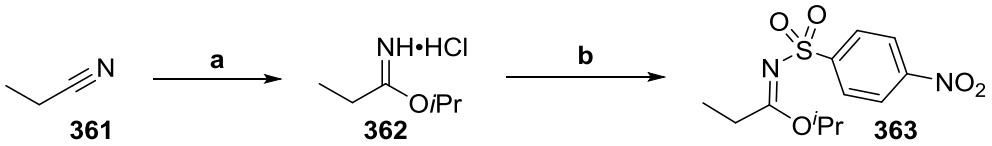
7.3 Mannich reaction of Sulfonyl Imidates to N-*DPP Aldimines*

In 2008, Kobayashi *et al.* introduced sulfonyl imidates such as **359** as moderately low pK_a ester surrogates and showed that their addition to a range of aromatic imines could be effectively catalysed by DBU **62**, an organosuperbase, with high levels of diastereocontrol (Scheme 72).[252]



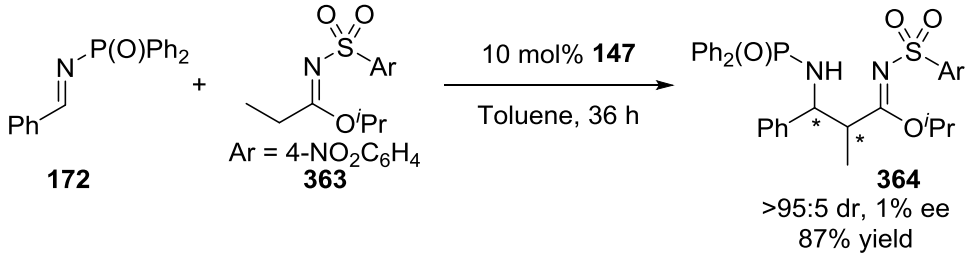
Scheme 72 Kobayashi's diastereoselective addition of sulfonylimidates 359 **to imines catalysed by DBU.**

The authors subsequently expanded the scope to include aliphatic imines[253] and a range of Michael acceptors such as acrylates and activated crotonic esters.[254] P-1 and P-2 phosphazenes as well as Verkade bases were necessary to promote the reactions owing to the relatively high pK_a values of the pro-nucleophile. Whilst the reactions were highly diastereoselective, the use of achiral superbases necessarily did not allow for enantiocontrol and, therefore we reasoned that these challenging pro-nucleophiles would provide an ideal opportunity for our BIMP catalysts. Barbas reported an isolated enantioselective conjugate addition of sulfonyl imidates bearing α-aromatic substituents to enals under iminium catalysis, although the scope was limited with poor diastereocontrol but with examples of good levels of enantiocontrol.[255]



Scheme 73 Synthesis of sulfonylimidate 363**: a) ^{i}PrOH, HCl (g), rt, 2 h, 33% yield; b) 4-nitrobenzenesulfonyl chloride, 10 mol% DMAP, NEt_3, CH_2Cl_2, rt, 14 h, 72% yield.**

The sulfonyl imidates can be readily synthesised in two steps by initial addition of an alcohol to a nitrile in the presence of anhydrous hydrogen chloride (Scheme 73). Propionitrile **361** was treated on a 5 g scale with isopropanol and gaseous HCl (generated by the addition of conc. H_2SO_4 to anhydrous $CaCl_2$). Purification by simple filtration afforded the imidate **362** as the hydrochloride salt in 33% yield. The sulfonyl imidate **363** was then synthesised by treatment of the salt **362** with 4-nitrobenzenesulfonyl chloride, catalytic DMAP and triethylamine in 72% yield.



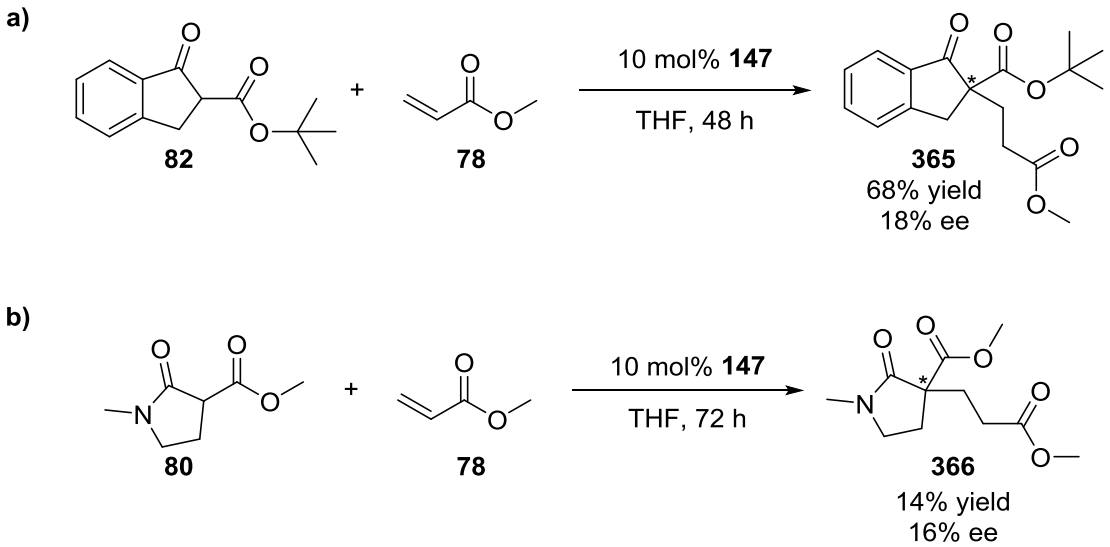
Scheme 74 BIMP catalysed Mannich reaction of sulfonyl imidate 363 **to *N*-DPP aldimine** 172**.**

With the sulfonyl imidate in hand, the Mannich reaction to *N*-DPP aldimine **172** was trialled and pleasingly the product **364** was formed in near quantitative yield in just 36 h using 10 mol% of **147** (Scheme 74). The ee in the formation of **364** was disappointingly low (1%) but nevertheless high levels of diastereocontrol were observed with excellent reactivity. To continue further with this class of pro-nucleophiles a full catalyst screen would be required.[xxxii]

[xxxii] Other sulfonyl imidates were synthesised varying the electron deficiencies on the protecting group. We found that reactions with *N*-tosyl proceeded slower than with **363** and the use of 2-pyridyl or 3,5-$(CF_3)_2C_6H_3$ substituents to proceed similarly to **363**. Other protecting groups on the imine such as *N*-Boc and *N*-Ts were also trialled but no improvements in the enantioselectivity were observed. A preliminary screen of solvents did not enhance the ee beyond 9% and the above example is included as a proof of principle.

7.4 Addition of Cyclic 1,3-Dicarbonyls to Unactivated Acrylic Esters

In 2008, Rigby and Dixon reported the conjugate addition of a range of β-ketoesters to activated acrylic esters (such as *N*-acyl pyrroles and thioesters) using bifunctional cinchona alkaloid catalysts (see section 1.6).[110] The reaction allows the construction of quaternary carbon centres in good yields and enantioselectivities; however the use of activated esters is cumbersome from both atom economy and synthesis perspectives. Moreover, the authors mention that when ethyl acrylate was used as the electrophile no trace of product was observed. The enantioselective addition of indanone derived β-ketoesters such as **82** to unactivated acrylic esters has no general solution and we believed that our BIMP catalysts could address this. Deng published the conjugate addition to enals to afford the aldehyde which can then be oxidised to the ester.[256] The reaction is amenable to asymmetric phase transfer catalysis using *Cinchona* ammonium salts, although 7 days are required to achieve a moderate yield of 55%.[257]



Scheme 75 a) Addition β-ketoester 82 **to methyl acrylate** 78**; b) Addition of pyrrolidinone** 80 **to methyl acrylate using** 147**.**

Accordingly, we trialled the addition of **82** to methyl acrylate using catalyst **147** and pleasingly the conversion to the product **365** was smooth at room temperature. The product was isolated in 68% yield after 48 h with a promising ee of 18% (Scheme 75a). Similarly,

the addition of pyrrolidinone ester **80** to methyl acrylate was attempted. The reaction proceeded much more slowly, presumably due to the lower acidity of the pro-nucleophile **80**, and the product **366** was isolated in 14% yield and 16% ee after 96 h (Scheme 75b). Whilst the enantioselectivities are currently only moderate in these two conjugate addition reactions, proofs of principle have been established. The bifunctional iminophosphorane organocatalysts display high reactivity profiles in an array of challenging reactions and provide compelling evidence for enhanced basicity leading to improved reactivity.

7.5 Conjugate Addition of α-Aryl Acetates to Phenyl Methacrylate

During the course of our studies into the conjugate addition of alkyl and benzyl thiols to α-substituted α,β-unsaturated esters, the unexpected formation of the side product **320** was observed (see section 4.5.5 and Figure 74). The α-proton of the ester of the product – formed from the addition of 1-propanethiol to the α-substituted α,β-unsaturated ester **287t** – was sufficiently acidic to be removed by the BIMP catalyst and hence the substrate underwent a conjugate addition with excess electrophile present in the reaction mixture.

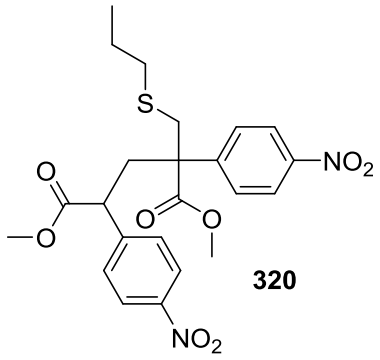
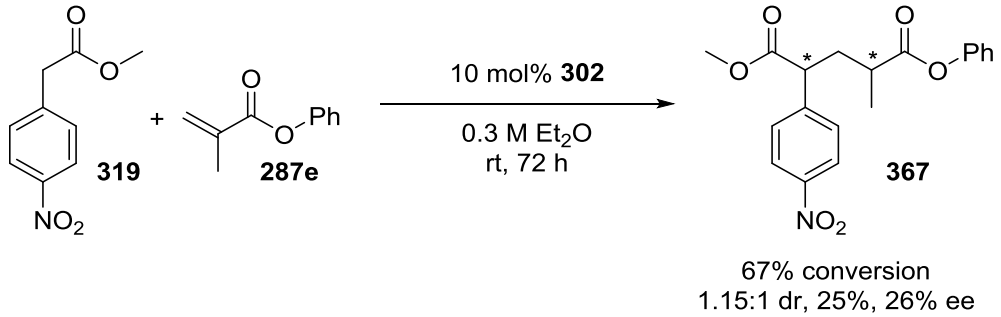


Figure 74 Unexpected side product 320 **in the SMA of 1-propanethiol to** 287t**.**

We realised that this fortuitous observation could be exploited in new reactivity studies by using methyl 2-(4-nitrophenylacetate) **319** as a pro-nucleophile (Scheme 76). The BIMP catalysts should be basic enough to deprotonate the substrate to afford the active nucleophile which could then add into a range of electrophiles. A survey of the literature revealed that a range of electron deficient aryl acetates and arylacetonitriles have been

added to enals under iminium catalysis.[258,259] Feng *et al.* used a chiral zirconium catalyst in the addition of arylacetonitriles to alkylidene malonates in high yields and diastereoselectivities.[260] In 2012, Barbas and co-workers reported that pyrazoleamide substituted 4-nitrophenylacetates were highly effective in the conjugate addition to nitro-olefins catalysed by tertiary amine bifunctional organocatalysts.[261] In both of the examples, either the pro-nucleophile or the electrophile was activated to increase the reactivity and therefore the addition of **319** to simple α,β-unsaturated esters such as **287e** would be desirable.



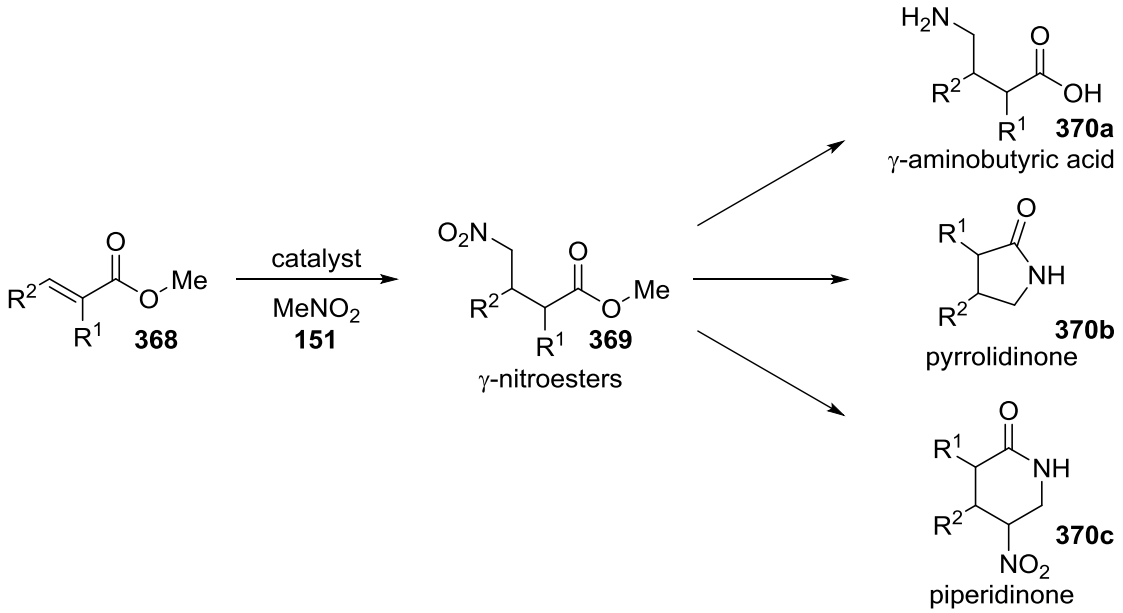
Scheme 76 Michael addition reaction between 319 **and phenyl methacrylate** 287e **catalysed by** 302**.**

Using 4-nitrophenyl acetate **319** as a pro-nucleophile, the addition into phenyl methacrylate was attempted using D-phenylglycine derived catalyst **148** but no evidence of product was observed. When we performed the reaction using catalyst **302**, which was found to be optimal in the sulfa-Michael addition reaction, we were delighted to observe the formation of product **367** (Scheme 76). The diastereoselectivity and enantioselectivity are, at present, only moderate but these could be improved by a systematic optimisation of the reaction parameters. An interesting extension of this reaction would be the replacement of the electron deficient arene to biologically significant heteroarenes such as pyridine. This would provide direct access to a range of enantioenriched chiral building blocks bearing pyridine with additional functional groups present for further manipulations.

7.6 Nitromethane in Conjugate Additions to α,β-Unsaturated Esters

7.6.1 Introduction and Importance of γ-Nitroesters

Nitromethane appeared to be an excellent pro-nucleophile in a range of asymmetric transformations with our BIMP catalysts. We thus wondered whether we could catalyse its asymmetric union to α,β-unsaturated esters such as methacrylic esters or crotonic esters. The products formed from this transformation are γ-nitroesters **369** which are of great synthetic value (Scheme 77). Reduction of the nitro group to afford the amine and ester hydrolysis allows the formation of γ-aminobutyric acid (GABA) and its analogues **370a**, an extremely important class of compounds that act as neurotransmitters in the central nervous system.[262,263] Alternatively, the γ-aminobutyric esters can undergo lactamisation to yield the pyrrolidinone **370b** or the γ-nitroesters can be used in a nitro-Mannich lactamisation cascade to afford the piperidinone **370c**.



Scheme 77 Addition of nitromethane to α,β-unsaturated esters allows the formation of γ-nitroesters 369 **which can be derivatised to biologically significant γ-aminobutyric acids (GABA), piperidinones and pyrrolidinones.**

Pregabalin **371** (trade name Lyrica, Figure 75) is prescribed as an anticonvulsant drug used for neuropathic pain and had total sales of $2.36 billion in 2013.[264] An efficient asymmetric synthesis of the γ-nitroester from the Michael addition reaction between the

appropriate β-substituted α,β-unsaturated ester and nitromethane would be very attractive. Baclofen **372**,[56] rolipram **373** and paroxetine **374**[265] have previously been synthesised using organocatalysts by the Dixon group and others. These strategies rely on the conjugate addition between malonates and the corresponding nitro-olefin.

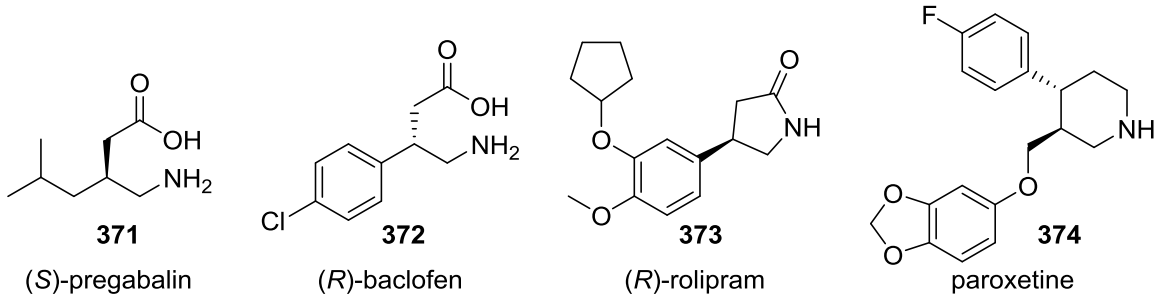


Figure 75 Drug molecules that can be accessed from enantiopure γ-nitroesters.

Owing to the synthetic utility of the γ-nitroester products formed from the conjugate addition of nitroalkanes to α,β-unsaturated esters various groups have developed metal and organocatalytic strategies for asymmetric variants (Figure 76). Kanemasa and co-workers, using a nickel based catalyst, required a pyrazole crotonic ester **375a** for the enantioselective addition of nitromethane.[266] In 2012, Shibasaki *et al.* exploited the soft-soft interaction between a thioamide **375b** and a copper catalyst to effectively promote the Michael addition of nitromethane.[267] Takemoto and co-workers, investigated the addition of various activated methylene compounds to α,β-unsaturated imides such as **375c** using a tertiary amine Brønsted base bifunctional organocatalyst and found that the reaction with nitromethane required 6 days to go to completion at room temperature.[213] Similarly, Soós *et al.* used a cinchona derived bifunctional organocatalyst to investigate the addition of nitromethane to chalcone and *N*-acyl pyrroles **375d**.[236] In an alternative strategy, Jørgensen, using a prolinol derived iminium catalyst added nitroalkanes to a range of enals **375e** and in one pot oxidised the products to form γ-nitroesters.

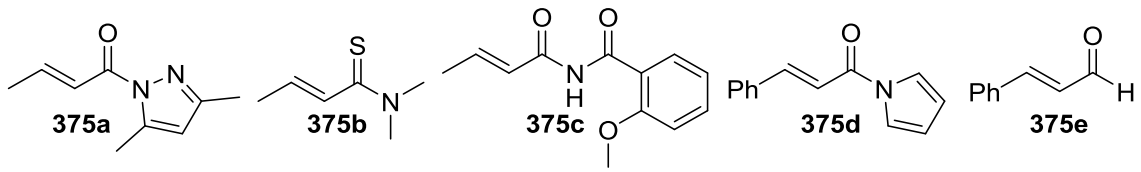
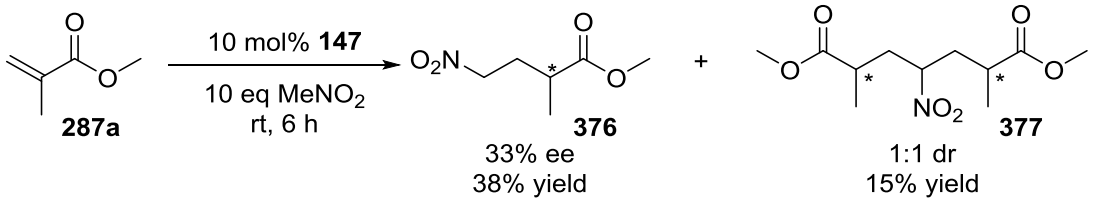


Figure 76 Activated β-substituted α,β-unsaturated ester surrogates used in metal and organocatalytic additions of nitromethane.

The use of activating groups requires additional steps for their installation and removal during a synthesis whilst lowering the atom efficiency. A general strategy for the direct addition of nitroalkanes to unactivated α,β-unsaturated esters remained elusive using both metal based catalysts and organocatalysts and therefore provided an opportunity for the BIMP catalysts.

7.6.2 Addition of Nitromethane to Methyl Methacrylate

As a starting point, we trialled the addition of nitromethane **151** to methyl methacrylate **287a** using catalyst **147** (Scheme 78). All starting material was consumed within 6 h and pleasingly we isolated the desired product **376** in 38% yield and 33% ee. A side product **377** was observed which was formed by the γ-nitroester **376** undergoing a second Michael addition reaction to methyl methacrylate. The bis-addition product is probably formed as a result of the increased acidity of the secondary nitroalkane (due to the stabilisation of a more substituted double bond when the nitronate is formed).[201] The formation of the bis-adduct has been observed previously when studying the addition of nitromethane to methyl methacrylate catalysed by DBU under microwave irradiation.[268] Furthermore, Fukuyama and co-workers observed exclusive formation of the triester when they catalysed the addition of nitromethane to methyl acrylate as the first step in the synthesis of the potent immunosuppressant FR901483.[269]



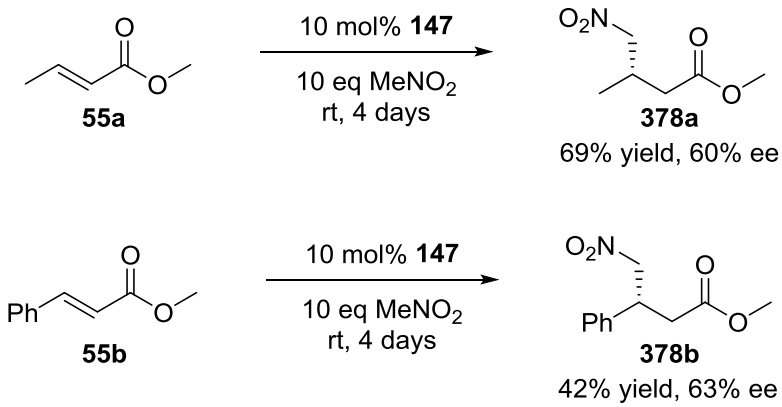
Scheme 78 Addition of nitromethane to methyl methacrylate catalysed by 147**.**

Although excellent levels of reactivity were observed with a promising starting enantioselectivity of 33% ee, the competing formation of the double addition adduct **377** was a deterrent. Despite a large excess of nitromethane **151** (as it was used as solvent) the second addition clearly proceeded much faster than the initial Michael addition.

7.6.3 Addition of Nitromethane to Methyl Crotonate and Methyl Cinnamate

As a related alternative reaction, we postulated the enantioselective conjugate addition of nitromethane **151** to methyl crotonate **55a** could be catalysed by the BIMP catalysts. The sporadic reports in the literature for the synthesis of the racemic compound require the use of strong organic bases such as DBU[270] and TMG[271] or inorganic bases such as K_2CO_3.[272] Long reaction times (24 days),[271] microwave irradiation[268] or elevated temperatures are also required.

The enantiocontrol in this reaction stems from the initial nucleophilic attack of the pro-nucleophile to one face of the electrophile. Under very concentrated conditions (10 eq $MeNO_2$) and with 10 mol% of catalyst **147** the addition of nitromethane to methyl crotonate was investigated. We were delighted to observe the formation of the γ-nitroester **378a** in good yield (69%) and with an extremely promising ee of 60%. The analogous reaction using methyl cinnamate **55b** was performed and the γ-nitro ester **378b** was isolated in 42% yield after 4 days and in 63% ee.



Scheme 79 Addition of nitromethane to methyl crotonate and methyl cinnamate catalysed by 147**.**

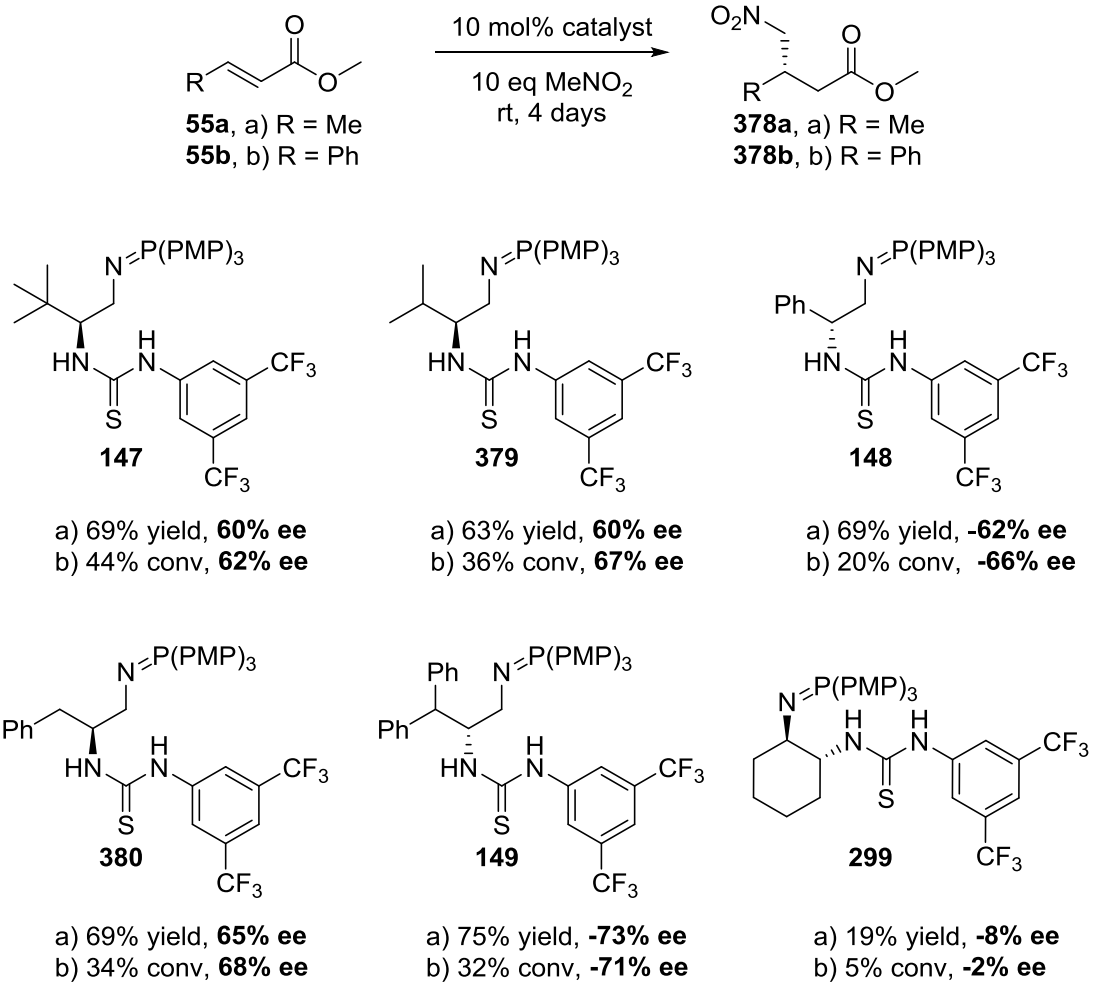
Encouraged by this proof of principle we decided to actively pursue optimisation studies on this reaction. If a screen of our catalyst library did not reveal a satisfactory candidate, this reaction would provide an ideal platform with which to design and evaluate new catalysts.

7.6.4 Optimisation of the Catalyst Scaffold

The reactions could be easily purified by eluting the reaction mixture through a pipette of silica to remove the polar catalyst residues. Remaining methyl crotonate was removed under a stream of nitrogen to afford pure γ-nitroester **378a**, whereas excess methylcinnamate could not be removed easily and conversion by ^{1}H NMR was reported instead. Due to the long reaction times and the ease of purification of the products, we saw the opportunity to develop medium throughput parallel screening techniques (Figure 77).

Figure 77 Medium throughput parallel screening setup in the conjugate addition of $MeNO_2$ to methyl crotonate and cinnamate.

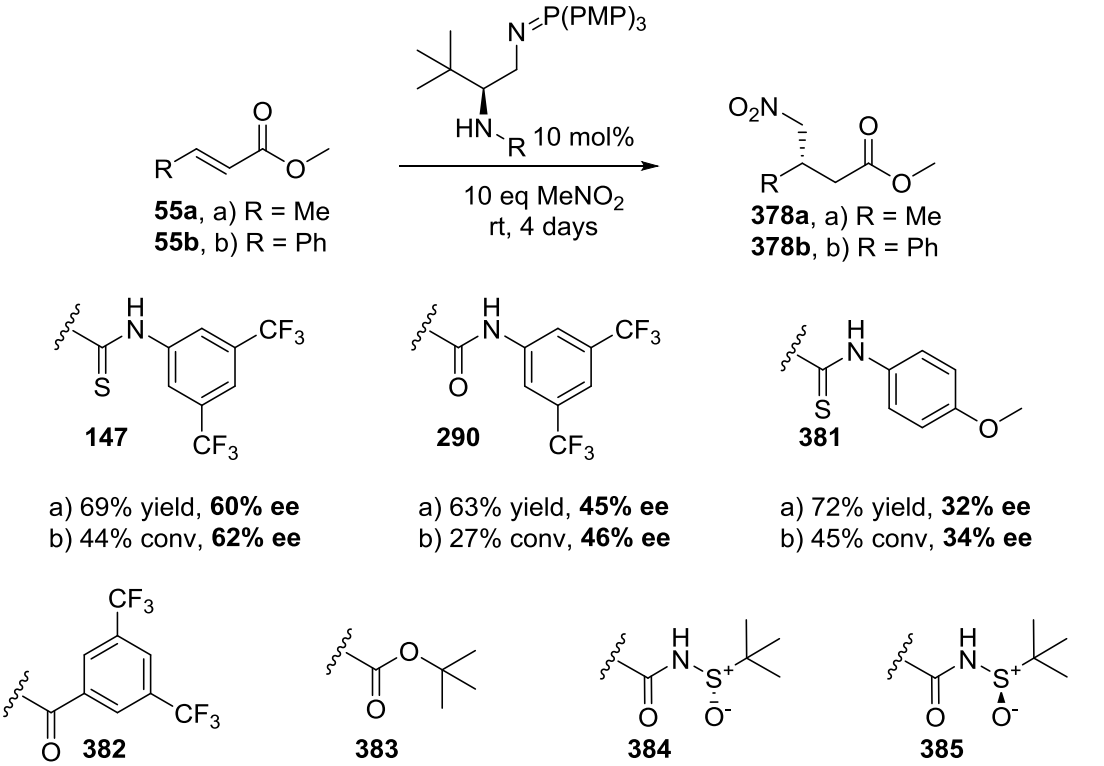
Catalysts **147**, **148** and **149** which had been isolated and characterised previously as colourless powders were weighed in directly to the reactions but all others were made *in situ* from the corresponding azide and tris(4-methoxyphenylphosphine) **146**. The catalyst formation reactions were left for 24 h at room temperature prior to the start of the reaction and the solvent removed before the addition of the reagents (Scheme 80). The L-valine and D-phenylglycine derived catalysts **379** and **148** afforded the γ-nitroesters with similar levels of enantiomeric excess as **147**. The enantiomeric excess with the L-phenylalanine catalyst **380** was marginally improved to 65% ee and the use of catalyst **149** afforded the γ-nitroester in 73% ee. The comparative reactions with methylcinnamate gave similar selectivities although conversion to the γ-nitroester was diminished.



Scheme 80 Investigation of the BIMP catalyst backbone in the addition of nitromethane to methyl crotonate and methyl cinnamate.

7.6.5 Effect of the Hydrogen-Bond Donor Group in the Addition of Nitromethane to Methyl Crotonate and Methyl Cinnamate

Despite the best enantioselectivity observed with the catalyst **149** we elected to screen a range of H-bond donor groups using the L-*tert*-leucine backbone because more examples were available in our catalyst database (Scheme 81). If an improvement was observed in enantioselectivity the analogous catalyst incorporating the benzhydryl moiety at the stereogenic centre would be synthesised and tested. Replacement of the thiourea with a urea moiety with catalyst **290** resulted in a drop in enantioselectivity to 45% and the use of **381**, an electron rich thiourea reduced the ee further. The use of catalyst **382** containing an electron deficient amide as the H-bond donor group lowered the ee to just 7% but the yield was increased to 84% in the formation of **378a**. This trend was exemplified further when the catalyst bearing a carbamate **383** was used; the ee diminished to 5 and 0% for methyl crotonate and cinnamate respectively and interestingly the yield for the formation of **378a** was quantitative.

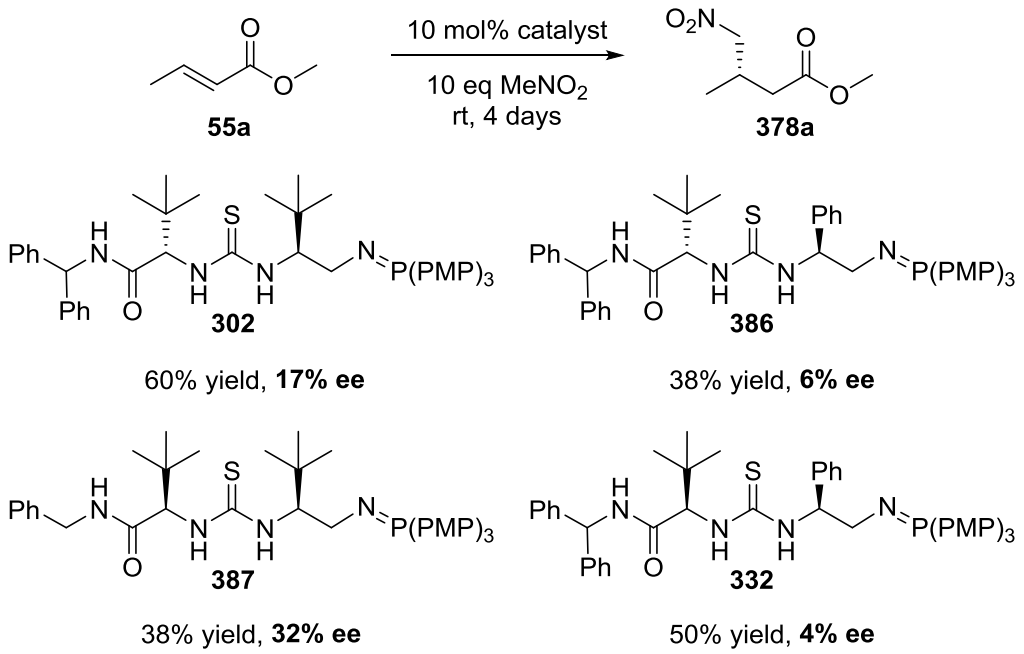


Scheme 81 H-bond donor screen in the addition of nitromethane to methyl crotonate and cinnamate.

Lastly, the diastereotopic *N*-sulfinyl urea catalysts **384** and **385** were evaluated. Ellman *et al.* developed chiral *N*-sulfinyl ureas as effective H-bond donor groups.[273] They were recently able to achieve high enantioselectivity in an enantioselective protonation reaction between α-substituted nitroalkenes and Meldrum's acid by using a catalyst that was only chiral at sulfur.[274] We incorporated the *N*-sulfinyl urea H-bond donor group with the *tert*-leucine derived 1,2-amino azide moiety. Disappointingly, although highly catalytically active, catalysts **384** and **385** did not impart good levels of enantiocontrol in the conjugate addition reaction of nitromethane to methyl crotonate or cinnamate.

From the H-bond donor group screen in Scheme 81 we concluded that an electron deficient thiourea was critical in providing good enantiocontrol in the conjugate addition. Paradoxically, the presence of the acidic thiourea H-bond appeared to retard the reaction and we therefore considered alternative catalyst designs. A subset of catalysts incorporating the thiourea amide moiety as H-bond donor groups, highly successful in the conjugate addition of thiols to α-substituted (chapter 4) and β-substituted[275] α,β-unsaturated esters were evaluated (Scheme 82).[xxxiii] Disappointingly, although the catalysts all promoted the Michael addition reaction of nitromethane to methyl crotonate the highest enantioselectivity achieved in the formation of the product **378a** was just 32% using catalyst **387**. Further development of the amide thiourea H-bond donor motif should allow the γ-nitroester to be formed with higher levels of enantiocontrol.

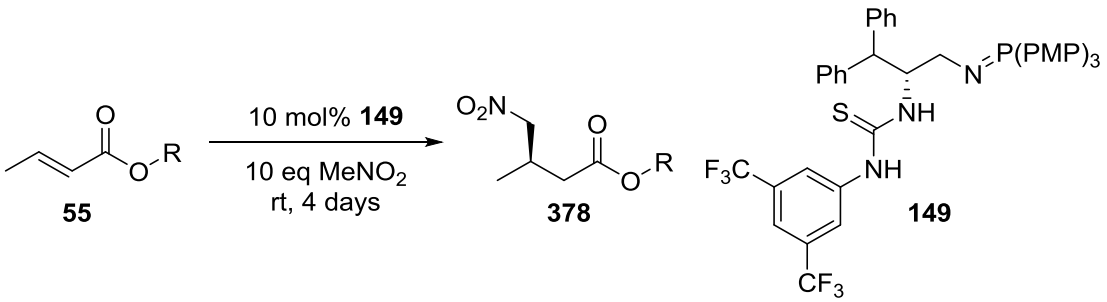
[xxxiii] The catalysts were synthesised according to the strategy outlined in section 4.4.



Scheme 82 Screen of BIMP catalysts incorporating the amide thiourea H-bond donor group in the addition of nitromethane to methyl crotonate.

7.6.6 Variation of the Ester Moiety in the Michael Addition of Nitromethane to Crotonic Esters

A broad selection of BIMP catalysts from the existing library were screened in the addition of nitromethane to methyl crotonate and methyl cinnamate with a maximum ee of 73% achieved. The opportunity was taken at this stage to briefly investigate the effect of the ester moiety of the α,β-unsaturated ester on the enantiocontrol in the Michael addition reaction with the best catalyst to date. To maximise the elegance and efficiency of the reaction, the use of simple ester moieties was desirable to increase the atom economy of the transformation.



Entry	R	55	Time / h	Product	Yield/ %	ee/ %
1	Me	**55a**	96	**378a**	75	73
2	Et	**55c**	96	**378c**	69	73
3	*i*Pr	**55d**	96	**378d**	45	56
4	Bn	**55e**	96	**378e**	89	69

Table 22 Effect of the ester moiety on the enantioselectivity in the addition of nitromethane to crotonic esters.

The Michael addition reaction using ethyl crotonate as the electrophile gave identical levels of enantiocontrol in the formation of the γ-nitroester **378c** to that observed with methyl crotonate in the formation of the γ-nitroester (Table 22, entries 1 and 2). The use of the isopropyl ester **55d** reduced the enantioselectivity in the reaction to 56% and the yield was diminished to 45% (Table 22, entry 3). The lower yield in the formation of **378d** is presumably due to increased steric interactions and reduced electrophilicity of the Michael acceptor as a result of increased inductively donating groups on the ester moiety. The γ-nitroester **378e** derived from benzyl crotonate was however synthesised in 89% yield and 69% ee (Table 22, entry 4).

The screen of the ester moiety of the β-substituted α,β-unsaturated ester revealed the enantioselectivity imparted to the γ-nitroester product **378** was only marginally affected by the ester moiety. Therefore, in the remainder of the optimisation studies methyl crotonate and cinnamate were used. Once a suitable catalyst has been identified for the efficient formation of the γ-nitroester **378** a full ester screen will be undertaken as part of the substrate scope.

7.6.7 Incorporation of Alternative Hydrogen Bond Donor Groups into BIMP Catalysts

With no improvement in the enantioselectivity observed, we decided to actively pursue new designs of organocatalysts incorporating the triaryliminophosphorane moiety. Various multifunctional tertiary amine Brønsted base H-bond donor catalysts have been proposed as superior catalysts to bifunctional catalysts (Figure 78). A publication by Lu and co-workers caught our attention where they inserted an amino acid linker into a bifunctional cinchona thiourea catalyst to yield a 'trivalent' catalyst **388**.[276] The presence of the chiral linker was found to be effective in promoting the conjugate addition of oxindoles to vinyl sulfones. In a related catalyst design, Palomo *et al.* recently introduced catalysts such as **389** which incorporated ureidopeptides as efficient H-bond donor groups, and the authors applied them in the conjugate addition of 5*H*-thiazol-4-ones to nitro-olefins; a reaction where cinchona derived bifunctional thiourea catalysts only afforded moderate levels of enantiocontrol.[277] In 2008, Wang and co-workers reported that their thiourea sulfonamide tertiary amine catalyst was highly effective in the nitro-Mannich reaction of nitroalkanes to *N*-Boc imines (Scheme 35c)[174] and in the conjugate addition of thiols to β-substituted α,β-unsaturated fluorinated esters (see section 4.2.3).[212,214,215]

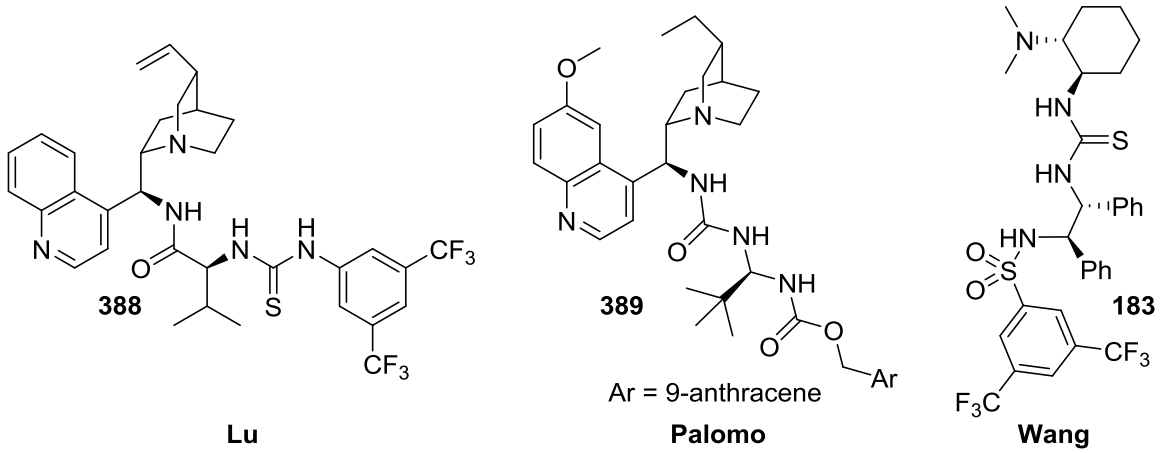
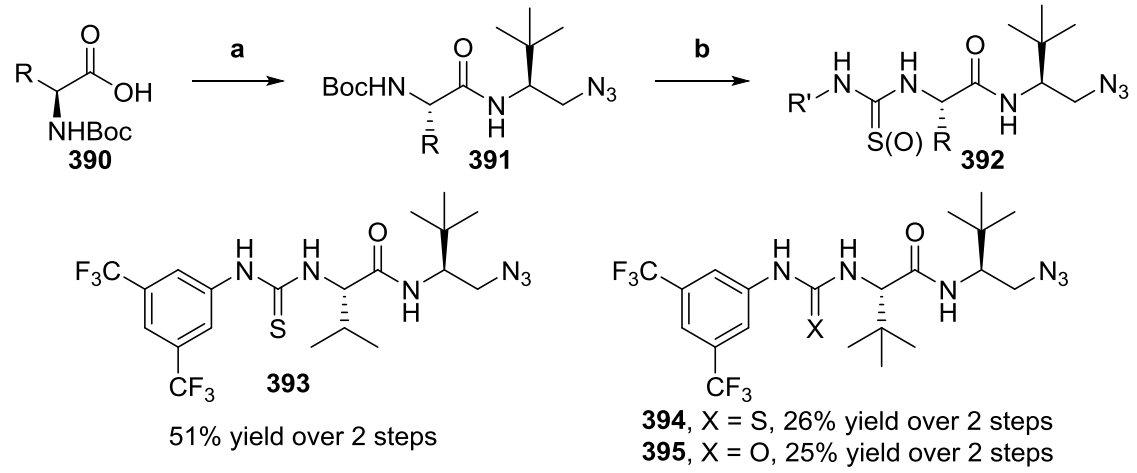


Figure 78 A selection of multifunctional tertiary amine Brønsted base H-bond donor catalysts.

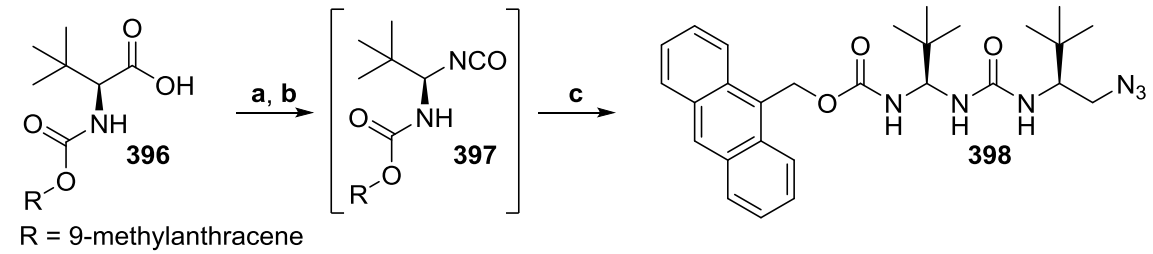
In a related strategy to that adopted during the development of the amide thiourea based BIMP catalysts in section 4.4, we incorporated the alternative H-bond donor groups with our efficacious chiral 1,2-amino azide moiety.



Scheme 83 Synthesis of BIMP catalyst precursors incorporating an amino acid linker; a: ClC(O)OEt, NEt_3, THF, 0 °C, 1 h then 125**, TFA, rt, 14 h; b: TFA, 0 °C, 2 h, then 3,5-$(CF_3)_2C_6H_3NCS$ or 3,5-$(CF_3)_2C_6H_3NCO$, Et_2O, rt, 14 h.**

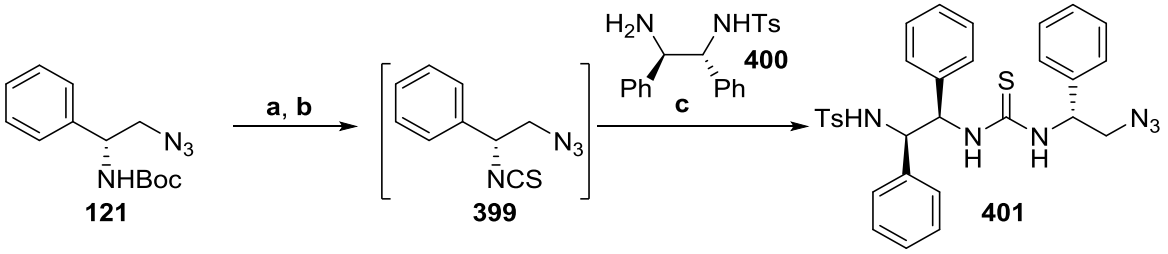
The synthesis of the catalysts containing an α-amino acid linker **392** was accomplished by activation of the *N*-Boc protected α-amino acid **390** to the mixed anhydride using ethyl chloroformate and trapping with the crude amino azide **212** [synthesised by the *N*-Boc deprotection of **125**] to afford the C-linked amino acid residue **391** (Scheme 83). Cleavage of the *N*-Boc group and coupling to an isocyanate or isothiocyanate yielded the catalyst precursors **392** in moderate yields over 2 steps.

The synthesis of a ureidopeptide containing BIMP catalyst was accomplished following an adaptation to Palomo's procedure.[277] The carboxylic acid of carbamate **390** was activated to the mixed anhydride and treated with sodium azide to afford the acyl azide. A Curtius rearrangement generated the isocyanate **397** which was trapped with amino azide **212** to give the BIMP precursor **398** in 40% yield over three steps.



Scheme 84 Synthesis of ureidopeptide azide 398**; a: ^{i}BuOC(O)Cl, NMM, THF, –20 °C, 20 min; b: NaN_3, CH_2Cl_2, reflux, 2 h; c:** 125**, TFA then CH_2Cl_2, 16 h, 40% yield over three steps.**

To accomplish the synthesis of a thiourea sulfonamide catalyst, the crude isothiocyanate **399**, synthesised by the *N*-Boc deprotection of **121** and then treatment with thiophosgene, was condensed with diphenyl diamine **400** to yield the azide **401** in 53% yield.

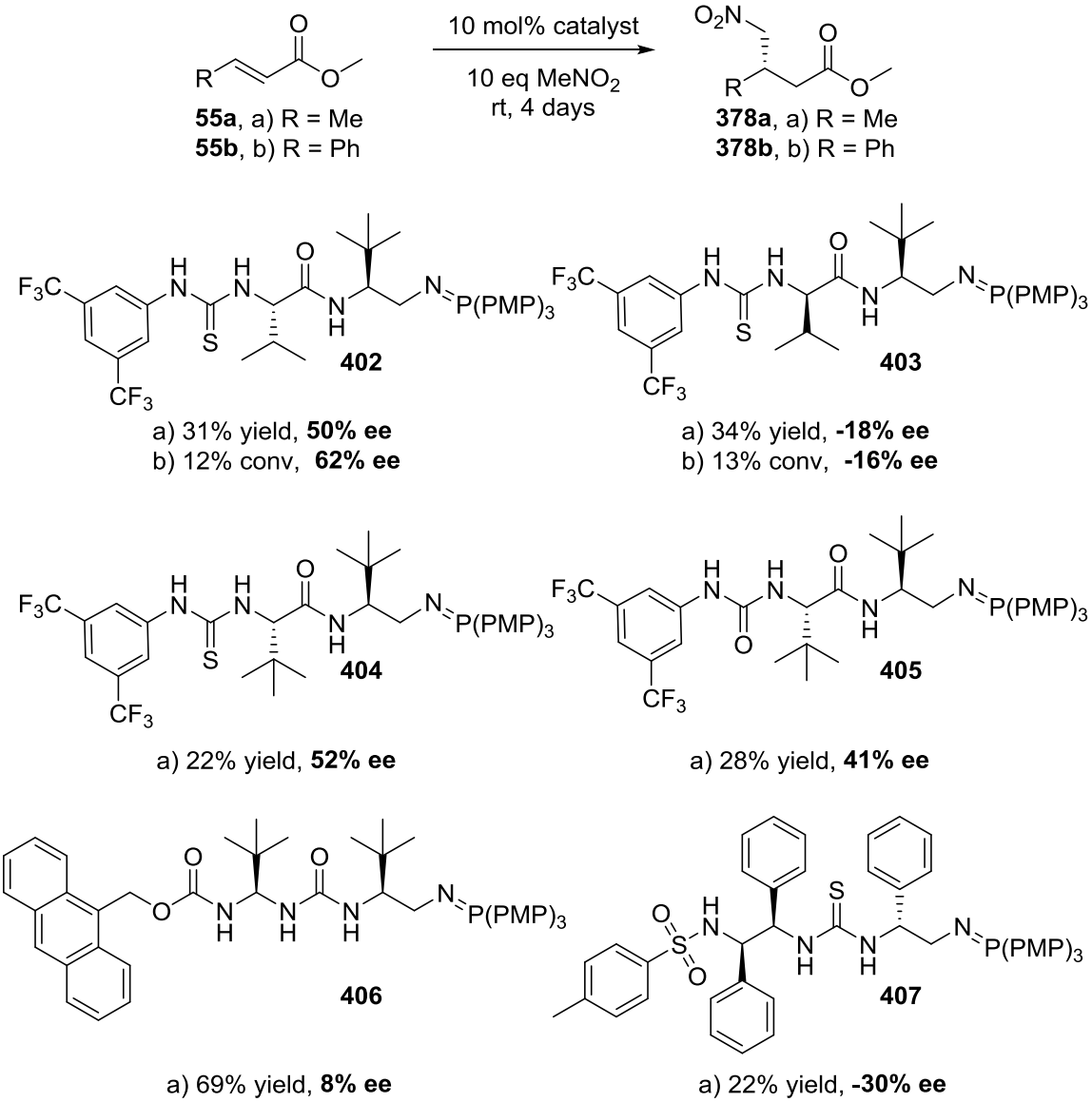


Scheme 85 Synthesis of thiourea sulfphonamide azide 401**; a: TFA, 0 °C, 2 h; b: $Cl_2C(S)$, $NaHCO_3$, CH_2Cl_2, 0 °C, 30 min, c:** 400**, THF, rt 14 h, 53% over 3 steps.**

7.6.8 Evaluation of Novel Multivalent Iminophosphorane Catalysts

With a variety of new azide containing alternative H-bond donor groups synthesised, we next evaluated the performance of the corresponding active iminophosphorane catalysts in the conjugate addition of nitromethane to methyl crotonate and methyl cinnamate (Scheme 86). Tris(4-methoxyphenylphosphine) was used as the phosphine component for sake of comparison. Catalyst **402**, containing L-valine as the linker afforded the γ-nitroester **378a** in 50% ee but only in a modest yield of 31% and the result with methyl cinnamate as the electrophile was similar. The diastereomeric catalyst **403**, using D-valine as a linker, gave similarly low levels of conversion but with significantly impaired levels of enantiocontrol. The opposite major enantiomer was obtained showing that in this catalyst system the distal stereocenter was dominant, which is in contrast to that observed for the BIMP catalysts incorporating the amide thiourea H-bond donor groups (see section 4.4).

This suggested that alternative catalyst designs which do not incorporate the *tert*-leucine derived aminoazide moiety may be more effective in imparting higher levels of enantiocontrol in the reaction. Catalysts incorporating L-*tert*-leucine as a linker were evaluated but there was only a marginal improvement in enantioselectivity to 52% ee when using **404**. The urea analogue **405** reduced the enantioselectivity to 41%.



Scheme 86 Evaluation of alternative H-bond donor group catalysts in the addition of nitromethane.

The ureidopeptide iminophosphorane **406**, synthesised by performing the Staudinger reaction in CH_2Cl_2 due to poor solubility of the azide in Et_2O, was evaluated and found to be highly catalytically active in the reaction. Disappointingly the product was only formed in 8% ee. Finally, the enantioselectivity in the formation of γ-nitroester **378a** using

thiourea sulfonamide catalyst **407** was 30%, however the product was formed in just 22% yield. Further structure-activity-enantioselectivity relationships and overall improvements to these novel catalyst designs are clearly required.

7.6.9 Investigations into the Nature of the Iminophosphorane Moiety

The modular design of the BIMP catalysts (section 2.1 and Figure 79) facilitated the generation of a library of catalysts with three points of diversity. In both the ketimine nitro-Mannich reaction (chapter 3) and the sulfa-Michael addition (chapter 4) the effect of the catalyst backbone and H-bond donor groups on the enantioselectivity of the reaction was extensively investigated. However, fewer alterations to the phosphine component and hence iminophosphorane moiety of the BIMP catalysts were made. A full evaluation of the iminophosphorane moiety in the aforementioned transformations was not required as the products were successfully formed with high levels of enantiomeric excess by varying the H-bond donor group and the catalyst backbone.

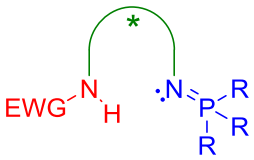
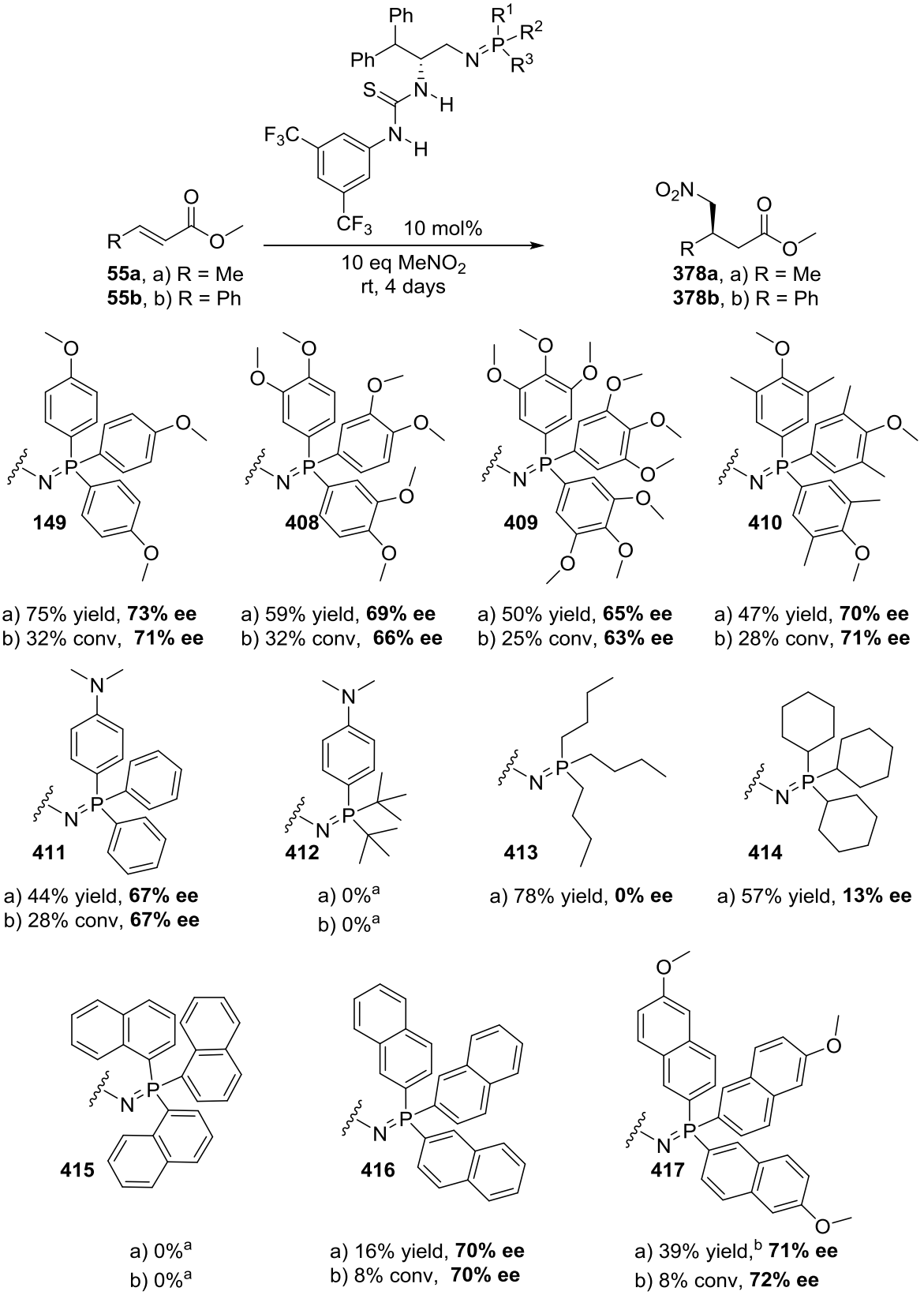


Figure 79 Original BIMP catalyst design.

The Michael addition of nitromethane to β-substituted α,β-unsaturated esters was therefore an ideal platform with which to investigate further catalyst structures. L-Serine derived BIMP catalysts incorporating the benzhydryl moiety at the stereogenic centre and the 3,5-$(CF_3)_2C_6H_3$ thiourea were synthesised with a range of trivalent phosphines and evaluated (Scheme 87).



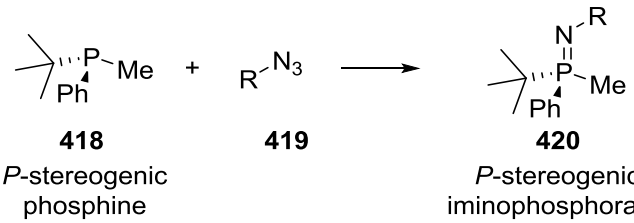
Scheme 87 Screen of the phosphine moiety in the addition of nitromethane to methyl crotonate and cinnamate; [a] The synthesis of the iminophosphorane was attempted at 100 °C in toluene for 20 h; [b] reaction was performed in 0.20 mL of toluene as cosolvent due to the limited solubility of 417 **in nitromethane.**

Increasing the electron density on the phosphine by the addition of methoxy units or methyl substituents in the *meta* position with catalysts **408 - 410** did not increase the ee in the formation of **378a** or **378b**. Incorporating *tert*-butyl groups into the phosphine was not successful and this is likely due to difficulties associated with synthesising the iminophosphorane. In general, the synthesis of iminophosphoranes with phosphines containing *ortho* substituted aryls, or branched alkyls groups was problematic even when performing the Staudinger reaction at elevated temperatures which can probably be attributed to increased repulsive steric interactions in the extrusion of N_2 from the phosphazide intermediate (Scheme 13). Incorporation of linear or cyclic alkyl phosphines to afford the catalysts **413** and **414** was successful; however the ability of the catalysts to impart enantiocontrol in the formation of **378a** or **378b** was significantly reduced. The use of $P(1\text{-}Np)_3$ derived BIMP **415** did not yield the γ-nitroester addition product and this is likely due to issues with the formation of the iminophosphorane. The 2-substituted naphthyl derivatives **416** and **417** were however catalytically active and gave similar enantioselectivities in the formation of **378a** or **378b** to catalyst **149**. The rate in the Michael addition reaction with **417** was enhanced relative to **416** as a result of the EDG on the aromatic. Due to the poor solubility of catalyst **417** in 10 eq of nitromethane, an equal volume of CH_2Cl_2 as cosolvent was added.

From the screen of BIMP catalysts incorporating a range of trivalent phosphines (Scheme 87), it was evident that the nature of the iminophosphorane played a crucial role in imparting enantiocontrol in the formation of **378a** or **378b**. Unfortunately, to date a superior phosphine to tris(4-methoxyphenylphosphine) has not been identified and further phosphine components should be considered.

7.6.10 Iminophosphorane Catalysts Bearing P-Stereogenic Phosphines

In an attempt to increase the enantioselectivity in the formation of γ-nitroesters **378a** or **378b**, we considered the incorporation of *P*-stereogenic phosphines into the BIMP catalyst design. *P*-Stereogenic phosphines are trivalent phosphines with three different substituents around the central phosphorous atom and are increasingly important ligands in asymmetric synthesis. For example in 2012, Riera and Verdaguer described the use of *P*-stereogenic iminophosphoranes as ligands in a rhodium catalysed enantioselective [2+2+2] cycloaddition of enediyines.[278] Numerous methods have been developed for the preparation of *P* stereogenic preparation such as the use of chiral auxiliaries[279] or by resolution methods[280] and recently catalytic asymmetric variants have also been reported.[281]

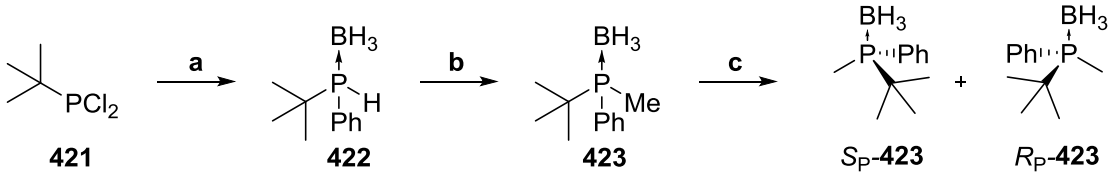


Scheme 88 A representative *P*-stereogenic iminophosphorane derived from a chiral or achiral azide.

We hypothesised that the use of *P*-stereogenic phosphines as the phosphine component of the iminophosphorane would enhance the enantioselectivity imparted in the formation of β-nitroester **378a**. To establish a proof of principle that *P*-stereogenic iminophosphoranes were effective Brønsted bases phosphine **418** was selected (Scheme 88).

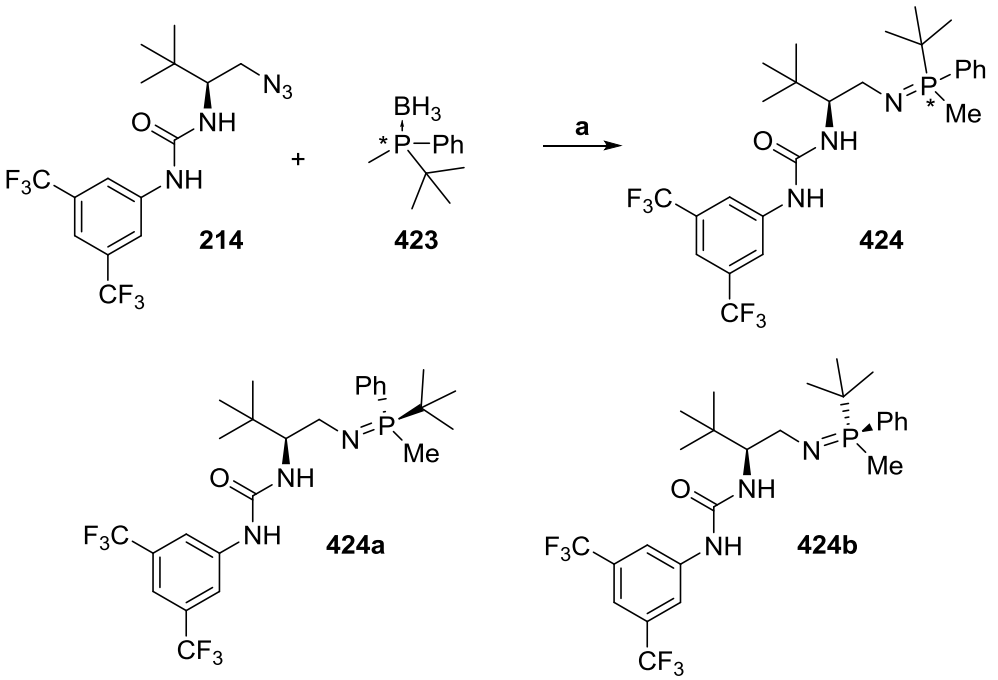
To enable rapid access of both enantiomers of the chiral tertiary phosphine we elected to use preparative chiral HPLC. As tertiary phosphines containing one more alkyl substituents are susceptible to oxidation the phosphines were synthesised and stored as the phosphine borane complex **423** (Scheme 89). Furthermore, HPLC conditions for the analytical separation of the enantiomers of **423** have been reported. The racemic tertiary phosphine borane complex was synthesised in two steps from *tert*-butyldichlorophosphine **421**. *Tert*-

Butyldichlorophosphine was treated at –78 °C with 1 equivalent of phenylmagnesium bromide and to the reaction mixture were sequentially added lithium aluminium hydride and BH_3•THF to afford the secondary phosphine borane **422** in 64% yield. The synthesis of the racemic tertiary phosphine borane **423** was accomplished by deprotonation of **422** using ^{n}BuLi and subsequent quenching with methyl iodide to afford rac-**423** in 91% yield.



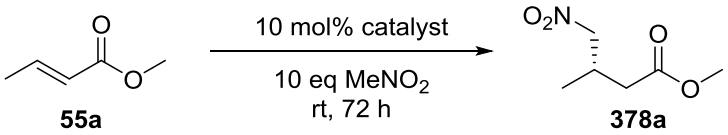
Scheme 89 a: PhMgBr, THF, -78 °C to rt, 1 h, then $LiAlH_4$, BH_3•THF, 0 °C to rt, 14 h, 64% yield; b: ^{n}BuLi, Et_2O, –78 °C to rt, 1 h then MeI, –78 °C to rt, 14 h, 91% yield; c: preparative chiral HPLC, Chiralpak-AS, 99:1 hexane :^{i}PrOH.

The enantiomers of **423** were then separated by preparative chiral HPLC (up to 40 mg injected per run) with a maximum of 6 mg of each enantiomer obtained with >98% ee and the remainder of the material was recovered as mixtures of the two enantiomers. The poor separation on the chiral HPLC column and apolar nature of **423** prevented the separation of more enantiopure samples of **423** per injection. Nevertheless, sufficient quantities of each enantiomer were obtained to perform proof of concept experiments.



Scheme 90 Synthesis of *P*-stereogenic BIMPs 424a **and** 424b**; a: DABCO, toluene, 55 °C, 2 h then** 214**, 16 h, 55 °C.**

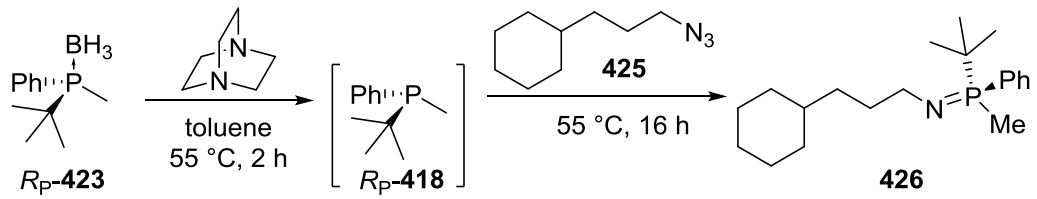
According to a procedure by Giordano and Buono, the enantiopure free phosphine **418** was synthesised by treatment of **423** with DABCO in toluene for 2 h at 55 °C (Scheme 90).[282] To avoid isolation of the phosphine, azide **214** was added to the reaction mixture and stirring maintained for 16 h. Analysis by LRMS and TLC were taken as evidence for the formation of the iminophosphorane which was then used crude as catalyst in the addition of nitromethane to methyl crotonate.



Entry	Catalyst	Yield/ %	ee/ %
1	**424a**	43	13
2	**424b**	40	16
3	**426**	84[a]	0

Table 23 Evaluation of *P*-stereogenic iminophosphorane catalysts in the addition of nitromethane to methyl crotonate; [a] Reaction was quenched after 48 h.

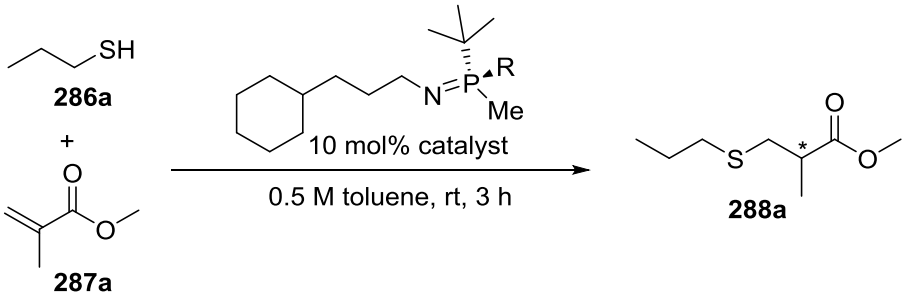
Disappointingly, the enantioselectivity imparted by the diastereomeric catalysts **424a** and **424b** was significantly reduced to 13 and 16% ee respectively in the addition of nitromethane to methyl crotonate (Table 23, entries 1 and 2). Catalyst **426**, derived from the achiral azide **425** was synthesised (Scheme 91) and evaluated in the Michael addition reaction and although it was highly catalytically active there was no enantiocontrol imparted in the formation of **378a** (Table 23, entry 3).



Scheme 91 Synthesis of 426**.**

Whilst the *P*-stereogenic catalyst **426** was unable to impart any enantioselectivity in the formation of **378a**, we postulated that it may be efficacious in the sulfa-Michael addition of 1-propanethiol **286a** to methyl methacrylate **287a** as the enantiodetermining step in this reaction is protonation of the prochiral transient enolate (section 4.8). Accordingly, we

evaluated **426** in the SMA reaction under the previously developed conditions for the screen of catalysts (Figure 41) and **288a** was afforded in excellent yield with a modest 5% ee (Table 24, entry 1). The analogous reaction was performed with catalyst **427**, bearing a 1-naphthyl group as the aromatic substituent.[xxxiv] Although the reaction rate was slightly diminished the enantioselectivity was marginally enhanced to 8% (Table 24, entry 2).



Entry	R	Catalyst	Yield/ %	ee/ %
1	Ph	**426**	99	5
2	1-Np	**427**	57	8

Table 24 Evaluation of *P*-stereogenic iminophosphoranes 426 **and** 427 **in the SMA reaction between propanethiol and methyl methacrylate.**

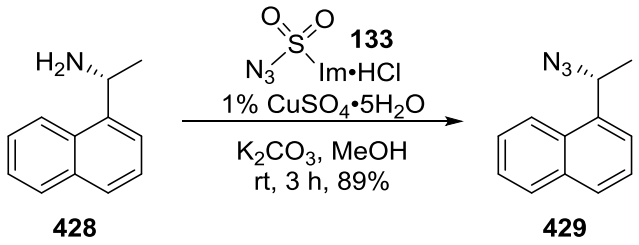
Although the enantioselectivities imparted by the *P*-stereogenic iminophosphoranes were low, a proof of principle has nevertheless been established. Further work exploring this catalyst design is clearly required and variations to both the azide component and the stereogenic phosphine moiety should be studied.[xxxv] Alternative iminophosphorane catalysts derived from commercially available enantiomerically pure phosphines should also be evaluated with both chiral and achiral azides. As many chiral phosphine ligands are readily available, this would rapidly allow access diversification of the catalyst library. Due to time constraints, this catalyst design has not been fully investigated but with

[xxxiv] The iminophosphorane catalyst **427** was synthesised in an analogous manner to **426** (see Section 8.2.11).
[xxxv] To further evaluate the *P*-stereogenic iminophosphorane catalyst design an alternative synthesis of the chiral phosphines is required as only small quantities of **423** could be separated per injection on the HPLC due to poor separation of the enantiomers. In preliminary work to this end, we were able to separate the enantiomers of secondary phosphine oxides by preparative chiral HPLC with injections of up to 300 mg of the racemate.

sufficient optimisation, iminophosphorane catalyst incorporating *P*-stereogenic phosphines and other enantiopure phosphines should be effective asymmetric organocatalysts.

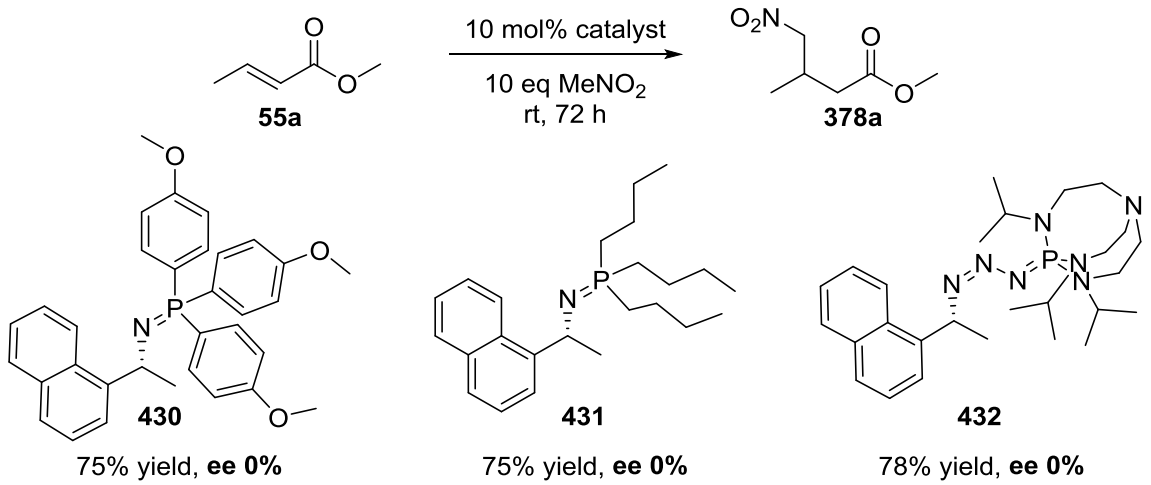
7.6.11 Miscellaneous Iminophosphorane Structures in the Michael Addition Reaction of Nitromethane to Methyl Crotonate

Several chiral iminophosphoranes that did not contain a hydrogen bond donor group were synthesised and evaluated in the addition of nitromethane to methyl crotonate. Enantiopure naphthyl amine **428** was reacted with the diazotransfer reagent **133** to afford **429** in good yield (Scheme 92).



Scheme 92 Synthesis of azide 429 ***via*** **diazotransfer.**

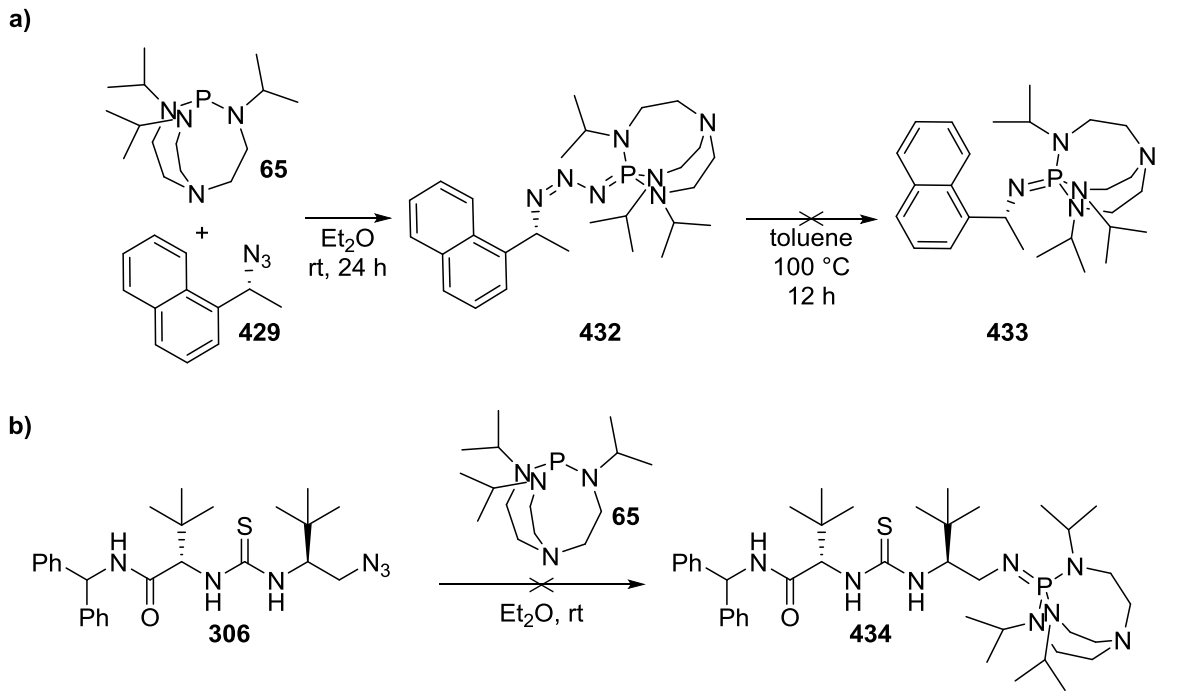
The active iminophosphorane catalysts could be then be made *in situ* and evaluated in the conjugate addition of nitromethane to methyl crotonate. Catalysts **430** and **431** derived from tris(4-methoxyphenylphosphine) and tributylphosphine respectively were synthesised at room temperature and were both highly catalytically active in the Michael addition reaction (Scheme 93). There was however no enantiocontrol imparted from the chiral azide backbone and in both cases **378a** was formed as the racemate.



Scheme 93 Evaluation of 1-naphthyl azide derived iminophosphorane catalysts 430 – 432 **in the Michael addition of nitromethane to crotonate.**

An attempt was also made to synthesise an iminophosphorane catalyst from a Verkade base (proazaphosphatrane).[283] At room temperature, the Verkade base **65** was treated with 1.1 eq of azide **429** and the reaction stirred for 24 h (Scheme 94 a). The slight excess of azide was used to ensure that all the strongly Brønsted basic Verkade base was consumed, to avoid **65** acting as the catalytic species. After 24 h, the exclusive formation of the phosphazide was observed by LRMS and we opted to evaluate it in the Michael addition reaction. Pleasingly **432** was found to be catalytically active but was unable to impart any enantiocontrol in the formation of **378a**. To generate the iminophosphorane equivalent, the Staudinger reaction would need to be performed at high temperature to extrude nitrogen gas. An initial attempt to generate **433** was made by heating the azide and **65** at 100 °C for 12 h; however several phosphorous species were observed in the ^{31}P NMR spectrum of the reaction mixture and therefore the reaction mixture was not evaluated in the conjugate addition reaction.

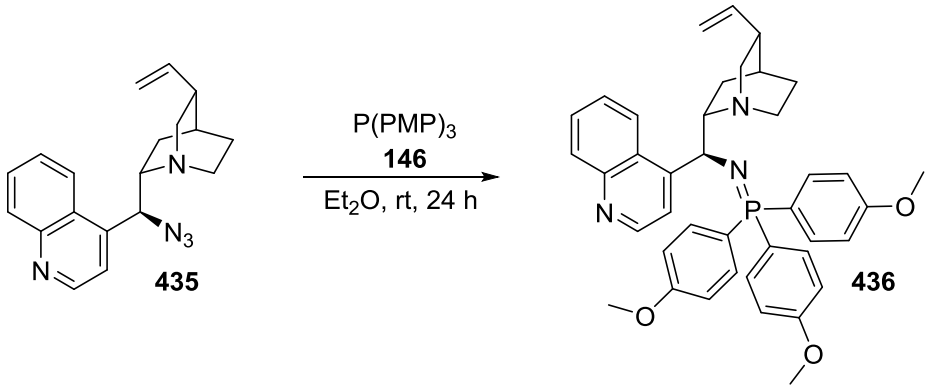
An attempt was also made to incorporate the Verkade base into a bifunctional catalyst bearing a non-acidic thiourea moiety but the Staudinger reaction did not proceed between azide **306** and **65** (Scheme 94b). We assumed this was due to protonation of the proazaphosphatrane **65** from a thiourea proton as a result of the high basicity of **65**.



Scheme 94 a) Synthesis of 432 **and attempted synthesis of iminophosphorane** 433**; b) attempted incorporation of a Verkade base as the phosphine moiety with an azide incorporating a non-acidic thiourea group.**

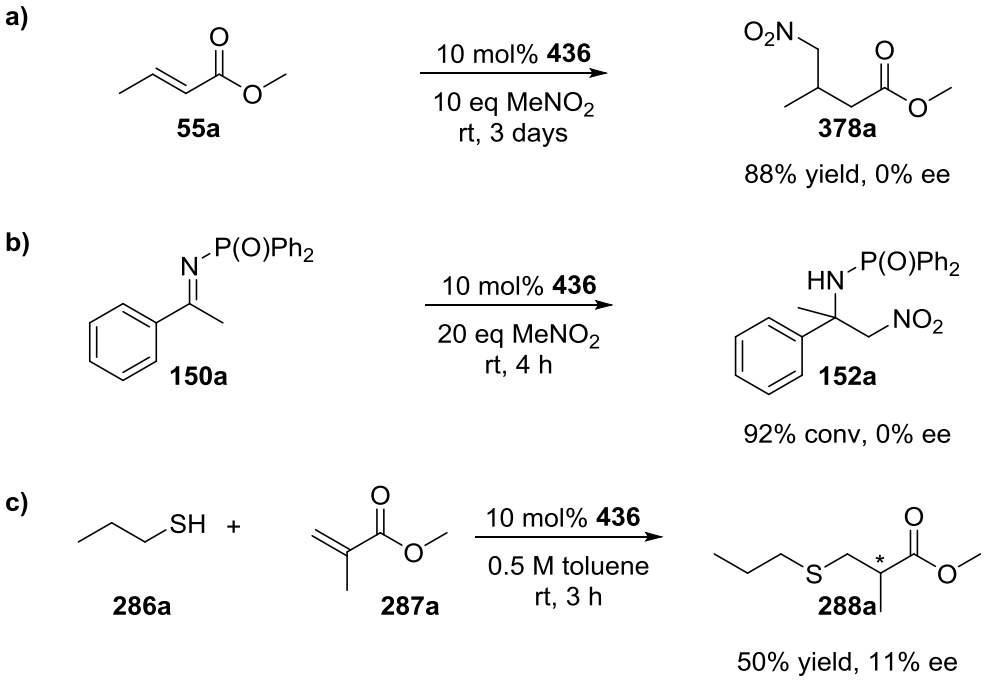
Alternatively, we considered the use of cinchona alkaloids as the chiral backbone as they have been shown to be an incredible source of chirality for a diverse range of asymmetric transformations in organocatalysis and as ligands.[284] Initial work in the Dixon Group on chiral superbases focussing on P1-phosphazenes (triaminoiminosphosphoranes), utilised the cinchona alkaloid structure as the chiral backbone (Scheme 10).[114] The catalyst imparted a modest level of enantiocontrol in the ring opening of aziridines using β-ketoesters, a reaction that necessitates strong bases to proceed.

In a similar vein, we synthesised triaryliminophosphorane catalyst **436** from azide **435** and tris(4-methoxyphenylphosphine) **146** at rt for 24 h in Et_2O (Scheme 95). TLC and low resolution mass spectrometry were taken as evidence for the formation of the active catalyst which was used *in situ*.



Scheme 95 Synthesis of cinchona derived triaryliminophosphorane.

The catalyst **436** was tested in the addition of nitromethane to methyl crotonate **55a** and whilst excellent levels of reactivity where observed there was no stereocontrol in the formation of **378a** reaction (Scheme 96a). As a comparison, the ketimine nitro-Mannich reaction between **150a** and nitromethane was tested and similarly, the reaction proceeded rapidly with near full conversion after 4 hours but the product **152a** was formed as the racemate (Scheme 96b).



Scheme 96 Evaluation of the efficacy of catalyst 436 **in a) the addition of nitromethane to methyl crotonate; b) the ketimine nitro-Mannich reaction; c) the SMA of propanethiol methyl methacrylate.**

Finally, catalyst **436** was evaluated in the sulfa-Michael addition of 1-propanethiol **286a** to methyl methacrylate **287a** under the same catalyst screening conditions used in Section 4.4 (Scheme 96c). Pleasingly, the β-mercaptoester **288a** was formed in 11% ee. As the

enantiodetermining step in this reaction is the protonation of the transient prochiral enolate, it seems reasonable that catalyst **436** by providing a chiral proton source (from the protonated iminophosphorane) could offer some asymmetric induction in the SMA reaction to α-substituted α,β-unsaturated esters.

Although catalyst **436** was shown to be an effective Brønsted base as it catalysed the three aforementioned reactions that required the use of organosuperbases to proceed, it did not appear to have the structural requirements to be an effective chiral catalyst. Further work into this class of catalyst should investigate the possibility of incorporating a H-bond donor group such as a hydroxyl or thiourea moiety into the catalyst design (Figure 80).

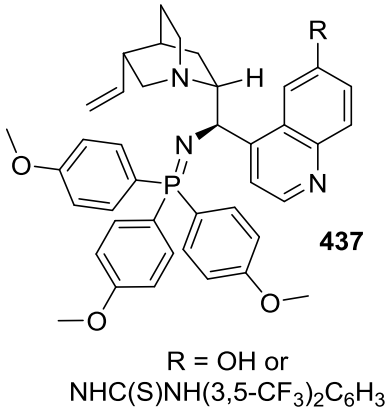


Figure 80 Putative design for further cinchona alkaloid triaryliminophosphorane catalysts.

7.7 Conclusion

This chapter has highlighted the performance of the bifunctional iminophosphorane catalysts in a range of transformations. We actively pursued the complimentary aspects of new reactivity leading to novel catalyst designs and the addition of nitromethane to unactivated β-substituted α,β-unsaturated esters was chosen as the platform for extensive catalyst development. Quantitative yields were obtained and enantioselectivities of up to 73% demonstrated. Further optimisation is required in order to strike the optimal balance between rate and enantiocontrol. Several preliminary novel catalyst systems have been

synthesised and evaluated but further structure-activity-enantioselectivity relationships are required to exploit the full efficacy of the designs.

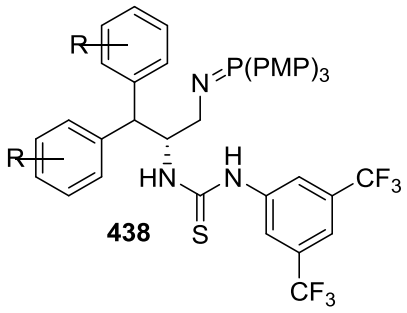


Figure 81 Structural modifications to the substituent at the stereogenic centre of a BIMP catalyst for further catalyst development to optimise the addition of nitromethane to β-substituted α,β-unsaturated esters.

Due to time constraints, we have been unable to improve the enantiocontrol in the conjugate addition reaction and as a first port of call, variations to the substituents at the stereogenic centre should be investigated in the catalysts shown in Scheme 80 such as catalyst **438** (Figure 81). Modifications to the aromatic groups of the benzhydryl moiety should have an effect on the enantioselectivity and rate in the addition of nitromethane to α,β-unsaturated esters. These catalysts can be synthesised by the nucleophilic attack of the corresponding aromatic Grignard to the serine ester using the same strategy outlined in Section 2.4.3. The full substrate scope of the reaction between β-substituted α,β-unsaturated esters and nitromethane will be investigated once the appropriate catalyst has been identified.

7.8 Concluding Remarks and Future Directions

Over the course of the DPhil, the new class of bifunctional catalysts, incorporating a novel organosuperbase, have been shown to be efficacious in a range of challenging asymmetric transformations. We have successfully applied the catalysts on preparative scale (10 and 20 g scale) to two novel methodologies, where tertiary amine bifunctional organocatalysts are impotent, with efficient loadings as low as 0.05 mol%. The methodologies were of

broad scope and in each case the products were derivatised to highlight the synthetic utility of the enantioenriched products. Rate enhancements by up to a factor of 1300 have been demonstrated relative to a tertiary amine bifunctional organocatalysts in a known challenging Michael addition reaction.

In the pursuit of enhancing the enantiocontrol in reactions of interest, many catalyst designs were proposed and the iterative changes evaluated. Whilst some catalysts consistently performed better than others, there was no 'go to' catalyst that was able to catalyse all reactions with high levels of enantiocontrol. To alleviate this, the creation of a catalyst library that can enable rapid catalyst screening – much like that used in the optimisation of ligands for transition metal catalysed reactions – was critical.

Initial conformational studies of select BIMP catalysts revealed interesting dynamic behaviour in solution. Further work into the full elucidation of catalyst ground and reaction transition states, through the aid of computational analysis, kinetic and NMR studies will provide insights into directions for future catalyst designs.

Throughout the project, we sought to address some of the perceived limitations, largely high catalyst loadings and long reaction times, associated with the use of organocatalysis as a widespread technology in industry as a green and environmentally benign alternative to metal based catalysts. We anticipate that with the advances developed during this DPhil and from other research groups around the world, organocatalysis will continue to find broad use in the pharmaceutical, agrochemical and fine chemical industries in the near future.

8 Experimental

8.1 General experimental

8.1.1 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.

8.1.2 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.

8.1.3 Spectroscopy

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded using Bruker DPX-200, Bruker DPX-400, Bruker DQX-400, Bruker AVIII400, Bruker AVC-500 and Bruker DRX-500 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 (ESI) 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; $\mathbf{[\alpha]_D^T}$ 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). (+) and (–) compound number prefixes indicate the sign of the optical rotation. **Enantiomeric excesses** were determined by HPLC analysis on an Agilent 1200 Series instrument using a chiral stationary phase column specified in the individual experiment or by GC analysis on an Agilent 7820A instrument employing a chiral stationary phase column specified in the individual experiment and by comparing the samples with the appropriate racemic mixtures.

8.1.4 Melting points

Melting points (MP) were recorded in degrees Celsius (°C), using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected.

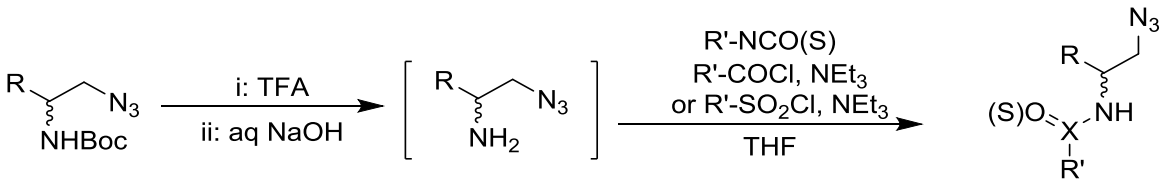
8.1.5 Compound naming

Compound names are those generated by ACD LABS 12.0 software following the IUPAC nomenclature.

8.2 Synthesis of Iminophosphorane Precursors and Catalysts

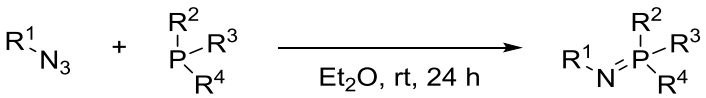
8.2.1 General Procedures

General Procedure I**: Synthesis of BIMP Azide Precursors from *N*-Boc Amino Azides**



To the *N*-Boc protected amino azide 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 (brine), dried ($MgSO_4$) and concentrated under a N_2 stream. The crude reaction was diluted with THF (0.29 M) and the iso(thio)cyanate (1.1 eq) [or acyl/sulfonyl chloride (1.1 eq) and triethylamine (1.2 eq)] were added. Stirring was maintained for 14 hours and the volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography and/or trituration as specified in the individual experiment to afford the catalyst precursor.

General Procedure II **for the *In Situ* Generation of BIMP Catalysts**



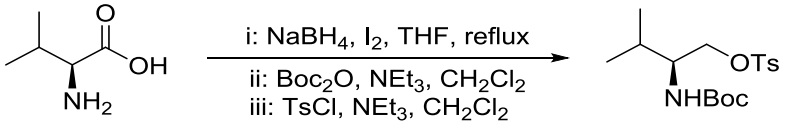
To the corresponding organoazide (0.020 mmol, 1.0 eq) and trivalent phosphine (0.020 mmol, 1.0 eq) under an argon atmosphere was added Et_2O (0.1 mL) and the reaction mixture stirred at rt for 24 h. The formation of the iminophosphorane catalyst was

confirmed by LRMS and TLC, and the volatiles were removed under a stream of nitrogen to yield the crude product which was used as a catalyst without further purification.

8.2.2 Synthesis of L-Valine-Derived Scaffold

8.2.2.1 Synthesis and characterisation of 118

(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutyl 4-methylbenzenesulfonate **118**



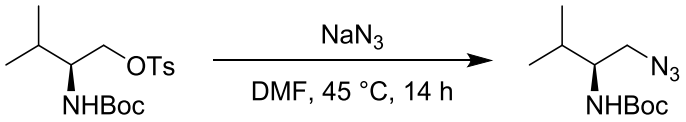
According to a modified literature procedure,[145] to a solution of sodium borohydride (3.47 g, 91.5 mmol, 2.4 eq) in THF (100 mL) was added L-valine (4.46 g, 38.1 mmol, 1.0 eq). The reaction mixture was cooled to 0 °C and a solution of iodine (9.64 g, 38.1 mmol, 1.0 eq) in THF (25 mL) was added dropwise *via* cannula 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 (50 mL) and stirring was maintained for 3 hours and the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL), washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. The crude material was dissolved in CH_2Cl_2 (135 mL) and triethylamine (6.28 mL, 45.5 mmol, 1.18 eq) was added and the reaction mixture was cooled to 0 °C using an ice bath. Boc anhydride (9.8 g, 45.5 mmol, 1.18 eq) was added and stirring was maintained at 0 °C for one hour and then 8 hours at room temperature. The reaction mixture was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and volatiles removed *in vacuo*. Purification by flash column chromatography [4:1 Petrol: EtOAc then 3:2 Petrol: EtOAc]

afforded the *N*-Boc protected amino alcohol as a pale yellow oil in 68% yield (5.09 g). To a solution of the amino alcohol (1.9 g, 9.4 mmol, 1.0 eq) in CH_2Cl_2 (31 mL) at 0 °C were added sequentially triethylamine (1.6 mL, 11.3 mmol, 1.2 eq) and *p*-toluenesulfonyl chloride (1.95 g, 10.3 mmol, 1.1 eq). Stirring was maintained for 16 h whereupon the reaction mixture was partitioned by the addition of H_2O (30 mL) and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organics were washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [4:1 Petrol: EtOAc then 3:2 Petrol: EtOAc] afforded the title compound **118** as a colourless solid in 68% yield (2.28 g).

MP 70 -74 °C [lit. 64 - 65 °C][285]; $\mathbf{[\alpha]_D^{23}}$ = - 15.0 (c = 0.80, $CHCl_3$), [lit -20.8, c = 3.50][285]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.88 (d, *J* = 7.0 Hz, 3 H, ($C\underline{H}_3$)CH(CH_3)), 0.92 (d, *J* =7.0 Hz, 3 H, (CH_3)CH($C\underline{H}_3$)), 1.43 (s, 9 H, OC($C\underline{H}_3$)$_3$), 1.76 - 1.93 (m, 1 H, (CH_3)C$\underline{H}$(CH_3)), 2.47 (s, 3 H, Ar$C\underline{H}_3$), 3.46 - 3.57 (m, 1 H, C$\underline{H}$C$H_A$$H_B$O), 4.04 (dd, *J* = 10.0, 3.5 Hz, 1 H, CHC$\underline{H}_A$$H_B$O), 4.11 (dd, *J* =10.0, 3.5 Hz, 1 H, CHC$H_A$$\underline{H}_B$O), 4.62 (d, *J* = 9.0 Hz, 1 H, N$\underline{H}$), 7.37 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}$), 7.81 (d, *J* = 8.0 Hz, 2 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 18.8 (($\underline{C}H_3$)CH(CH_3)), 19.4 ((CH_3)CH($\underline{C}H_3$)), 21.8 (Ar$\underline{C}H_3$), 28.4 (OC($\underline{C}H_3$)$_3$), 29.1 ((CH_3)$\underline{C}$H(CH_3)), 54.9 ($\underline{C}$HC$H_A$$H_B$O), 70.2 (CH$\underline{C}$$H_A$$H_B$O), 79.7 (O$\underline{C}$($CH_3$)$_3$), 128.1 (Ar$\underline{C}$H), 130.0 (Ar$\underline{C}$H), 132.6 (Ar$\underline{C}$), 145.1 (Ar$\underline{C}$), 155.6 ($\underline{C}$=O). Data is consistent with that given in the literature.[286]

8.2.2.2 Synthesis and characterisation of 116

tert-Butyl [(2*S*)-1-azido-3-methylbutan-2-yl]carbamate 116

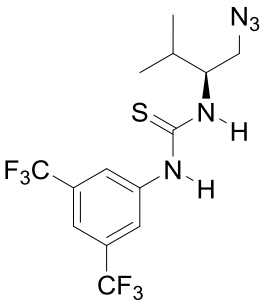


To a stirred solution of tosylate **118** (2.28 g, 6.38 mmol, 1 eq) in DMF (21 mL) was added sodium azide (456 mg, 7.02 mmol, 1.1 eq) at room temperature. The reaction mixture was warmed to 45 °C and stirring was maintained for 14 h. The reaction mixture was cooled to room temperature then diluted with water (50 mL) and Et_2O (30 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organics were washed with brine (30 mL) and dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography [petrol then 4:1 petrol: Et_2O] to afford the title compound **116** as a pale yellow amorphous solid (740 mg, 51 % yield).

$[\alpha]_D^{23}$ = -23.0 (c = 0.50, $CHCl_3$), [lit -31.2, c = 0.17][287]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.92 (d, *J* = 7.0 Hz, 3 H, ($C\underline{H}_3$)CH(CH_3)), 0.94 (d, *J* = 7.0 Hz, 3 H, (CH_3)CH($C\underline{H}_3$)), 1.44 (s, 9 H, OC($C\underline{H}_3$)$_3$), 1.79 ('octet', *J* = 7.0 Hz, 1 H, (CH_3)C$\underline{H}$(CH_3)), 3.27 – 3.45 (m, 2 H, CHC$\underline{H}_A\underline{H}_BN_3$), 3.46 - 3.56 (m, 1 H, C$\underline{H}$CH_AH$_B$N$_3$), 4.55 (d, *J* = 8.0 Hz, 1 H, N$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 18.5 (($\underline{C}H_3$)CH(CH_3)), 19.6 ((CH_3)CH($\underline{C}H_3$)), 28.5 (OC($\underline{C}H_3$)$_3$), 29.9 ((CH_3)$\underline{C}$H(CH_3)), 53.2 (CH$\underline{C}$H$_A$H$_B$N$_3$), 55.7 ($\underline{C}$HCH$_A$H$_B$N$_3$), 79.7 (O$\underline{C}$(CH_3)$_3$), 155.7 ($\underline{C}$=O). Data is consistent with that given in the literature.[288]

8.2.2.3 Synthesis and characterisation of 115

1-[(2*S*)-1-Azido-3-methylbutan-2-yl]-3-[3,5-bis(trifluoromethyl)phenyl]thiourea **115**



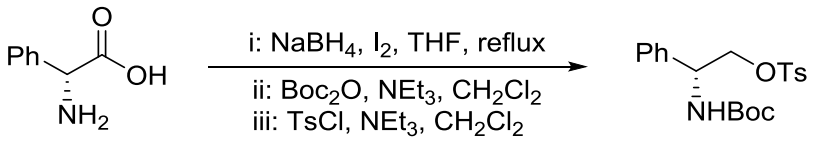
Azide **116** (228 mg, 1.00 mmol) was reacted with TFA (1.0 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.20 mL, 1.1 mmol, 1.1 eq) was added according to General Procedure **I**. Purification by flash column chromatography [Petrol then 9:1 Petrol: Et_2O] afforded the title compound **115** as a colourless solid (222 mg, 56 % yield).

$[\alpha]_D^{23}$ = - 6.4 (c = 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.99 (d, *J* = 6.6 Hz, 3H, one of $CH(C\underline{H}_3)_2$), 1.02 (d, *J* = 6.6 Hz, 3H, one of $CH(C\underline{H}_3)_2$), 1.93 (dq, *J* = 14.3, 6.9 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.60 (dd, *J* = 12.6, 4.4 Hz, 1H, $CHC\underline{H}_aH_bN_3$), 3.79 (dd, *J* = 12.6, 4.1 Hz, 1H, $CHCH_a\underline{H}_bN_3$), 4.42 (br s, 1H, $C\underline{H}NHC{=}S$), 6.19 (br s, 1H, $CHN\underline{H}C{=}S$), 7.75 (s, 1H, Ar<u>H</u>), 7.81 (s, 2H, Ar<u>H</u>), 8.29 (br s, 1H, $CHNHC{=}SN\underline{H}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 19.0 (one of $CH(\underline{C}H_3)_2$), 19.3 (one of $CH(\underline{C}H_3)_2$), 29.7 ($\underline{C}H(CH_3)_2$), 52.0 ($CH\underline{C}H_2N_3$), 60.0 ($\underline{C}HNHC{=}S$), 119.6 - 119.8 (m, Ar<u>C</u>H), 122.7 (q, J_{CF} = 272.7 Hz, $\underline{C}F_3$), 123.9 (q, J_{CF} = 3.8 Hz, Ar<u>C</u>H), 133.3 (q, J_{CF} = 34.3 Hz, Ar<u>C</u>CF_3), 138.5 (Ar<u>C</u>NH), 180.6 (<u>C</u>=S); **^{19}F NMR** (470 MHz, $CDCl_3$) δ ppm - 63.1; **IR** ν_{max}/cm^{-1} 3248, 2111, 1536, 1383, 1276, 1129; **MP** 112 - 115 °C; **HRMS** (ESI+): calcd. for $C_{14}H_{15}F_6N_5NaS$ $[M+Na]^+$ 422.0845, found 422.0831.

8.2.3 Synthesis of D-Phenylglycine-Derived Scaffold

8.2.3.1 Synthesis and characterisation of 120

(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2-phenylethyl 4-methylbenzenesulfonate **120**



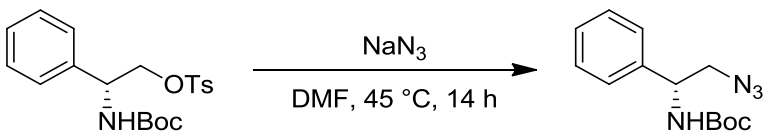
According to a modified literature procedure,[145] to a solution of sodium borohydride (3.47 g, 91.5 mmol, 2.4 eq) in THF (100 mL) was added D-phenylglycine (5.75 g, 38.1 mmol, 1.0 eq). The reaction mixture was cooled to 0 °C and a solution of iodine (9.64 g, 38.1 mmol, 1.0 eq) in THF (25 mL) was added dropwise *via* cannula 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 (50 mL) and stirring was maintained for 3 hours and the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL), washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. The crude material was dissolved in CH_2Cl_2 (135 mL) and triethylamine (6.28 mL, 45.5 mmol, 1.18 eq) was added and the reaction mixture was cooled to 0 °C using an ice bath. Boc anhydride (9.8 g, 45.5 mmol, 1.18 eq) was added and stirring was maintained at 0 °C for one hour and then 8 hours at room temperature. The reaction mixture was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and volatiles removed *in vacuo* to afford the protected amine as an amorphous colourless solid. To the crude amino alcohol in CH_2Cl_2 (127 mL) at 0 °C was added sequentially triethylamine (5.85 mL, 41.9 mmol, 1.1 eq) and *p*-toluenesulfonyl chloride (7.26 g, 38.1 mmol, 1.0 eq). stirring was maintained for 16 h whereupon the reaction mixture was

partitioned by the addition of H_2O (100 mL) and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [4:1 Petrol: EtOAc then 3:2 Petrol: EtOAc] afforded the title compound **120** as a colourless solid in 48% yield over three steps (7.10 g).

MPT 121 - 122 °C [lit. 123 - 124 °C][289]; $\mathbf{[\alpha]_D^{24}}$ = -2.0 ($CHCl_3$, c = 0.90), [lit -2.2, c = 3.0][290]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.44 (s, 9 H, OC(CH_3)$_3$) 2.46 (s, 3 H, ArCH_3) 4.13 - 4.35 (m, 2 H, CHCH_AH_BO) 4.95 (br. s., 1 H, CHNHSO$_2$) 5.20 (br. s., 1 H, CHNHSO$_2$) 7.23 (d, *J* = 7.5 Hz, 2 H, ArH) 7.28 - 7.36 (m, 5 H, ArH) 7.69 (d, *J* = 8.0 Hz, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 21.8 (ArCH$_3$), 28.4 (OC(CH$_3$)$_3$), 53.5 (NHCHCH$_A$H$_B$O), 71.6 (NHCHCH$_A$H$_B$O), 80.3 (OC(CH$_3$)$_3$), 126.7 (ArCH), 128.0 (ArCH), 128.1 (ArCH), 128.9 (ArCH), 130.0 (ArCH), 132.5 (ArC), 137.9 (ArC), 145.1 (ArC), 155.0 (C=O). Data is consistent with that given in the literature.[290]

8.2.3.2 Synthesis and characterisation of 121

tert-Butyl [(1*R*)-2-azido-1-phenylethyl]carbamate **121**



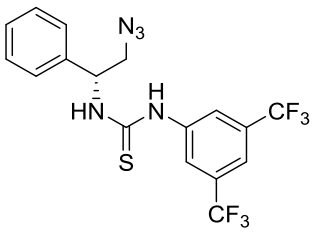
To a stirred solution of tosylate **120** (5.53 g, 14.1 mmol, 1 eq) in DMF (47 mL) was added sodium azide (1.01 g, 15.6 mmol, 1.1 eq) at room temperature. The reaction mixture was warmed to 45 °C and stirring was maintained for 14 h. The reaction mixture was cooled to room temperature then diluted with water (100 mL) and Et_2O (60 mL). The aqueous phase was extracted with Et_2O (2 x 30 mL) and the combined organics were washed with brine (50 mL) and dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by

flash column chromatography [petrol then 9:1 petrol: EtOAc] to afford the title compound **121** as a colourless solid (2.83 g, 76 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.45 (s, 9 H, OC($C\underline{H}_3$)$_3$), 3.55 - 3.69 (m, 2 H, CHC$\underline{H}_2N_3$), 4.89 (br. s., 1 H, C$\underline{H}$NHCO), 5.15 (d, *J* = 7.5 Hz, 1 H, CHN$\underline{H}$CO), 7.28 - 7.43 (m, 5 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 28.3 (OC($\underline{C}H_3$)$_3$, 54.1 ($\underline{C}$HNHCO), 55.6 (CH$\underline{C}H_2N_3$), 80.1 (O$\underline{C}$(CH$_3$)$_3$, 126.5 (Ar$\underline{C}$H), 128.0 (Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 139.3 (Ar$\underline{C}$), 155.1 ($\underline{C}$=O); **$[\alpha]_D^{24}$** = - 7.48 (c = 1.32, $CHCl_3$), lit. **$[\alpha]_D$** -8.7 (1.0, $CHCl_3$)[291]; **MP** 82 - 84 ˚C; **HRMS** (ESI+): calcd. for $C_{13}H_{18}N_4NaO_2$ $[M+Na]^+$ 285.1322, found 285.1312. Data consistent with that given in the literature.[291]

8.2.3.3 Synthesis and characterisation of 122

1-[(1*R*)-2-Azido-1-phenylethyl]-3-[3,5-bis(trifluoromethyl)phenyl]thiourea **122**



Azide **121** (1.50 g, 5.73 mmol) was reacted with TFA (5.7 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.2 mL, 6.3 mmol, 1.1 eq) was added according to General Procedure **I**. Purification by flash column chromatography [Petrol then 9:1 Petrol: EtOAc] afforded the title compound **122** as a colourless solid (2.01 g, 81 % yield).

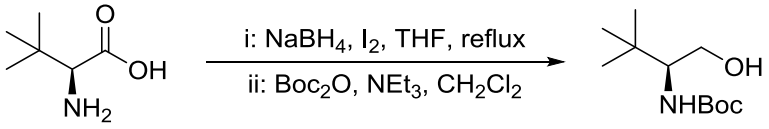
$[\alpha]_D^{24}$ = + 16.8 (c = 1.14, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 3.78 (dd, *J* = 12.5, 5.0 Hz, 1 H, CHC$\underline{H}_A$H$_B$N$_3$), 3.90 (dd, *J* = 12.5, 5.0 Hz, 1 H, CHCH$_A\underline{H}_B$N$_3$), 5.69 (br s, 1 H, C$\underline{H}$NHC=S), 6.93 (br s, 1 H, CHN$\underline{H}$C=S), 7.28 - 7.43 (m, 5 H, Ar$\underline{H}$), 7.72 (s, 1 H, Ar$\underline{H}$), 7.77 (s, 2 H, Ar$\underline{H}$), 8.54 (br s, 1 H, CHNHC=SN$\underline{H}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 54.9 (CH$\underline{C}H_2N_3$), 57.7 ($\underline{C}$HNHC=S), 119.6 (spt, J_{CF} = 3.2 Hz, Ar$\underline{C}$H), 122.7 (q, J_{CF} = 273.0 Hz, $\underline{C}F_3$), 123.8 (m, Ar$\underline{C}$H), 126.6 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 133.0 (q, J_{CF} = 33.6 Hz, Ar$\underline{C}CF_3$), 137.4 (Ar$\underline{C}$), 138.6 (Ar$\underline{C}$NH), 180.2 ($\underline{C}$=S); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm - 63.1; **IR** ν_{max}/cm^{-1} 3214, 3031, 2102, 1542, 1470, 1382, 1334,

1280, 1169, 1126; **MP** 136 - 137 °C; **HRMS** (ESI+): calcd. for $C_{17}H_{13}F_6N_5NaS$ $[M+Na]^+$ 456.0688, found 456.0695.

*8.2.4 Synthesis of L-*tert*-Leucine Derived Scaffold*

8.2.4.1 Synthesis and characterisation of 128

tert-Butyl [(2*S*)-1-hydroxy-3,3-dimethylbutan-2-yl]carbamate **128**



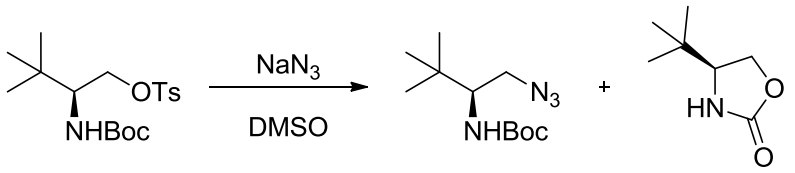
According to a modified literature procedure,[145] to a solution of sodium borohydride (6.95 g, 183 mmol, 2.4 eq) in THF (200 mL) was added L-*tert*-leucine (10.0g, 76.2 mmol, 1.0 eq). The reaction mixture was cooled to 0 °C and a solution of iodine (19.3 g, 76.2 mmol, 1.0 eq) in THF (50 mL) was added dropwise *via* cannula 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 (100 mL) and stirring was maintained for 3 hours and the reaction mixture was extracted with CH_2Cl_2 (3 x 100 mL), washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. According to a modified literature procedure,[292] the crude material was dissolved in CH_2Cl_2 (270 mL) and triethylamine (12.5 mL, 89.9 mmol, 1.18 eq) was added and the reaction mixture was cooled to 0 °C using an ice bath. Boc anhydride (19.6 g, 89.9 mmol, 1.18 eq) was added and stirring was maintained at 0 °C for one hour and then 8 hours at room temperature. The reaction mixture was washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and volatiles removed *in vacuo*. Purification by flash column

chromatography [200 g silica gel, 4:1 Petrol: EtOAc then 3:2 Petrol: EtOAc] afforded the title compound **128** as a colourless solid in 70% yield (11.5 g).

$[\alpha]_D^{24}$ -5.7 (c = 1.6, $CHCl_3$) (lit **$[\alpha]_D^{25}$**= - 5.5 (c = 1.0, $CHCl_3$); **MP** 106 - 108 ˚C (lit. 105 °C)[293]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.93 (s, 9H, CHC($C\underline{H}_3$)$_3$), 1.44 (s, 9H, OC($C\underline{H}_3$)$_3$), 2.58 (br. s., 1H, $CH_2O\underline{H}$), 3.33 - 3.58 (m, 2H, C<u>H</u>NHC=O and $CHCH_A\underline{H}_B$OH), 3.70 - 3.94 (m, 1H, $CHC\underline{H}_AH_B$OH), 4.71 (br. s, 1H, CHN<u>H</u>C=O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.8 (CHC($\underline{C}H_3$)$_3$), 28.3 (OC($\underline{C}H_3$)$_3$), 33.6 (CH<u>C</u>(CH_3)$_3$), 60.9 (<u>C</u>HNHC=O), 63.0 ($CH\underline{C}H_2OH$), 79.5 (O<u>C</u>(CH_3)$_3$), 157.2 (<u>C</u>=O);. Data consistent with that given in the literature.[294]

8.2.4.2 Synthesis and characterisation of 125 and 126

<u>*tert*-Butyl [(2*S*)-1-azido-3,3-dimethylbutan-2-yl]carbamate **125** and (4*S*)-4-*tert*-butyl-1,3-oxazolidin-2-one **126**</u>



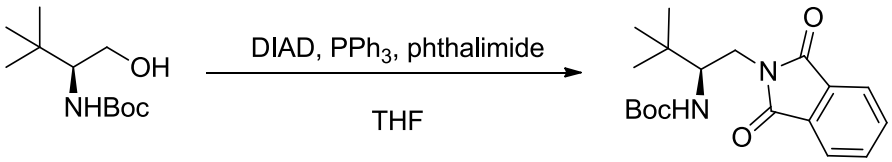
To a solution of **123**[295] (1.57 g, 4.23 mmol, 1.0 eq) in DMF (15 mL) at RT was added sodium azide (303 mg, 4.65 mmol, 1.1 eq) and the reaction mixture warmed to 60 ˚C for 8 h. The reaction mixture was cooled to rt and diluted with H_2O (30 mL) and Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL). Combined organics were washed with brine and dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petrol: Et_2O 9:1 then Petrol: Et_2O 1:1] eluted first **125** as a colourless solid (332 mg, 32%) then **126** as a pale yellow solid (145 mg, 26%).

Spectroscopic data for **125** is reported in Section 8.2.4.6.

126: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.89 (s, 9 H, CHC(C$\underline{H}_3$)$_3$), 3.59 (ddd, *J* = 9.0, 6.0, 1.0 Hz, 1 H, NHC$\underline{H}$CH$_A$H$_B$O), 4.17 (dd, *J* = 9.0, 6.0 Hz, 1 H, NHCHC$\underline{H}_A$H$_B$O), 4.35 (t, *J* = 9.0Hz, 1 H, NHCHCH$_A\underline{H}_B$O), 7.09 (br. s., 1H, N$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 24.7 (CHC($\underline{C}$H$_3$)$_3$), 33.2 (CH$\underline{C}$(CH$_3$)$_3$), 61.5 (NH$\underline{C}$HCH$_A$H$_B$O), 66.5 (NHCH$\underline{C}$H$_A$H$_B$O), 160.7 ($\underline{C}$=O); **[α]$_D^{24}$** +3.2 (c = 1.0, $CHCl_3$) (lit [α]$_D^{25}$ = + 12 (c = 1.80, $CHCl_3$)[296]; **MP** 114 – 115 ˚C (lit. 120 ˚C)[297]. Data consistent with that given in the literature.[296]

8.2.4.3 Synthesis and characterisation of 129

tert-Butyl [(2*S*)-1-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3,3-dimethylbutan-2-yl]carbamate **129**



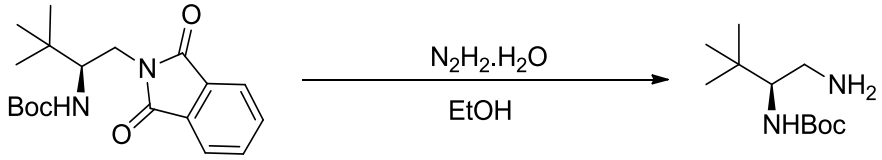
According to a modified literature procedure,[298] to a solution of alcohol **128** (11.5 g, 53.0 mmol, 1.0 eq), phthalimide (7.79 g, 53.0 mmol, 1.0 eq) and triphenylphosphine (13.9 g, 53.0 mmol, 1.0 eq) in THF (330 mL) at 0 ˚C was added dropwise DIAD (11.5 mL, 58.3 mmol, 1.1 eq). The reaction mixture was warmed to room temperature and stirring was maintained for 16 hours and the volatiles were removed *in vacuo*. Purification by flash column chromatography [300 g silica gel, petrol, then petrol: EtOAc 9:1, then petrol: EtOAc 4:1] afforded the title compound as a colourless solid in 89% yield (16.2 g).

[α]$_D^{24}$ = + 39.4 (c = 1.09, $CHCl_3$), lit **[α]$_D$** = +48.7 (c = 0.46, $CHCl_3$)[293]; **MP** 149-151 °C (lit. 146-147 °C)[293]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.99 (s, 9H, CHC(C$\underline{H}_3$)$_3$), 1.08 (s, 9H, OC(C$\underline{H}_3$)$_3$), 3.53 - 3.67 (m, 1H, CHCH$_A\underline{H}_B$N), 3.67 - 3.89 (m, 2H, C$\underline{H}$NHC=O and CHC$\underline{H}_A$H$_B$N), 4.46 (d, *J* = 10.6 Hz, 1H, CHN$\underline{H}$C=O), 7.65 (dd, *J* = 5.3, 3.0 Hz, 2H, Ar$\underline{H}$), 7.79 (dd, *J* = 5.2, 2.9 Hz, 2H, Ar$\underline{H}$);

^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 26.4 (CHC($\underline{C}H_3)_3$), 27.9 (OC($\underline{C}H_3)_3$), 33.6 (CH$\underline{C}$(CH-$_3)_3$), 38.6 (CH$\underline{C}H_2$N), 57.4 ($\underline{C}$HNHC=O), 78.9 (O$\underline{C}$($CH_3)_3$), 123.1 (Ar$\underline{C}$H), 132.1 (Ar$\underline{C}$), 133.7 (Ar$\underline{C}$H), 156.0 (N$\underline{C}$(=O)O), 168.4 (N$\underline{C}$(=O)C). All characterisation data agree with those published in the literature.[293]

8.2.4.4 Synthesis and characterisation of 130

<u>*tert*-Butyl [(2*S*)-1-amino-3,3-dimethylbutan-2-yl]carbamate **130**</u>

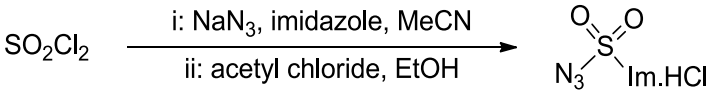


According to a modified literature procedure,[298] to a solution of **129** (16.2 g, 46.8 mmol, 1.0 eq) in EtOH (234 mL) at room temperature was added hydrazine monohydrate (3.4 mL, 70.2 mmol, 1.5 eq). The reaction mixture was heated to reflux and stirring was maintained for 16 hours. The reaction mixture was allowed to cool to room temperature and filtered. The precipitate was washed with CH_2Cl_2 (3 x 100 mL) and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography [CH_2Cl_2 then CH_2Cl_2: MeOH 9:1] afforded the title compound **130** as a colourless solid in 99% yield (10.0 g).

$[\alpha]_D^{25}$ = + 7.20 (c = 0.94, $CHCl_3$), lit. **$[\alpha]_D$** = + 9.8 (c = 0.48, $CHCl_3$)[293]; **MP** 82-84 °C (lit. 84 °C)[293]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.89 (s, 9H, CHC(C$\underline{H}_3)_3$), 1.43 (s, 9H, OC(C$\underline{H}_3)_3$), 1.91 (br. s., 2H, CHCH$_2$N$\underline{H}_2$), 2.32 - 2.52 (m, 1H, CHCH$_A\underline{H}_B$NH$_2$), 2.95 ('d', *J* = 12.6 Hz, 1H, CHC$\underline{H}_A$H$_B$NH$_2$), 3.33 (td, *J* = 10.4, 2.3 Hz, 1H, C$\underline{H}$NHC=O), 4.52 (d, *J* = 10.4 Hz, 1H, CHN$\underline{H}$C=O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.5 (CHC($\underline{C}H_3)_3$), 28.4 (OC($\underline{C}H_3)_3$), 34.2 (CH$\underline{C}$($CH_3)_3$), 42.2 (CH$\underline{C}$H$_2$NH$_2$), 62.2 ($\underline{C}$HNHC=O), 79.2 (O$\underline{C}$($CH_3)_3$), 156.9 ($\underline{C}$=O). All characterisation data agree with those published in the literature.[293]

8.2.4.5 Synthesis and characterisation of 133•HCl

1*H*-imidazole-1-sulfonyl azide hydrochloride **133**•HCl[xxxvi]



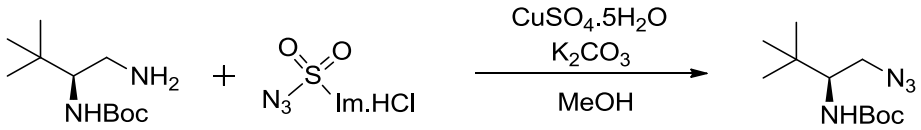
According to a literature procedure,[146] to a suspension of sodium azide (2.21 g, 34.0 mmol, 1.0 eq) in acetonitrile (34 mL) at 0 °C was added sulfuryl chloride (2.8 mL, 34 mmol, 1.0 eq) dropwise behind a blastshield. The reaction mixture was allowed to warm to room temperature and stirring was maintained for 10 h. The reaction mixture was then cooled to 0 °C, then imidazole (4.40 g, 64.6 mmol, 1.9 eq) was added portionwise and the reaction mixture was allowed to warm to room temperature and stirring maintained for 3 h. The reaction mixture was diluted with EtOAc (65 mL), washed with H_2O (2 x 65 mL) then saturated $NaHCO_3$ (2 x 65 mL), dried over $MgSO_4$ and filtered. A solution of HCl in EtOH [obtained by the dropwise addition of acetyl chloride (3.60 mL, 51.0 mmol, 1.5 eq) to ethanol at 0 ˚C (8.50 mL)] was added dropwise to the filtrate with stirring, the reaction mixture chilled in an ice-bath, filtered and the filter cake washed with EtOAc (3 x 10 mL) to afford the title compound **133**•HCl as a colourless solid (4.78 g, 67% yield).

^{1}H NMR (400 MHz, D_2O) δ ppm 7.61 (t, *J* = 1.8 Hz, 1 H), 8.02 (t, *J* = 1.9 Hz, 1 H), 9.46 (t, *J* = 1.4 Hz, 1 H); **^{13}C NMR** (100 MHz, D_2O) δ ppm 120.6, 123.2, 138.0. Data is consistent with that given in the literature.[146] Safety issues have been reported when synthesising and using this compound.[147]

[xxxvi] Care must be taken when following this procedure. All handling should be done behind a blastshield and the ratio of reagents and solvents should not be changed. The liquor from the crystallisation should not be concentrated as it may contain hydrazoic acid and should be disposed of accordingly. An explosion has been reported with this compound.

8.2.4.6 Synthesis and characterisation of *125*

tert-Butyl [(2*S*)-1-azido-3,3-dimethylbutan-2-yl]carbamate **125**

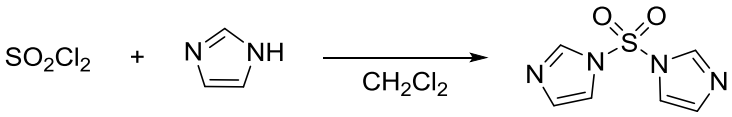


To a solution of amine **130** (1.25 g, 5.79 mmol, 1.0 eq), potassium carbonate (1.36 g, 9.84 mmol, 1.7 eq), copper sulfate pentahydrate (0.015 mg, 0.058 mmol, 0.01 eq) in MeOH (30 mL) behind a blastshield was added diazotransfer reagent **133**•HCl (1.44 g, 6.94 mmol, 1.2 eq) portionwise. Stirring was maintained for 14 h and then the volatiles were removed under a N_2 stream. The reaction mixture was diluted with H_2O (25 mL) and Et_2O (25 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organics were washed (brine), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography [petrol then petrol: EtOAc 9:1] yielded the title compound **125** (1.20 g, 85 % yield) as a colourless solid.

$[\alpha]_D^{24}$ = - 46.6 (c = 0.91, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.92 (s, 9 H, CHC($C\underline{H}_3$)$_3$), 1.44 (s, 9 H, OC($C\underline{H}_3$)$_3$), 3.20 (dd, *J* = 12.5, 8.5 Hz, 1H, CHC$H_A\underline{H}_BN_3$), 3.45 (dd, *J* = 12.5, 3.5 Hz, 1H, CHC$\underline{H}_AH_BN_3$), 3.54 - 3.67 (m, 1H, C$\underline{H}$NHC=O), 4.57 (d, *J* = 10.0 Hz, 1H, CHN$\underline{H}$C=O); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 26.5 (CHC($\underline{C}H_3$)$_3$), 28.3 (OC($\underline{C}H_3$)$_3$), 34.1 (CH$\underline{C}$(CH$_3$)$_3$), 51.9 (CH$\underline{C}H_2N_3$), 58.2 ($\underline{C}$HNHC=O), 79.4 (O$\underline{C}$(CH$_3$)$_3$), 155.7 ($\underline{C}$=O); **IR** ν_{max}/cm^{-1} 2970, 2095, 1700, 1519, 1367, 1247, 1171, 1054; **MP** 58 - 60 ˚C. **HRMS** (ESI+): calcd. for $C_{11}H_{22}N_4NaO_2$ $[M+Na]^+$ 265.1635, found 265.1634.

8.2.4.7 Synthesis and characterisation of 134

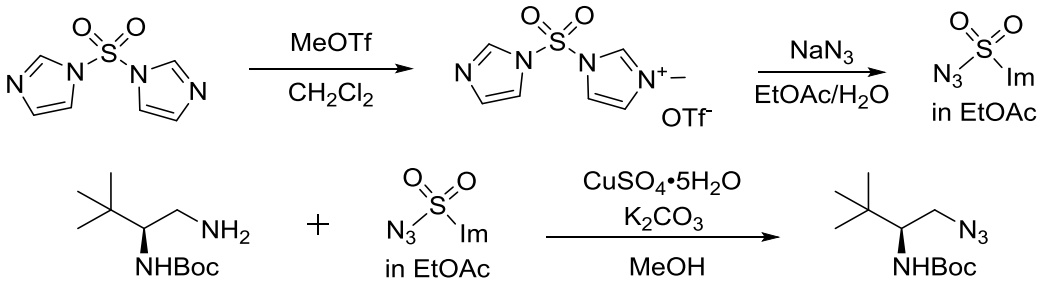
1,1'-*N*,*N*'-Sulfonyldiimidazole **134**



According to a literature procedure,[299] to a solution of imidazole (50 g, 734 mmol, 4.7 eq) in CH_2Cl_2 (400 mL) at 0 ˚C was added dropwise sulfuryl chloride (12.7 mL, 156 mmol, 1.0 eq). The reaction mixture was allowed to warm to rt and stirring maintained overnight whereupon the suspension was filtered, and the filtrate concentrated *in vacuo*. The crude material was purified by recrystallisation in refluxing isopropanol (110 mL) and slowly cooled to 0 ˚C overnight. The crystals were filtered, washed with cold isopropanol to afford the title compound **134** as a colourless solid in 82% yield (24.7 g).

MP 138 – 140 °C [lit. 143 – 144 °C][300]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.17 (br. d, *J* = 1.5 Hz, 2 H, ArH), 7.31 (t, *J* = 1.5 Hz, 2 H, ArH), 8.04 (br s, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 118.5 (ArCH), 131.8 (ArCH), 137.7 (ArCH). Data is consistent with that given in the literature.[299]

8.2.4.8 Synthesis of 125



To a solution of **134** (13.3 g, 67.0 mmol, 1.10 eq) in CH_2Cl_2 (122 mL) at 0 °C was added methyl triflate (6.9 mL, 60.9 mmol, 1.00 eq) dropwise. Stirring was maintained at 0 °C for 2 h whereupon the reaction mixture was filtered and the filtrate dried to afford **135** in 95%

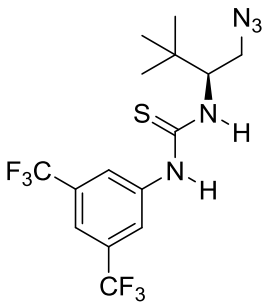
yield (20.8 g). The triflate salt (20.8 g, 57.4 mmol) was vigorously stirred at 0 °C in 1:1 H_2O/EtOAc (138 mL) for 30 min and then sodium azide (4.48 g, 68.9 mmol, 1.2 eq) was added portionwise. Stirring was maintained for 1 h and the layers were separated, the organic layer was dried (Na_2SO_4) to afford the crude diazotransfer reagent **133** as a solution in EtOAc.

To a solution of amine **130** (10.0 g, 46.3 mmol, 1.0 eq) in MeOH (126 mL) behind a blastshield was added sequentially K_2CO_3 (3.23 g, 23.4 mmol, 0.5 eq), $CuSO_4$•$5H_2O$ (180 mg, 0.47 mmol, 0.01 eq) and the diazotransfer reagent in EtOAc (57.4 mmol, 1.2 eq). Stirring was maintained for 19 h whereupon the suspension was filtered through Celite® and the volatiles removed *in vacuo*. Purification by flash column chromatography [125 g silica gel, petrol, then petrol: Et_2O 9:1, then petrol: Et_2O 3:2] afforded the title compound **125** as a colourless solid in 74% yield (8.34 g).

Spectroscopic data for **125** is reported in Section 8.2.4.6.

8.2.4.9 Synthesis and characterisation of 131

1-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-3-[3,5-bis(trifluoromethyl)phenyl]thiourea **131**



Azide **125** (1.50 g, 6.19 mmol) was reacted with TFA (6.0 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.10 mL, 6.20 mmol, 1.1 eq) was added according to General Procedure **I**. Purification by flash column chromatography [Petrol then 4/1 Petrol: Et_2O] afforded the title compound **131** as a colourless solid (2.24 g, 88% yield).

$[\alpha]_D^{23}$ = - 13.5 (c = 1.05, $CHCl_3$); **^{1}H NMR** (500 MHz, CD_3OD) δ ppm 0.93 (s, 9H, $C(C\underline{H}_3)_3$), 3.32 (dd, *J* = 12.9, 8.2 Hz, 1H, $CHCH_A\underline{H}_BN_3$), 3.51 (dd, *J* = 12.9, 3.8 Hz, 1H, $CHC\underline{H}_AH_BN_3$), 4.57 - 4.69 (m, 1H, C<u>H</u>NHC=S), 7.53 (s, 1H, Ar<u>H</u>), 8.14 (s, 2H, Ar<u>H</u>);

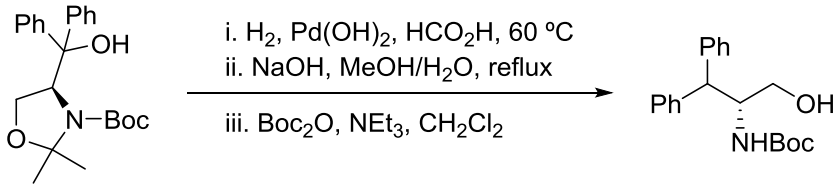
^{13}C NMR (125 MHz, CD_3OD) δ ppm 27.3 ($C(\underline{C}H_3)_3$), 35.8 ($\underline{C}(CH_3)_3$), 52.7 ($CH\underline{C}H_2N_3$), 62.8 ($\underline{C}HNHC{=}O$), 117.8 - 118.1 (m, Ar$\underline{C}$H), 123.7 - 124.0 (m, Ar$\underline{C}$H), 124.9 (q, J_{CF} = 271.9 Hz, $\underline{C}F_3$), 132.8 (q, J_{CF} = 33.3 Hz, Ar$\underline{C}CF_3$), 143.4 (Ar$\underline{C}$NH), 184.1 ($\underline{C}{=}S$); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm - 64.5; **IR** ν_{max}/cm^{-1} 2968, 2104, 1537, 1472, 1383, 1278, 1176, 1134; **MP** 164 - 167 °C; **HRMS** (ESI+): calcd. for $C_{15}H_{17}F_6N_5NaS$ $[M+Na]^+$ 436.1001, found 436.0992.

8.2.5 Synthesis of L-Serine Derived Scaffold

Compounds **139**[301,302] and **140**[303] were synthesised according to literature procedures by Dr M. G. Núñez and Dr Pavol Jakubec.

8.2.5.1 Synthesis and characterisation of 141

<u>*tert*-Butyl [(2*R*)-3-hydroxy-1,1-diphenylpropan-2-yl]carbamate **141**</u>



To a solution of compound **140** (2.63 g, 6.87 mmol, 1.00 eq) in formic acid (137 mL) under an argon atmosphere at rt was added 20% $Pd(OH)_2$ on carbon (Pearlman's catalyst) (658 mg, 25 weight%). The resulting suspension was degassed three times and then placed under a hydrogen atmosphere for 30 min.[xxxvii] The reaction mixture was warmed to 40 °C for 15 h[xxxviii] and then at 60 °C for 25 h. The reaction mixture was cooled to rt and the catalyst $_2$ was removed by filtration through a pad of Celite® washing with MeOH and CH_2Cl and the volatiles removed *in vacuo*. The resulting crude product was dissolved in

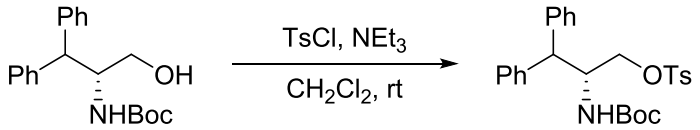
[xxxvii] An aliquot after 30 mins revealed cleavage of the acetyl and boc groups by ^{1}H NMR and LRMS analysis.
[xxxviii] An aliquot at this stage revealed partial cleavage of the benzylic alcohol and partial formation of the formate ester.

H_2O/MeOH (1:1, 172 mL), NaOH (2.59 g, 64.8 mmol, 9.43 eq) was added and the suspension was heated at reflux for 12 h. MeOH was removed *in vacuo*, the aqueous layer was extracted with $CHCl_3$/isopropanol (3:1) (4 × 60 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated to give 1.78 g of the crude amino alcohol. The crude amine was dissolved in CH_2Cl_2 (30 mL), NEt_3 (0.86 mL, 6.2 mmol) and Boc_2O (1.30 g, 5.96 mmol) were added and the reaction mixture was stirred at rt for 16 h whereupon the volatiles were removed *in vacuo*. The crude reaction mixture was purified by flash column chromatography [Petroleum either/EtOAc 4/1] to obtain **141** as a colourless solid in 68% yield over 3 steps (1.52 g).

$[\alpha]_D^{23}$ = - 28.4 (c = 1.12, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.35 (s, 9H, $OC(C\underline{H}_3)_3$), 2.54 (br s, 1H, O<u>H</u>), 3.47 (dd, *J* = 11.1, 4.5 Hz, 1H, $CHC\underline{H}_AH_BOH$), 3.67 (dd, *J* = 11.1, 3.0 Hz, 1H, $CHCH_A\underline{H}_BOH$), 4.18 (d, *J* = 10.9 Hz, 1H, $C\underline{H}CHCH_AH_BOH$), 4.50 (br s, 1H, C<u>H</u>NHC=O), 4.75 (d, *J* = 8.6 Hz, 1H, CHN<u>H</u>C=O), 7.15 - 7.23 (m, 2H, Ar<u>H</u>), 7.26 - 7.31 (m, 4H, Ar<u>H</u>), 7.32 - 7.37 (m, 4H, Ar<u>H</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 28.2 ($OC(\underline{C}H_3)_3$), 52.5 (<u>C</u>HCHCH$_2$OH), 54.8 (CH<u>C</u>HCH$_2$OH), 63.5 (CH_2OH), 79.6 ($O\underline{C}(CH_3)_3$), 126.5 (Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 128.4 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 141.4 (Ar<u>C</u>), 142.0 (Ar<u>C</u>), 156.0 (<u>C</u>=O); **IR** ν_{max}/cm^{-1} 3411, 1686, 1495, 1366, 1166, 1048; **MP** 108 - 111 °C; **HRMS** (ESI+): calcd. for $C_{20}H_{25}NNaO_3$ $[M+Na]^+$ 350.1727, found 350.1724.

8.2.5.2 Synthesis and characterisation of *142*

(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3,3-diphenylpropyl4-methylbenzenesulfonate **142**

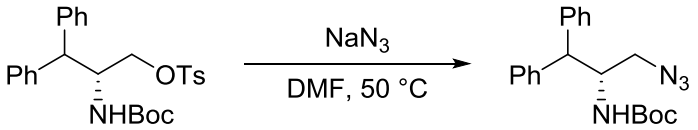


To a solution of **141** (1.70 g, 5.20 mmol, 1.0 eq) in CH_2Cl_2 (26 mL) was added NEt_3 (1.88 mL, 13.5 mmol, 2.6 eq) and TsCl (1.39 g, 7.27 mmol, 1.4 eq) and the reaction mixture was stirred at rt for 16 h whereupon the volatiles were removed *in vacuo*. The crude reaction mixture was purified by flash column chromatography [Petroleum ether to petroleum ether/EtOAc 4:1) to yield the title compound **142** as a colourless solid in 83% yield (2.07 g).

$[\alpha]_D^{23}$ = - 24.8 (c = 1.12, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.30 (s, 9H, $OC(C\underline{H}_3)_3$), 2.44 (s, 3H, $ArCH_3$), 3.78 ('d', *J* = 9.1 Hz, 1H, $CHC\underline{H}_AH_BO$), 4.04 - 4.17 (m, 2H, $CHC\underline{H}_AH_BO$ and $C\underline{H}CHCH_AH_BO$), 4.56 - 4.68 (m, 2H, $C\underline{H}NHC{=}O$ and $CHN\underline{H}C{=}O$), 7.10 - 7.21 (m, 6H, Ar<u>H</u>), 7.22 - 7.33 (m, 6H, Ar<u>H</u>), 7.71 (d, *J* = 8.2 Hz, 2H, Ar<u>H</u>); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 21.6 ($Ar\underline{C}H_3$), 28.1 ($OC(\underline{C}H_3)_3$), 51.9 ($\underline{C}HNHC{=}O$), 52.2 ($\underline{C}HCHCH_2O$), 70.3 ($\underline{C}H_2O$), 79.7 ($O\underline{C}(CH_3)_3$), 126.7 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 129.8 (Ar<u>C</u>H), 132.3 (Ar<u>C</u>H), 140.6 (Ar<u>C</u>), 140.9 (Ar<u>C</u>), 144.8 ($Ar\underline{C}CH_3$), 155.0 ($\underline{C}{=}O$); **IR** ν_{max}/cm^{-1} 1710, 1496, 1364, 1176; **MP** 137 - 139 °C; **HRMS** (ESI+): calcd. for $C_{27}H_{31}NNaO_5S$ $[M+Na]^+$ 504.1815, found 504.1810.

8.2.5.3 Synthesis and characterisation of 143

tert-Butyl [(2*R*)-3-azido-1,1-diphenylpropan-2-yl]carbamate **143**

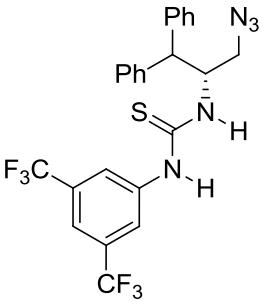


To a solution of **142** (2.05 g, 4.26 mmol, 1.0 eq) in DMF (14 mL) at rt was added NaN_3 (305 mg, 4.69 mmol, 1.1 eq) and then the reaction mixture was warmed to 50 ºC and stirring maintained for 16 h. After cooling to rt, the reaction mixture was partitioned by the addition of H_2O (20 mL) and Et_2O (40 mL). The aqueous layer was extracted with Et_2O (2 x 40 mL), the combined organics were washed with brine, dried ($MgSO_4$), and the volatiles removed *in vacuo*. The crude material was purified by flash column chromatography [petroleum ether to petroleum/Et_2O 9/1) to obtain the title compound **143** as a colourless solid in 68% yield (896 mg).

$[\alpha]_D^{23}$ = - 44.1 (c = 1.15, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.35 (s, 9H, $OC(C\underline{H}_3)_3$), 3.23 (dd, *J* = 12.3, 3.5 Hz, 1H, $CHC\underline{H}_A H_B N_3$), 3.53 ('d', *J* = 11.3 Hz, 1H, $CHCH_A\underline{H}_B N_3$), 4.10 (d, *J* = 10.7 Hz, 1H, $C\underline{H}CHCH_A H_B N_3$), 4.48 - 4.67 (m, 2H, C<u>H</u>NHC=O and CHN<u>H</u>C=O), 7.13 - 7.25 (m, 2H, Ar<u>H</u>), 7.25 - 7.39 (m, 8H, Ar<u>H</u>); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 28.2 ($OC(\underline{C}H_3)_3$), 52.7 ($\underline{C}HCHCH_2N_3$), 53.3 ($CHCH\underline{C}H_2N_3$), 53.3 ($CH\underline{C}HCH_2N_3$), 79.7 ($O\underline{C}(CH_3)_3$), 126.7 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 128.2 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 140.9 (Ar<u>C</u>), 141.5 (Ar<u>C</u>), 155.2 (<u>C</u>=O); **IR** ν_{max}/cm^{-1} 2099, 1689, 1511, 1298, 1166; **MP** 125 - 127 °C; **HRMS** (ESI+): calcd. for $C_{20}H_{25}N_4O_2$ $[M+H]^+$ 353.1972, found 353.1972.

8.2.5.4 Synthesis and characterisation of 144

1-[(2*R*)-3-Azido-1,1-diphenylpropan-2-yl]-3-[3,5-bis(trifluoromethyl)phenyl]urea **144**



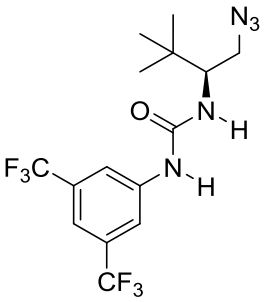
Azide **143** (710 mg, 2.02 mmol) was reacted with TFA (2.0 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.37 mL, 2.02 mmol, 1.0 eq) was added according to a modified General Procedure **I**. Purification by flash column chromatography [Petrol then 9:1 Petrol/Et_2O] afforded the title compound **144** as a colourless solid in 76% yield (803 mg).

$[\alpha]_D^{23}$ = - 103.2 (c = 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 3.28 (dd, *J* = 12.6, 2.2 Hz, 1H, CHC$\underline{H_a}H_bN_3$), 3.91 (dd, *J* = 12.6, 3.3 Hz, 1H, CHC$H_a\underline{H_b}N_3$), 4.22 (d, *J* = 11.3 Hz, 1H, C$\underline{H}$CHC$H_aH_bN_3$), 5.47 - 5.56 (m, 1H, C$\underline{H}$NHC=S), 5.91 - 6.05 (m, 1H, CHN$\underline{H}$C=S), 7.20 - 7.38 (m, 12H, Ar$\underline{H}$) 7.73 (s, 1H, Ar$\underline{H}$) 8.54 (br s, 1H, CHNHC=SN$\underline{H}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 51.8 (CHC$\underline{H_2}N_3$), 52.8 (C$\underline{H}$CHCH_2N_3), 57.0 (C$\underline{H}$CHCH_2N_3), 120.1 (sept, J_{CF} = 3.7 Hz, Ar$\underline{C}$H), 122.5 (q, J_{CF} = 272.7 Hz), 124.3 (q, J_{CF} = 3.7 Hz, Ar$\underline{C}$H), 127.3 (Ar$\underline{C}$H), 127.4 (Ar$\underline{C}$H), 127.7 (Ar$\underline{C}$H), 128.0 (Ar$\underline{C}$H), 129.1 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 133.3 (q, J_{CF} = 34.3 Hz), 137.7 (Ar$\underline{C}$NH), 140.1 (Ar$\underline{C}$), 140.5 (Ar$\underline{C}$), 179.7 ($\underline{C}$=S); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ ppm - 62.9; **IR** ν_{max}/cm^{-1} 2101, 1495, 1275, 1173, 1130; **MP** 50 – 53 °C; **HRMS** (ESI+): calcd. for $C_{24}H_{19}F_6N_5NaS$ $[M+Na]^+$ 546.1158, found 546.1158.

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

8.2.6.1 Synthesis and characterisation of 214

1-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-3-[3,5-bis(trifluoromethyl)phenyl]urea **214**

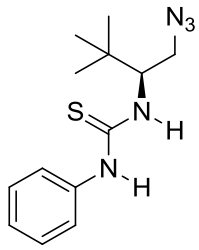


Azide **125** (242 mg, 1.00 mmol) was reacted with TFA (1.0 mL) then 3,5-bis(trifluoromethyl)phenyl isocyanate (0.19 mL, 1.1 mmol, 1.1 eq) was added according to General Procedure **I**. Purification by flash column chromatography [Petrol then 4/1 Petrol: Et_2O] afforded the title compound **214** as a colourless solid (280 mg, 71 % yield).

$[\alpha]_D^{23}$ = - 29.9 (c = 0.90, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.96 (s, 9H, $C(C\underline{H}_3)_3$), 3.29 (dd, *J* = 12.6, 8.2 Hz, 1H, $CHC\underline{H}_AH_BN_3$), 3.60 (dd, *J* = 12.6, 3.8 Hz, 1H, $CHCH_A\underline{H}_BN_3$), 3.84 (m, 1H, C<u>H</u>NH), 5.46 (br s, 1H, CHN<u>H</u>C=O), 7.46 (s, 1H, Ar<u>H</u>), 7.69 (br s, 1H, ArN<u>H</u>), 7.81 (s, 2H, Ar<u>H</u>); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 26.5 ($C(\underline{C}H_3)_3$), 34.1 ($\underline{C}(CH_3)_3$), 52.3 ($CH\underline{C}H_2N_3$), 57.9 (<u>C</u>HNHC=O), 116.1 (sept, J_{CF} = 3.8 Hz, Ar<u>C</u>H), 118.8 (q, J_{CF} = 3.8 Hz, Ar<u>C</u>H), 123.0 (q, J_{CF} = 272.7 Hz, $\underline{C}F_3$), 132.2 (q, J_{CF} = 33.4 Hz, Ar<u>C</u>CF_3), 140.2 (Ar<u>C</u>NH), 155.4 (<u>C</u>=O); **^{19}F NMR** (470 MHz, $CDCl_3$) δ ppm - 63.1; **IR** ν_{max}/cm^{-1} 3338, 2968, 2102, 1650, 1570, 1388, 1277, 1175, 1133; **MP** 164 - 166 °C; **HRMS** (ESI+): calcd. for $C_{15}H_{17}F_6N_5NaO$ $[M+Na]^+$ 420.1230, found 420.1224.

8.2.6.2 Synthesis and characterisation of 215

1-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-3-phenylthiourea **215**

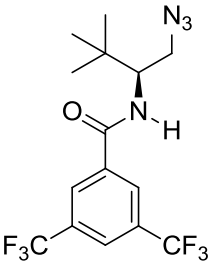


Azide **125** (242 mg, 1.00 mmol) was reacted with TFA (1.0 mL) then phenyl isothiocyanate (0.13 mL, 1.1 mmol, 1.1 eq) was added according to General Procedure **I**. Purification by flash column chromatography [Petrol then 4/1 Petrol: Et_2O] afforded the title compound **215** as a colourless solid (188 mg, 68 % yield).

$[\alpha]_D^{23}$ = + 35.1 (c = 1.02, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.91 (s, 9H, $C(CH_3)_3$), 3.36 (dd, *J* = 12.8, 5.8 Hz, 1H, $CHCH_AH_BN_3$), 3.67 (dd, *J* = 12.8, 4.2 Hz, 1H, $CHCH_AH_BN_3$), 4.59 (br s, 1H, CHNH), 6.09 (d, *J* = 9.3 Hz, 1H, CHNHC=SNH), 7.26 (d, *J* = 7.6 Hz, 2H, ArH), 7.29 - 7.36 (m, 1H, ArH), 7.40 - 7.50 (m, 2H, ArH), 8.48 (br s, 1H, CHNHC=SNH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.9 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 51.3 ($CHCH_2N_3$), 61.7 (CHNH), 125.5 (ArCH), 127.6 (ArCH), 130.2 (ArCH), 135.6 (ArC), 180.9 (C=S); **IR** ν_{max}/cm^{-1} 3259, 2963, 2098, 1596, 1532, 1497, 1450, 1296; **MP** 60 - 62 °C; **HRMS** (ESI+): calcd. for $C_{13}H_{19}N_5NaS$ $[M+Na]^+$ 300.1253, found 300.1258.

8.2.6.3 Synthesis and characterisation of 216

N-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-3,5-bis(trifluoromethyl)benzamide **216**

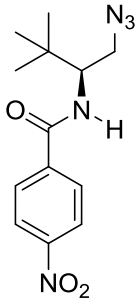


Azide **125** (242 mg, 1.00 mmol) was reacted with TFA (1.0 mL) then triethylamine (0.17 mL, 1.2 mmol, 1.2 eq) and 3,5-bis(trifluoromethyl)benzoyl chloride (0.20 mL, 1.1 mmol, 1.1 eq) was added according to General Procedure **I**. Purification by flash column chromatography [Petroleum ether, 4/1 then 1/1 Petroleum ether/Et_2O] afforded the title compound **216** as a colourless solid (233 mg, 61 % yield).

$[\alpha]_D^{25}$ = +16.4 (c = 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.04 (s, 9H, C($C\underline{H}_3$)$_3$), 3.45 (dd, *J* = 12.9, 8.5 Hz, 1H, CHC$\underline{H}_A$H$_B$N$_3$), 3.67 (dd, *J* = 12.9, 3.8 Hz, 1H, CHCH$_A$$\underline{H}_BN_3$), 4.23 (dd, *J* = 8.3, 3.8 Hz, 1H, C$\underline{H}$NHC=O), 7.94 (s, 1H, Ar$\underline{H}$), 8.16 (s, 2H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.7 (C($\underline{C}H_3$)$_3$), 34.4 ($\underline{C}$(CH$_3$)$_3$), 51.4 (CH$\underline{C}$H$_2$N$_3$), 57.2 ($\underline{C}$HCH$_2$N$_3$), 122.8 (q, J_{CF} = 272.4 Hz, $\underline{C}F_3$), 124.9 - 125.1 (m, Ar$\underline{C}$H)), 127.2 - 127.4 (m, Ar$\underline{C}$H), 132.1 (q, J_{CF} = 34.0 Hz, Ar$\underline{C}CF_3$), 136.6 (Ar$\underline{C}$C=O), 165.1 ($\underline{C}$=O); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm – 63.0; **IR** ν_{max}/cm^{-1} 2972, 2378, 2089, 1634, 1615, 1474, 1445, 1371, 1338, 1278, 1175, 1130, 906, 705, 682; **MP** 116 - 122 °C; **HRMS** (ESI+): calcd. for $C_{15}H_{16}F_6N_4NaO$ $[M+Na]^+$ 405.1121, found 405.1116.

8.2.6.4 Synthesis and characterisation of 217

N-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-4-nitrobenzamide **217**

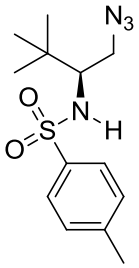


Azide **125** (100 mg, 0.413 mmol) was reacted with TFA (0.4 mL) then triethylamine (66 µL, 0.47 mmol, 1.2 eq) and 4-nitrobenzoyl chloride (84 mg, 0.45 mmol, 1.1 eq) was added according to General Procedure **I**. Purification by flash column chromatography [Petroleum ether, then 9/1 Petroleum ether/EtOAc] afforded the title compound **217** as a colourless solid (64 mg, 53 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.03 (s, 9H, C($C\underline{H}_3$)$_3$), 3.45 (dd, *J* = 12.9, 7.8 Hz, 1H, CHC$\underline{H}_A$H$_B$N$_3$), 3.66 (dd, *J* = 12.9, 4.0 Hz, 1H, CHCH$_A$$\underline{H}_BN_3$), 4.22 (ddd, *J* = 10.0, 7.7, 4.0 Hz, 1H, C$\underline{H}$NHC=O), 6.32 (d, *J* = 9.9 Hz, 1H, CHN$\underline{H}$C=O), 7.92 (d, *J* = 8.8 Hz, 2H, Ar$\underline{H}$), 8.27 (d, *J*=8.6 Hz, 2H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.8 (C($\underline{C}H_3$)$_3$), 34.4 ($\underline{C}$(CH$_3$)$_3$), 51.6 (CH$\underline{C}$H$_2$N$_3$), 57.0 ($\underline{C}$HCH$_2$N$_3$), 123.9 (Ar$\underline{C}$H), 128.2 (Ar$\underline{C}$H), 140.3 (Ar$\underline{C}$C=O), 149.6 (Ar$\underline{C}$NO$_2$), 165.9 ($\underline{C}$=O); **$[\alpha]_D^{25}$** = +25.7 (c = 1.11, $CHCl_3$); **MP** 114-119 °C. All spectroscopic data is consistent with that given in the literature.[304]

8.2.6.5 Synthesis and characterisation of 218

N-[(2S)-1-Azido-3,3-dimethylbutan-2-yl]-4-methylbenzenesulfonamide **218**

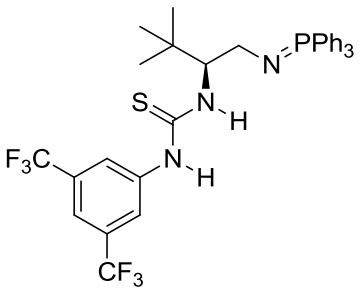


Azide **125** (100 mg, 0.413 mmol) was reacted with TFA (0.4 mL) then triethylamine (66 µL, 0.47 mmol, 1.2 eq) and tosyl chloride (87 mg, 0.45 mmol, 1.1 eq) was added according to General Procedure **I**. Purification by flash column chromatography [Petroleum ether, then 9/1 Petroleum ether/EtOAc] afforded the title compound **218** as a pale yellow solid (30 mg, 25 % yield). **$[\alpha]_D^{25}$** = - 39.4 (c = 0.87, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.90 (s, 9H, $C(C\underline{H}_3)_3$), 2.43 (s, 3H, $ArC\underline{H}_3$), 3.13 (ddd, *J* = 9.6, 4.8, 4.8 Hz, 1H, $C\underline{H}NHSO_2Ar$), 3.26 (dd, *J* = 12.9, 4.8 Hz, 1H, $CHC\underline{H}_AH_BN_3$), 3.31 (dd, *J* = 12.9, 4.8 Hz, 1H, $CHCH_A\underline{H}_BN_3$), 4.92 (d, *J* = 9.6 Hz, 1H, $CHN\underline{H}SO_2Ar$), 7.31 (d, *J* = 8.1 Hz, 2H, $Ar\underline{H}$), 7.80 (d, *J* = 8.3 Hz, 2H, $Ar\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 21.5 ($Ar\underline{C}H_3$), 26.9 ($C(\underline{C}H_3)_3$), 34.5 ($\underline{C}(CH_3)_3$), 51.9 ($CH\underline{C}H_2N_3$), 61.1 ($\underline{C}HNHSO_2Ar$), 127.0 ($Ar\underline{C}H$), 129.6 ($Ar\underline{C}H$), 138.2 ($Ar\underline{C}$), 143.4 ($Ar\underline{C}$); **IR** ν_{max}/cm^{-1} 3292, 2964, 2102, 1438, 1326, 1159, 1089, 964, 814, 669; **MP** 81 - 84 °C; **HRMS** (ESI+): calcd. for $C_{13}H_{20}N_4NaO_2S$ $[M+Na]^+$ 319.1199, found 319.1198.

8.2.7 Synthesis and Characterisation of Bifunctional Iminophosphorane Catalysts

8.2.7.1 Synthesis and characterisation of 145

1-[3,5-Bis(trifluoromethyl)phenyl]-3-{(2*S*)-3,3-dimethyl-1-[(triphenylphosphoranylidene)amino]butan-2-yl}thiourea **145**



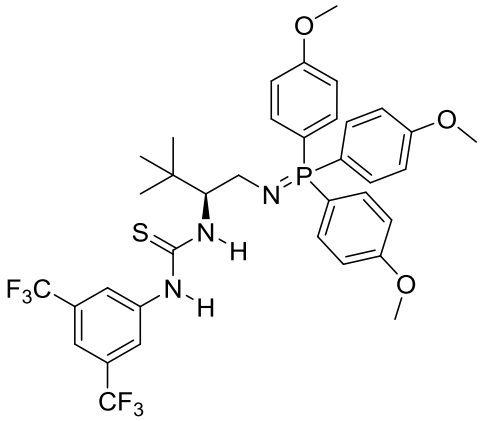
To azide **131** (300 mg, 0.726 mmol) in Et_2O (1.8 mL) under argon atmosphere was added triphenylphosphine (190 mg, 0.726 mmol) at rt. Stirring was maintained at rt for 26 h and the reaction mixture was then concentrated *in vacuo* to

afford a colourless foam. Pentane (4 mL) was added under N_2 and the mixture stirred vigorously for 2 h. The resultant suspension was filtered and the precipitate dried *in vacuo* to obtain compound **145** (344 mg, 73%) as a colourless solid.

$[\alpha]_D^{24}$ = - 64.4 (c = 1.40, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.96 (s, 9H), 3.04 ('q', *J* = 9.8 Hz, 1H), 3.41 ('t', *J* = 9.8 Hz, 1H), 3.76 (br s, 1H), 7.32 - 7.80 (m, 19 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 27.1, 33.7, 48.0, 69.9 (d, J_{CP} = 21.0 Hz), 116.5, 123.2 (q, J_{CF} = 272.8 Hz), 123.4, 128.1, 128.9 (J_{CP} = 12.4 Hz), 130.9 (q, J_{CF} = 33.4 Hz), 132.5 (d, J_{CP} = 9.5 Hz), 143.5, 183.7; **^{31}P NMR** (202 MHz, $CDCl_3$) δ ppm 21.9 (br s); **^{19}F NMR** (470 MHz, $CDCl_3$) δ ppm - 62.7; **IR** ν_{max}/cm^{-1} 2970, 1739, 1437, 1367, 1216; **MP** 96 - 99 °C; **HRMS** (ESI+): calcd. for $C_{33}H_{33}F_6N_3PS$ $[M+H]^+$ 648.2032, found 648.2024.

8.2.7.2 Synthesis and characterisation of 147

1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(2*S*)-3,3-dimethyl-1-{[tris(4-methoxyphenyl)phosphoranylidene]amino}butan-2-yl]thiourea **147**



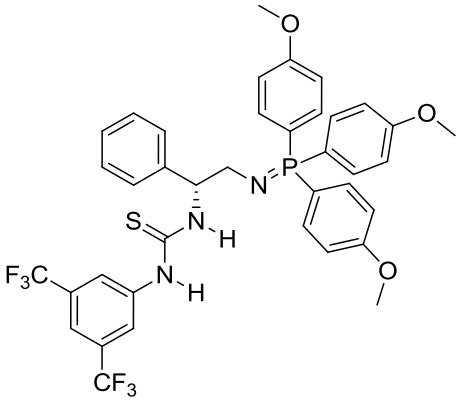
To azide **131** (500 mg, 1.21 mmol) in Et_2O (3.0 mL) under an argon atmosphere was added tris(4-methoxyphenyl)phosphine (426 mg, 1.21 mmol) at rt. Stirring was maintained at rt for 24 h and the reaction mixture was concentrated under a stream of N_2 until 1 mL of solvent remained. Pentane (1 mL) was added and the resultant thick precipitate was filtered. The precipitate was washed with pentane/Et_2O 1:1 (1 mL) and dried *in vacuo* to obtain compound **147** (786 mg, 88%) as a colourless solid.

$[\alpha]_D^{24}$ = - 54.4 (c = 1.02, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm; 0.95 (s, 9H), 2.91 ('q', *J* = 9.9 Hz, 1H), 3.23 (dd, *J* = 8.7, 5.5 Hz, 1H), 3.85 (s, 9H), 4.07 (br s, 1H), 6.99 (dd,

J = 8.7, 2.0 Hz, 6H), 7.24 (s, 1H), 7.27 (s, 2H), 7.40 - 7.70 (m, 7H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 27.1, 33.6 (br s), 47.1 (br s), 55.5, 65.1 (br s), 113.8 - 114.1 (m), 115.1 (d, J_{CP} = 14.3 Hz), 123.7 (q, J_{CF} = 272.8 Hz,), 123.9 (br s), 130.5 (q, J_{CF} = 32.0 Hz), 134.9 (d, J_{CP} = 11.4 Hz), 163.8, 181.7 (br s); **^{31}P NMR** (202 MHz, $CDCl_3$) δ ppm 29.8 (br s); **^{19}F NMR** (470 MHz, $CDCl_3$) δ ppm - 63.0; **IR** ν_{max}/cm^{-1} 2959, 1595, 1558, 1503, 1393, 1277, 1256, 1173, 1121; **MP** 148 - 150 °C; **HRMS** (ESI+): calcd. for $C_{36}H_{39}F_6N_3PS$ $[M+H]^+$ 738.2348, found 738.2343.

8.2.7.3 Synthesis and characterisation of 148

1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1*R*)-1-phenyl-2-{[tris(4-methoxyphenyl)phosphoranylidene]amino}ethyl]thiourea **148**



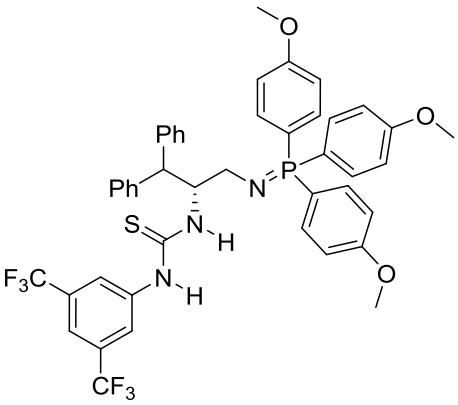
To azide **122** (500 mg, 1.16 mmol) in Et_2O (3.0 mL) under argon atmosphere was added tris(4-methoxyphenyl)phosphine (407 mg, 1.16 mmol) at rt. Stirring was maintained at rt for 24 h and the reaction mixture was then concentrated under a stream of N_2 until a thick precipitate was obtained. The precipitate was filtered, washed with Et_2O (1 mL) and dried *in vacuo* to obtain compound **148** (786 mg, 90%) as a colourless solid.

$[\alpha]_D^{24}$ = - 40.8 (c = 1.00, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 3.14 - 3.30 (m, 1H), 3.31 - 3.50 (m, 1H), 3.84 (s, 9H), 5.36 (br s, 1H), 6.95 (dd, *J* = 8.8, 1.9 Hz, 6H), 7.24 - 7.36 (m, 7H), 7.46 - 7.54 (dd, *J* = 11.3, 8.8 Hz, 6H), 7.59 - 7.78 (br s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 52.8 - 53.0 (m), 55.5, 62.4 (br s), 115.0 (d, J_{CP} = 13.4 Hz), 123.5, 123.6 (q, J_{CF} = 272.8 Hz), 124.1 (br s), 127.0, 127.8 - 128.1 (m), 128.8, 130.6 (q, J_{CF} = 32.4 Hz), 134.7 (d, J_{CP} = 11.4 Hz), 140.4 (br s), 163.7; **^{31}P NMR** (162 MHz, $CDCl_3$)

δ ppm 27.4 (br s); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm - 62.6; **IR** ν_{max}/cm^{-1} 2972, 1595, 1502, 1275, 1176, 1118, 1026; **MP** 136 - 142 °C; **HRMS** (ESI+): calcd. for $C_{38}H_{35}F_6N_3O_3PS$ $[M+H]^+$ 758.2035, found 758.2028.

8.2.7.4 Synthesis and characterization of 149

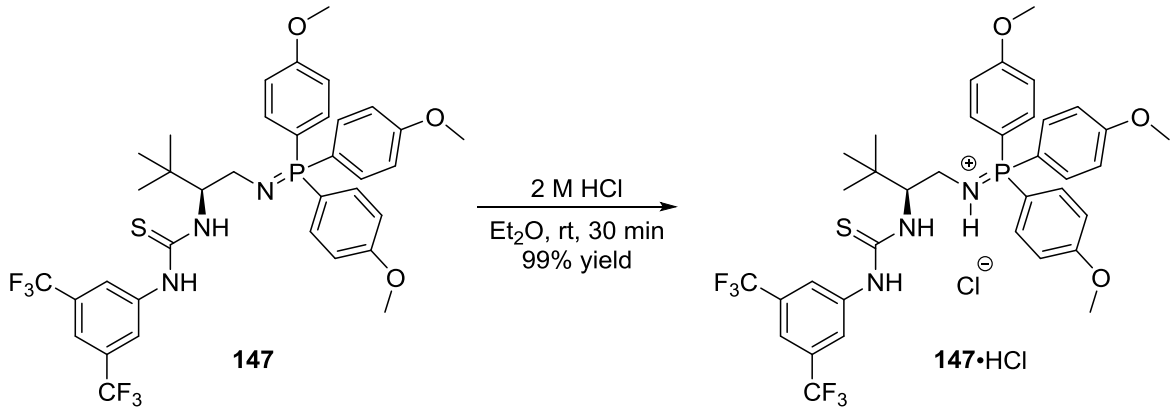
1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(2*R*)-1,1-diphenyl-3-{[tris(4-methoxyphenyl)-λ^5-phosphanylidene]amino}propan-2-yl]thiourea **149**



To azide **144** (436 mg, 0.832 mmol) in Et_2O (2.1 mL) under argon atmosphere was added tris(4-methoxyphenyl)phosphine (293 mg, 0.832 mmol) at rt. Stirring was maintained at rt for 24 h and then pentane (2.0 mL) was added and the resultant thick precipitate was filtered. The precipitate was washed with pentane/Et_2O 1:1 (1 mL) and dried *in vacuo* to obtain the title compound **149** as a colourless solid (630 mg, 90%).

MP 168 - 170 °C; **$[\alpha]_D^{24}$** = - 18.0 (c = 0.59, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 2.99 (br. s, 1H), 3.10 (br. s, 1H), 3.82 (s, 9H), 3.97 - 4.09 (m, 1H), 5.11 (br. s, 1H), 6.88 (d, *J* = 5.5 Hz, 6H), 7.11 - 7.21 (m, 6H), 7.22 - 7.31 (m, 7H), 7.31 - 7.45 (m, 6H), 7.63 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 50.3, 55.0, 55.6, 59.9, 115.0 (d, J_{PC} = 11.4 Hz), 123.8 (q, J_{FC} = 272.8 Hz), 126.6, 126.9 (br. s), 128.1, 128.5, 128.8, 128.9 (br. s), 130.6 (q, J_{FC} = 32.4 Hz), 134.9 (J_{PC} = 11.5 Hz), 142.9, 163.7; **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 27.6 (br s); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm - 62.6; **IR** ν_{max}/cm^{-1} 3027, 2963, 1624, 1594, 1499, 1471, 1388, 1258, 1118, 1028, 804, 700; LRMS (ESI+): calcd. for $C_{45}H_{40}F_6N_3O_3PS$ $[M+H]^+$ 848.2, found 848.2.

8.2.7.5 Synthesis and characterisation of 147•HCl



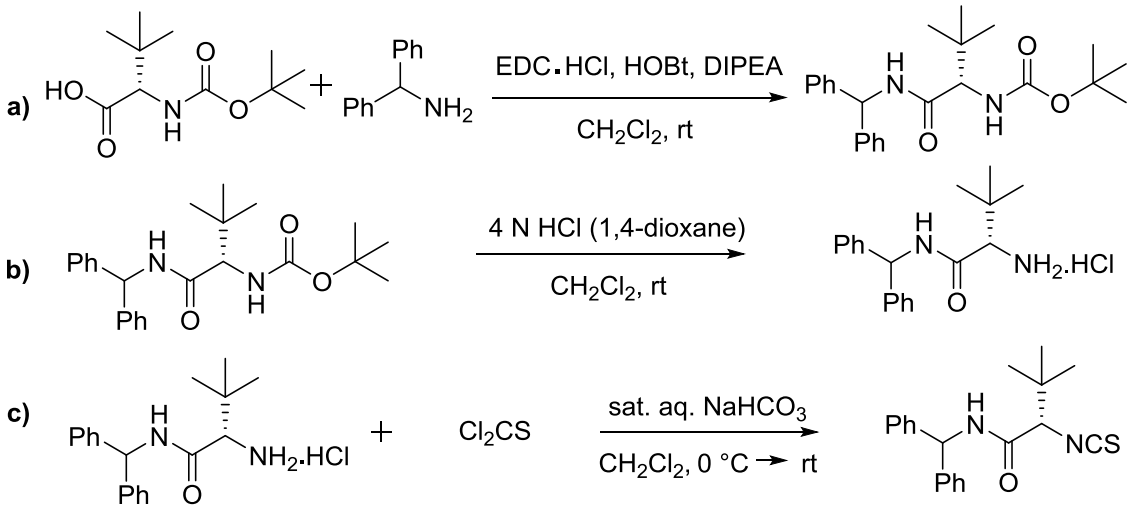
To a solution of **147** (400 mg, 0.543 mmol, 1 eq) in Et_2O (5 mL) was added a 2 M HCl solution in Et_2O (1.36 mL, 2.71 mmol, 5 eq). Stirring was maintained for 30 minutes and the volatiles removed *in vacuo*. Purification by flash column chromatography [EtOAc] afforded the title compound **147•HCl** as a colourless solid (440 mg, 99%).

$[\alpha]_D^{24}$ = + 12.0 (c = 0.9, $CHCl_3$). **^{1}H NMR** (500 MHz, CD_3CN) δ ppm 0.87 (s, 9H, $C(C\underline{H}_3)_3$), 3.11 - 3.22 (m, 1H, $CHC\underline{H}_ACH_BN$=P), 3.22 - 3.32 (m, 1H, $CHCH_AC\underline{H}_BNH$=P), 3.85 (s, 9H, $OC\underline{H}_3$), 4.44 (td, *J* = 10.1, 3.1 Hz, 1H, C<u>H</u>NHC=S), 5.70 – 5.76 (m, 1H, $CHCH_ACH_BN\underline{H}$=P), 7.08 - 7.17 (m, 6H, OCCAr<u>H</u>), 7.64 (s, 1H, Ar<u>H</u>), 7.68 – 7.74 (m, 6H, PCCAr<u>H</u>), 8.46 (s, 2H, Ar<u>H</u>), 8.86 (d, *J* = 10.1 Hz, 1H, CHN<u>H</u>C=S), 11.88 (s, 1H, CHNHC=SN<u>H</u>); **^{13}C NMR** (125 MHz, CD_3CN) δ ppm 27.0 ($C(\underline{C}H_3)_3$), 35.2 ($\underline{C}(CH_3)_3$), 43.8 ($CH\underline{C}H_2N_3$), 56.7 ($O\underline{C}H_3$), 63.7 (d, J_{PC} = 5.7 Hz, (<u>C</u>HNHC=S), 113.1 (d, J_{PC} = 112.5 Hz, N=PAr<u>C</u>), 116.4 (d, J_{PC} = 14.3 Hz, OCCAr<u>C</u>H), 117.1 (sept, J_{FC} = 3.8 Hz, Ar<u>C</u>H), 122.2 (q, J_{FC} = 3.8 Hz, Ar<u>C</u>H), 124.7 (q, J_{FC} = 271.8 Hz, CF_3), 131.8 (q, J_{FC} = 33.1 Hz, Ar<u>C</u>CF3), 136.7 (d, J_{PC} = 12.4 Hz, N=PCAr<u>C</u>H), 143.8 (Ar<u>C</u>NH), 165.7 (d, J_{PC} = 2.8 Hz, Ar<u>C</u>OCH_3) 184.3 (<u>C</u>=S); **^{31}P NMR** (202 MHz, CD_3CN) δ ppm 36.9; **^{19}F NMR** (470 MHz, CD_3CN) δ ppm - 63.4; **IR** ν_{max}/cm^{-1} 2964, 1595, 1276, 1182, 1117; **MP** 105 - 110 °C; **HRMS** (ESI+): calcd. for $C_{36}H_{39}F_6N_3O_3PS$ $[M]^+$ 738.2348, found 738.2344.

8.2.8 Synthesis of Catalysts Bearing Amide-Thiourea H-Bond Donor Groups

8.2.8.1 Synthesis and characterisation of 305

(2*S*)-*N*-(Diphenylmethyl)-2-isothiocyanato-3,3-dimethylbutanamide **305**



According to a literature procedure,[224]

a) To a stirred solution of EDC hydrochloride (909 mg, 4.75 mmol, 1.10 eq) and 1-hydroxybenzotriazole hydrate (644 mg, 4.75 mmol, 1.10 eq) in CH_2Cl_2 (26 mL) under a N_2 atmosphere at rt was added *N*,*N*-diisopropylethylamine (1.12 mL, 6.48 mmol, 1.5 eq) and benzhydrylamine (0.82 mL, 4.76 mmol, 1.10 eq) sequentially. Boc-L-*tert*-leucine (1.00 g, 4.32 mmol, 1.00 eq) was added in one portion and the reaction mixture was stirred for 20 h. The reaction was diluted with Et_2O (20 mL), washed with 0.5 N HCl (2 x 20 mL) and the organic phase extracted with Et_2O (10 mL). The combined organic was washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), 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 in CH_2Cl_2 (10.0 mL) under a N_2 atmosphere at rt was added 4 N HCl in 1,4-dioxane (10.3 mL, 42 mmol, 9.6 eq) over

5 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.

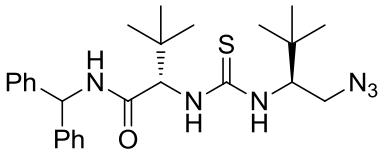
c) To a vigorously stirred solution of the crude product in CH_2Cl_2 (40 mL) under a N_2 atmosphere at 0 °C was added sat. aq. $NaHCO_3$ (40 mL), and the biphasic mixture was stirred for 20 min. Stirring was stopped and thiophosgene (0.330 mL, 4.32 mmol, 1.00 eq) was added to the organic layer. Immediately, 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 40 mL), washed with brine (30 mL), dried ($MgSO_4$), filtered and the volatiles removed *in vacuo* to afford the crude product **305** as a pale yellow solid in 84% yield over three steps (1.23g).

$[\alpha]_D^{20}$ = +47.5 (*c* 0.72, $CHCl_3$); **MP** 162-166 °C; **IR** (film) ν_{max}/cm^{-1}: 3297 (NH), 2965, 2117 (NCS), 1658 (C=O), 1526, 1452, 1237, 753, 699; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.08 (s, 9 H, C(C<u>H</u>$_3$)$_3$), 4.09 (s, 1 H, C<u>H</u>(CH$_3$)$_3$), 6.25 (d, *J* = 8.0 Hz, 1 H, Ph$_2$C<u>H</u>NH), 6.64 (d, *J* = 8.0 Hz, 1 H, N<u>H</u>), 7.21 - 7.28 (m, 4 H, Ar<u>H</u>), 7.28 - 7.41 (m, 6 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz)[xxxix] δ (ppm): 26.7 (C(<u>C</u>H$_3$)$_3$), 37.1 (<u>C</u>(CH$_3$)$_3$), 57.2 (Ph$_2$<u>C</u>HNH), 70.9 (<u>C</u>H(CH$_3$)$_3$), 127.3 (Ar<u>C</u>H), 127.5 (Ar<u>C</u>H), 127.7(Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 140.5 (Ar<u>C</u>), 140.8 (Ar<u>C</u>), 165.4 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{20}H_{22}N_2NaOS$) requires *m/z* 361.1345, found *m/z* 361.1328.

[xxxix] Quarternary carbon N<u>C</u>S not found in spectrum.

8.2.8.2 Synthesis and characterisation of 306

(2*S*)-2-({[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]carbamothioyl}amino)-*N*-(diphenylmethyl)-3,3-dimethylbutanamide **306**



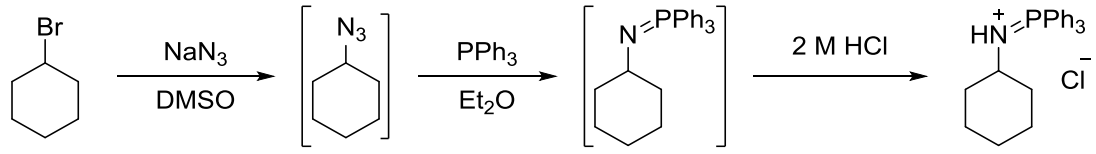
Azide **125** (409 mg, 1.69 mmol, 1.10 eq) was reacted with isothiocyanate **305** (520 mg, 1.54 mmol, 1.00 eq) according to a modified General Procedure **I**. The reaction mixture was purified by FCC (petroleum ether/EtOAc = 4/1 to 3/2) to afford the title compound **306** as a colourless solid in 90% yield (661 mg).

$[\alpha]_D^{20}$ = -33.4 (*c* 0.54, $CHCl_3$); **MP** 200 - 202 °C; **IR** (film) ν_{max}/cm^{-1}: 2963, 2098, 1649, 1529, 1348, 752, 699; **^{1}H NMR** (MeOD-d_4, 500 MHz) δ (ppm): 0.98 (s, 9 H, one of C(=O)CHC(C$\underline{H}_3$)$_3$ or NHCHC(C$\underline{H}_3$)$_3$), 1.01 (s, 9 H, one of C(=O)CHC(C$\underline{H}_3$)$_3$ or NHCHC(C$\underline{H}_3$)$_3$), 3.28 - 3.35 (m, 1 H, CHC$\underline{H}_A$H$_B$N$_3$), 3.52 (dd, *J* = 13.0, 3.5 Hz, 1 H, CHCH$_A$$\underline{H}_BN_3$), 4.67 (dd, *J* = 8.0, 3.5 Hz, 1 H, C$\underline{H}$CH$_2$N$_3$), 5.02 (s, 1 H, C(=O)C$\underline{H}$(CH$_3$)$_3$), 6.18 (s, 1 H, Ph$_2$C$\underline{H}$NH), 7.19 - 7.35 (m, 10 H, Ar$\underline{H}$); **^{13}C NMR** (MeOD-d_4, 125 MHz) δ (ppm): 27.4, 27.5 (C(=O)CHC(C$\underline{H}_3$)$_3$ and NHCHC(C$\underline{H}_3$)$_3$) 35.7, 35.7 (C(=O)CHC(CH$_3$)$_3$ and NHCHC(CH$_3$)$_3$), 53.1 (CHC$\underline{H}_2$N$_3$), 58.5 (Ph$_2$C$\underline{H}$NH), 63.5 (C$\underline{H}$CH$_2$N$_3$), 66.7 (C(=O)C$\underline{H}$(^{t}Bu)), 128.2 (Ar$\underline{C}$H), 128.6 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 129.4 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 129.7 (Ar$\underline{C}$H), 142.9 (Ar$\underline{C}$), 143.2 (Ar$\underline{C}$), 172.9 ($\underline{C}$=O), 186.1 ($\underline{C}$=S); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{26}H_{36}N_6NaOS$) requires *m/z* 503.2564, found *m/z* 503.2552.

8.2.9 pK_{BH+} Estimation of Iminophosphorane Salts 110a·HCl and 110b·HCl in CD_3CN

8.2.9.1 Synthesis and characterisation of iminophosphorane salt 110a·HCl

(Cyclohexylimino)(triphenyl)-λ^5-phosphane hydrochloride **110a·HCl**

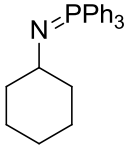


NaN_3 (877 mg, 13.5 mmol) was added to a solution of bromocyclohexane (2.00 g, 12.3 mmol) in DMSO (41 mL) and the reaction mixture was stirred at 60 ºC for 16 h. After cooling to rt, H_2O (40 mL) was added and it was extracted with Et_2O (3 x 40 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under a stream of N_2. The resulting crude was dissolved in Et_2O (25 mL) under argon atmosphere and triphenylphosphine (3.22 g, 12.3 mmol) was added. Stirring was maintained at rt for 20 h, a solution of 2 M HCl in Et_2O (18.0 mL, 36.0 mmol) was added and the resulting solution was stirred at rt for 1 h. After evaporation of the solvents, the resulting crude was purified by flash column chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to obtain **110a·HCl** (1.10 g, 23% over 3 steps) as a colourless solid.

^{1}H NMR (400 MHz, CD_3CN) δ ppm 0.93 - 1.13 (m, 3H), 1.42 - 1.51 (m, 1H), 1.59 - 1.80 (m, 6H), 2.65 - 2.79 (m, 1H), 7.60 - 7.70 (m, 6H), 7.76 - 7.93 (m, 9H), 8.24 (t, J = 9.4 Hz, 1H); **^{13}C NMR** (100 MHz, CD_3CN) δ ppm 26.1, 26.5, 36.3, 36.4, 54.7 (d, J_{CP} = 2.4 Hz), 123.8 (d, J_{CP} = 102.5 Hz), 130.9 (d, J_{CP} = 13.5 Hz), 135.1 (d, J_{CP} = 11.1 Hz), 136.0 (d, J_{CP} = 2.4 Hz); **^{31}P NMR** (162 MHz, CD_3CN) δ ppm 35.6; **IR** ν_{max}/cm^{-1} 3397, 2922, 2848, 1438, 1113, 1082; **MP** 194 - 198 °C; **HRMS** (ESI+): calcd. for $C_{24}H_{27}NOP$ $[M]^+$ 360.1876, found 360.1869.

8.2.9.2 Synthesis and characterisation of 110a

(Cyclohexylimino)(triphenyl)-λ^5-phosphane **110a**

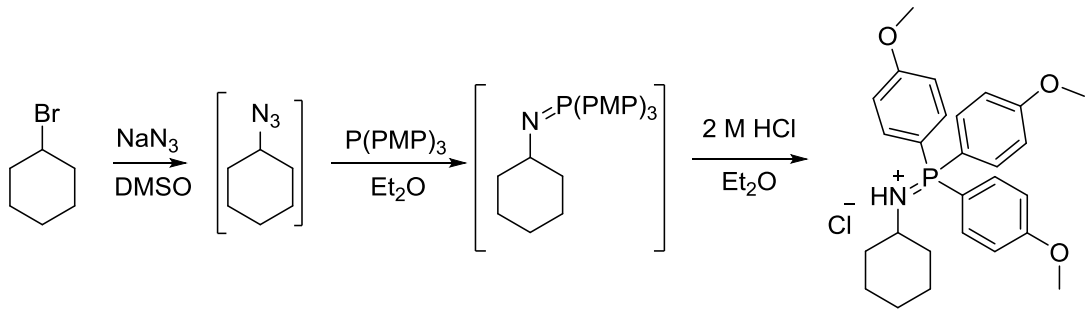


PS-BEMP (63.0 mg, 2.2 mmol/g, 0.138 mmol) was added to a solution of iminophosphorane salt **110a·HCl** (50.0 mg, 0.126 mmol) in CH_2Cl_2 (1.0 mL) under argon atmosphere. The reaction mixture was stirred at rt for 1 h and then filtered, concentrated under a stream of N_2 and dried under vacuum to obtain **110a** (43.0 mg, 95%) as a colourless oil.

^{1}H NMR (400 MHz, CD_3CN) δ ppm 1.03 - 1.16 (m, 3H), 1.28 - 1.40 (m, 2H), 1.44 - 1.50 (m, 1H), 1.59 - 1.67 (m, 4H), 2.80 - 2.95 (m, 1H), 7.45 - 7.56 (m, 6H), 7.55 - 7.61 (m, 3H), 7.66 - 7.73 (m, 6H); **^{13}C NMR** (100 MHz, CD_3CN) δ ppm 26.7, 27.0, 39.6, 39.7, 54.9 (d, J_{CP} = 3.2 Hz), 130.0 (d, J_{CP} = 12.0 Hz), 132.3 (d, J_{CP} = 96.0 Hz), 133.2 (d, J_{CP} = 3.2 Hz), 133.9 (d, J_{CP} = 9.6 Hz); **^{31}P NMR** (162 MHz, CD_3CN) δ ppm 9.4; **HRMS** (ESI+): calcd. for $C_{24}H_{27}NP$ $[M+H]^+$ 360.1876, found 360.1862.

8.2.9.3 Synthesis and characterisation of 110b·HCl

(Cyclohexylimino)[tris(4-methoxyphenyl)]-λ^5-phosphane hydrochloride **110b·HCl**



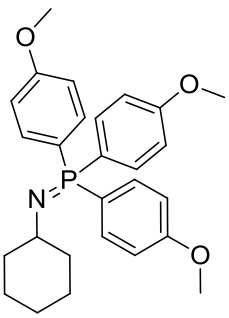
NaN_3 (219 mg, 3.37 mmol) was added to a solution of bromocyclohexane (500 mg, 3.06 mmol) in DMSO (10 mL) and the reaction mixture was stirred at 60 ºC for 16 h. After cooling to rt, H_2O (15 mL) was added and it was extracted with Et_2O (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under a stream of N_2.

The resulting crude was dissolved in Et_2O (12 mL) under argon atmosphere and tris(4-methoxyphenyl)phosphine (560 mg, 1.59 mmol) was added. Stirring was maintained at rt for 20 h, a solution of 2 M HCl in ether (4.60 mL, 9.20 mmol) was added and the resulting solution stirred at rt for 1 h. After evaporation of the solvents, the resulting crude was purified by flash column chromatography (CH_2Cl_2/MeOH 20:1) to obtain **110b·HCl** (850 mg, 57% over 3 steps) as a colourless foam.

^{1}H NMR (400 MHz, CD_3CN) δ ppm 0.94 - 1.10 (m, 3H), 1.42 - 1.51 (m, 1H), 1.59 - 1.74 (m, 6H), 2.58 - 2.77 (m, 1H), 3.87 (s, 9H), 6.75 (t, *J* = 9.6 Hz, 1H), 7.09 - 7.19 (m, 6H), 7.69 - 7.79 (m, 6H); **^{13}C NMR** (100 MHz, CD_3CN) δ ppm 26.2, 26.5, 36.4, 36.4, 54.2 (d, J_{CP} = 1.6 Hz), 56.9, 115.0 (d, J_{CP} = 111.3 Hz), 116.4 (d, J_{CP} = 14.3 Hz), 137.0 (d, J_{CP} = 12.7 Hz), 165.7 (d, J_{CP} = 3.2 Hz); **^{31}P NMR** (162 MHz, CD_3CN) δ ppm 34.1; **IR** ν_{max}/cm^{-1} 3300, 2934, 2843, 1593, 1503, 1262, 1113; **MP** 89 - 93 °C; HRMS (ESI+): calcd. for $C_{27}H_{33}NO_3P$ $[M]^+$ 450.2193, found 450.2181.

8.2.9.4 Synthesis and characterisation of 110b

(Cyclohexylimino)[tris(4-methoxyphenyl)]-λ^5-phosphane **110b**



PS-BEMP (51.5 mg, 2.2 mmol/g, 0.113 mmol) was added to a solution of iminophosphorane salt **110b·HCl** (50.0 mg, 0.103 mmol) in CH_2Cl_2 under argon atmosphere. The reaction mixture was stirred at rt for 1 h and then filtered, concentrated and dried under vacuum to obtain **110b** (45.0 mg, 97%) as a colourless oil.

^{1}H NMR (400 MHz, CD_3CN) δ ppm 1.03 - 1.14 (m, 3H), 1.21 - 1.33 (m, 2H), 1.43 - 1.50 (m, 1H), 1.55 - 1.66 (m, 4H), 2.75 - 2.92 (m, 1H), 3.81 (s, 9H), 3.81 (s, 3H), 6.94 - 7.03 (m, 6H), 7.51 - 7.60 (m, 6H); **^{13}C NMR** (100 MHz, CD_3CN) δ ppm 26.8, 27.2, 40.1, 40.2, 55.0 (d, J_{CP} = 4.0 Hz), 56.5, 115.2 (d, J_{CP} = 11.9 Hz), 124.8 (d, J_{CP} = 102.5 Hz), 135.5 (d,

J_{CP} = 10.3 Hz), 163.5 (d, J_{CP} = 2.4 Hz); **^{31}P NMR** (162 MHz, CD_3CN) δ ppm 8.9; **HRMS** (ESI+): calcd. for $C_{27}H_{33}NO_3P$ $[M+H]^+$ 450.2193, found 450.2179.

8.2.9.5 pK_{BH+} Measurement of iminophosphorane salt 110a·HCl in CD_3CN

110a·HCl (20.0 mg, 0.050 mmol) and tetramethylguanidine (6.3 μL, 0.050 mmol) were dissolved in CD_3CN. The ^{13}C NMR and ^{31}P NMR were measured and the chemical shift of the **C**H-N=PPh_3 and CH-N=**P**Ph_3 were used to estimate the equilibrium ratio and the equilibrium constant of the reaction.[305] The equilibrium constant was then used, with the known pK_{BH+} of TMG in CD_3CN (pK_{BH+} = 23.3)[143,144] to determine the estimated pK_{BH+} of **110a·HCl**. The experiment was repeated three times.[xl]

8.2.9.6 pK_{BH+} Measurement of iminophosphorane salt 110b·HCl in CD_3CN

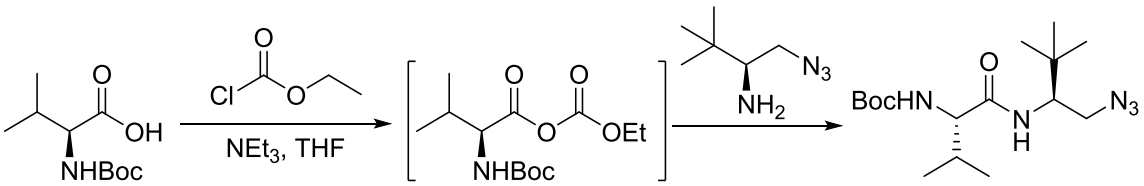
110b·HCl (20.0 mg, 0.041 mmol) and tetramethylguanidine (5.2 μL, 0.041 mmol) were dissolved in CD_3CN. The ^{13}C NMR and ^{31}P NMR were measured and the chemical shift of the **C**H-N=PPh_3 and CH-N=**P**Ph_3 were used to estimate the equilibrium ratio and the equilibrium constant of the reaction.[305] The equilibrium constant was then used, with the known pK_{BH+} of TMG in CD_3CN (pK_{BH+} = 23.3)[143,144] to determine the estimated pK_{BH+} of **110b·HCl**. The experiment was repeated three times.

[xl] The pK_{BH+} determination experiments were performed in collaboration with M.G.N..

8.2.10 Synthesis and Characterisation of BIMP Catalyst Precursors Bearing Alternative H-Bond Donor Groups

8.2.10.1 Synthesis and characterisation of 438

N-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-N^2-(*tert*-butoxycarbonyl)-L-valinamide **438**



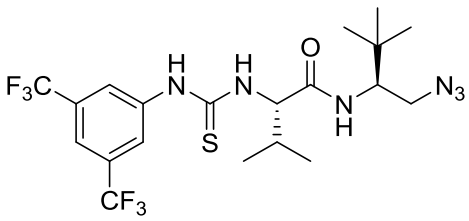
According to a modified literature procedure,[306] to a stirred solution of *N*-Boc L-valine (217 mg, 1.00 mmol, 1.00 eq) in THF (10 mL) at 0 °C was added sequentially triethylamine (0.35 mL, 2.5 mmol, 2.5 eq) and then ethyl chloroformate (105 µL, 1.1 mmol, 1.1 eq) dropwise. Stirring was maintained for 1 h and then the crude amino azide [obtained according to part I of General Procedure **I** using azide **125** (242 mg, 1.00 mmol, 1.00 eq)] 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 flash column chromatography [Petroleum ether to petroleum ether/EtOAc 4/1] afforded the title compound **438** as a colourless solid in 88% yield (300 mg).

MPT 157 - 158 °C; $\mathbf{[\alpha]_D^{20}}$ = -56.8 (c = 0.5, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3340, 3302, 2970, 2105, 1687, 1650, 1559; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.87 (s, 9 H, CHC($C\underline{H}_3$)$_3$), 0.90 (d, *J* = 7.0 Hz, 3 H, ($C\underline{H}_3$)CH(CH_3)), 0.93 (d, *J* = 7.0 Hz, 3 H, (CH_3)CH($C\underline{H}_3$)), 1.37 (s, 9 H, OC($C\underline{H}_3$)$_3$), 1.98 – 2.15 (m, 1 H, (CH_3)C$\underline{H}$(CH_3)), 3.20 (dd, *J* = 12.5, 8.0 Hz, 1 H, CHC$\underline{H}_A$$H_B$$N_3$), 3.48 (dd, *J* = 12.5, 4.0 Hz, 1 H, CHC$H_A$$\underline{H}_B$$N_3$), 3.74 (t, *J* = 7.5 Hz, 1 H, C$\underline{H}$CH(CH_3)$_2$), 3.89 (ddd, *J* = 10.0, 8.0, 4.0 Hz, 1 H, C$\underline{H}$C$H_A$$H_B$$N_3$), 5.03 (d, *J* = 9.0 Hz,

1 H, NHCHCH), 6.09 (d, *J* = 10.0 Hz, 1 H, NHCHCH$_A$H$_B$N$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 18.1 ((CH$_3$)CH(CH$_3$)), 19.4 ((CH$_3$)CH(CH$_3$)), 26.6 (CHC(CH$_3$)$_3$), 28.3 (OC(CH$_3$)$_3$), 29.9 ((CH$_3$)CH(CH$_3$)), 34.1 (CHC(CH$_3$)$_3$), 51.9 (CHCH$_A$H$_B$N$_3$), 56.1 (CHCH$_A$H$_B$N$_3$), 60.8 (CHCH(CH$_3$)$_2$), 79.9 (OC(CH$_3$)$_3$), 156.1 (OC(=O)NH), 171.8 (C(=O)NH); **HRMS** (ESI+): calcd. for $C_{16}H_{31}N_5NaO_3$ $[M+Na]^+$ 364.2319, found 364.2319.

8.2.10.2 Synthesis and characterisation of 393

N-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-N^2-{[3,5-bis(trifluoromethyl)phenyl]carbamothioyl}-L-valinamide **393**



Azide **438** (240 mg, 0.704 mmol, 1.0 eq) was reacted with TFA (0.7 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.15 mL, 0.77 mmol, 1.1 eq) was added according to a modified General Procedure **I** 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 **393** as a colourless solid in 58% yield (209 mg).

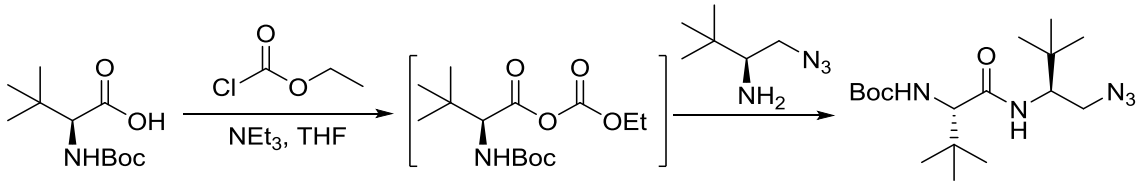
MPT 179 – 181 °C; **$[\alpha]_D^{20}$** = -106.3 (c = 1.02, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3303, 2969, 2103, 1653, 1538, 1383, 1278, 1132; **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.87 (s, 9 H, CHC(CH$_3$)$_3$), 1.18 (d, *J* = 7.0 Hz, 3 H, (CH$_3$)CH(CH$_3$)), 1.20 (d, *J* = 6.5 Hz, 3 H, (CH$_3$)CH(CH$_3$)), 2.08 - 2.29 (m, 1 H, (CH$_3$)CH(CH$_3$)), 3.23 (dd, *J* = 13.0, 9.5 Hz, 1 H, NHCHCH$_A$H$_B$N$_3$), 3.66 (dd, *J* = 13.0, 3.5 Hz, 1 H, NHCHCH$_A$H$_B$N$_3$), 3.88 (td, *J* = 9.5, 3.5 Hz, 1 H, NHCHCH$_A$H$_B$N$_3$), 4.82 (t, *J* = 8.5 Hz, 1 H, NHCHCH), 6.35 (d, *J* = 9.5 Hz, 1 H, NHCHCH$_A$H$_B$N$_3$), 7.54 (s, 1 H, ArH), 8.05 (s, 2 H, ArH), 8.52 (br d, *J* = 7.5 Hz, 1 H, (C=S)NHCHCH), 8.84 (s, 1 H, ArNHC(=S)); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 19.2

(($\underline{C}H_3$)CH(CH_3)), 19.6 ((CH_3)CH($\underline{C}H_3$)), 26.4 (CHC($\underline{C}H_3$)$_3$), 30.6 ((CH_3)$\underline{C}$H(CH_3)), 34.0 (CH$\underline{C}$(CH_3)$_3$), 51.8 (NHCH$\underline{C}H_AH_BN_3$), 57.4 (NH$\underline{C}$HC$H_AH_BN_3$), 65.1 (NH$\underline{C}$HCH), 118.2 (spt, J_{FC} = 3.8 Hz, Ar$\underline{C}$H), 123.0 (q, J_{FC} = 272.8 Hz, ArC$\underline{C}F_3$), 124.2 (q, J_{FC} = 3.8 Hz, Ar$\underline{C}$H), 131.4 (q, J_{FC} = 33.7 Hz, Ar$\underline{C}CF_3$), 140.0 (Ar$\underline{C}$), 174.3 ($\underline{C}$(=O)NH), 181.8 ($\underline{C}$=S); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm -63.0; **HRMS** (ESI+): calcd. for $C_{20}H_{26}F_6N_6NaOS$ $[M+Na]^+$ 535.1685, found 535.1683.

8.2.10.3 Synthesis and characterisation of 439

<u>*N*-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-N^2-(*tert*-butoxycarbonyl)-3-methyl-L-valinamide</u>

<u>439</u>



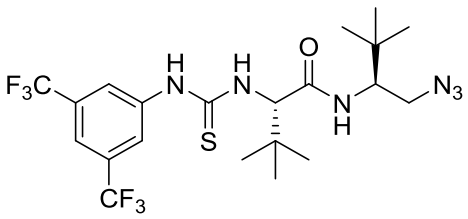
According to a modified literature procedure,[306] to a stirred solution of L-Boc *tert*-Leucine (693 mg, 3.00 mmol, 1.00 eq) in THF (30 mL) at 0 °C was added sequentially triethylamine (1.05 mL, 7.5 mmol, 2.5 eq) and then ethyl chloroformate (316 µL, 3.30 mmol, 1.1 eq) dropwise. Stirring was maintained for 1 h and then the crude amino azide [obtained according to part **I** of General Procedure **I** using azide **125** (726 mg, 3.00 mmol, 1.00 eq)] as a solution in Et_2O (12 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 (40 mL) and CH_2Cl_2 (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organics were washed (brine), dried ($MgSO_4$) and the volatiles concentrated *in vacuo*. Purification by flash column chromatography [petroleum ether to petroleum

ether/EtOAc 4/1] afforded the title compound **439** as colourless solid in 55% yield (582 mg).

MPT 134 – 136 °C; $[\alpha]_D^{20}$ = -30.5 (c = 0.79, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3337, 2966, 2099, 1702, 1657, 1521, 1367, 1173; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.93 (s, 9 H, CHC($C\underline{H}_3$)$_3$), 1.04 (s, 9 H, CHC($C\underline{H}_3$)$_3$), 1.43 (s, 9 H, OC($C\underline{H}_3$)$_3$), 3.27 (dd, *J* = 12.5, 8.0 Hz, 1 H, CHC$\underline{H}_A$H$_B$N$_3$), 3.58 (dd, *J* = 12.5, 4.0 Hz, 1 H, CHCH$_A$$\underline{H}_BN_3$), 3.80 (d, *J* = 9.5 Hz, 1 H, O(C=O)NHC$\underline{H}$), 3.95 (ddd, *J* = 10.0, 8.0, 4.0 Hz, 1 H, NHC$\underline{H}$CH$_A$H$_B$N$_3$), 5.21 (d, *J* = 9.5 Hz, 1 H, O(C=O)N$\underline{H}$CH), 5.83 (br. d, *J* = 10.0 Hz, 1 H, N$\underline{H}$CHCH$_A$H$_B$N$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.5 (CHC($\underline{C}$H$_3$)$_3$), 26.6 CHC($\underline{C}$H$_3$)$_3$), 28.3 (OC($\underline{C}$H$_3$)$_3$), 33.9 (CH$\underline{C}$(CH$_3$)$_3$), 34.1 (CH$\underline{C}$(CH$_3$)$_3$), 52.0 (CH$\underline{C}$H$_A$H$_B$N$_3$), 55.7 ($\underline{C}$HCH$_A$H$_B$N$_3$), 62.7 (OC(=O)NH$\underline{C}$H), 79.7 (O$\underline{C}$(CH$_3$)$_3$), 156.0 (O$\underline{C}$(=O)NH), 171.3 ($\underline{C}$(=O)NH); **HRMS** (ESI+): calcd. for $C_{17}H_{33}N_5NaO_3$ $[M+Na]^+$ 378.2476, found 378.2472.

8.2.10.4 Synthesis and characterisation of 394

N-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-*N*^{2}-{[3,5-bis(trifluoromethyl)phenyl]carbamothioyl}-3-methyl-L-valinamide **394**



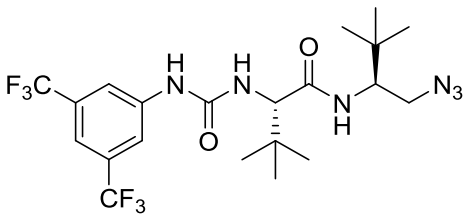
Azide **439** (124 mg, 0.350 mmol, 1.0 eq) was reacted with TFA (0.35 mL) then 3,5-bis(trifluoromethyl)phenyl isothiocyanate (64 µL, 0.35 mmol, 1.0 eq) was added according to a modified General Procedure **I** using Et_2O (2.0 mL). Purification by flash column chromatography [petroleum ether to petroleum ether/Et_2O 4/1] afforded the title compound **394** as a colourless solid in 47% yield (86 mg).

MPT 169 – 170 °C; $[\alpha]_D^{20}$ = -38.1 (c = 1.11, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3314, 2967, 2104, 1651, 1527, 1383, 1277, 1179, 1134; **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.86 (s, 9 H,

$CHC(C\underline{H}_3)_3$), 1.17 (s, 9 H, $CHC(C\underline{H}_3)_3$), 3.20 (dd, *J* = 13.0, 9.0 Hz, 1 H, $NHCHC\underline{H}_AH_BN_3$), 3.65 (dd, *J* = 13.0, 3.5 Hz, 1 H, $NHCHCH_A\underline{H}_BN_3$), 3.88 (ddd, *J* = 10.0, 9.0, 3.5 Hz, 1 H, $NHC\underline{H}CH_AH_BN_3$), 5.08 (d, *J* = 9.5 Hz, 1 H, NH(C=S)NHC<u>H</u>), 5.86 (d, *J* = 10.0 Hz, 1 H, $N\underline{H}CHCH_AH_BN_3$), 7.61 (s, 1 H, Ar<u>H</u>), 7.86 (br. d, *J* = 9.5 Hz, 1 H, NHC(=S)N<u>H</u>CH), 7.95 (s, 2 H, Ar<u>H</u>), 8.93 (s, 1 H, N<u>H</u>C(=S)NHCH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 26.5 ($CHC(\underline{C}H_3)_3$), 27.2 ($CHC(\underline{C}H_3)_3$), 33.8 ($CH\underline{C}(CH_3)_3$), 34.7 ($CH\underline{C}(CH_3)_3$), 51.8 ($NHCH\underline{C}H_AH_BN_3$), 56.7 ($NH\underline{C}HCH_AH_BN_3$), 67.0 (NHC(=S)NH<u>C</u>H), 118.7 (spt, J_{FC} = 3.8 Hz, Ar<u>C</u>H), 122.9 (q, J_{FC} = 273.1 Hz, $ArC\underline{C}F_3$), 124.5 (q, J_{FC} = 3.9 Hz, Ar<u>C</u>H), 131.9 (q, J_{FC} = 33.7 Hz, $Ar\underline{C}CF_3$), 139.6 (Ar<u>C</u>), 172.1 (<u>C</u>=O), 181.9 (<u>C</u>=S); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm -63.0; **HRMS** (ESI+): calcd. for $C_{21}H_{28}F_6N_6NaOS$ $[M+Na]^+$ 549.1842, found 549.1840.

8.2.10.5 Synthesis and characterisation of 395

<u>*N*-[(2*S*)-1-Azido-3,3-dimethylbutan-2-yl]-N^2-{[3,5-bis(trifluoromethyl)phenyl]carbamoyl}-3-methyl-L-valinamide **395**</u>

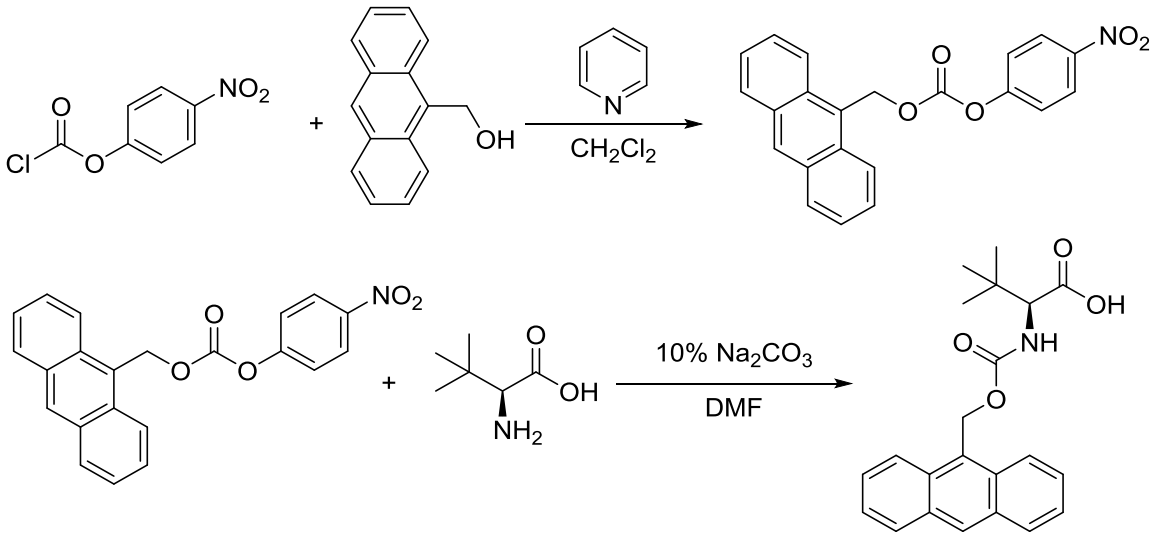


Azide **439** (124 mg, 0.35 mmol, 1.0 eq) was reacted with TFA (0.35 mL) then 3,5-bis(trifluoromethyl)phenyl isocyanate (60 µL, 0.35 mmol, 1.0 eq) was added according to a modified General Procedure **I** using Et_2O (2.0 mL). Purification by flash column chromatography [Petroleum ether to petroleum ether/Et_2O 4/1] afforded the title compound **395** as a colourless solid in 45% yield (80 mg). **MPT** 121 – 122 °C; **$[\alpha]_D^{20}$** = -22.4 (c = 1.25, $CHCl_3$); **IR** ν_{max}/cm^{-1} 3330, 2968, 2104, 1639, 1551, 1279, 1182, 1134; **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.78 (s, 9 H, $CHC(C\underline{H}_3)_3$), 1.18 (s, 9 H, $CHC(C\underline{H}_3)_3$), 3.20 (dd, *J* = 12.5, 9.5 Hz, 1 H, $NHCHC\underline{H}_AH_BN_3$), 3.65 (dd, *J* = 12.5, 3.0 Hz, 1 H, $NHCHCH_A\underline{H}_BN_3$), 3.82 ('td', *J* = 9.5,

3.0 Hz, 1 H, NHC<u>H</u>CH$_A$H$_B$N$_3$), 4.51 (d, *J* = 9.5 Hz, 1 H, NHC(=O)NHC<u>H</u>), 6.59 (d, *J* = 9.5 Hz, 1 H, N<u>H</u>CHCH$_A$H$_B$N$_3$), 6.89 (d, *J* = 9.5 Hz, 1 H, NHC(=S)N<u>H</u>CH), 7.38 (s, 1 H, Ar<u>H</u>), 7.75 (s, 2 H, Ar<u>H</u>), 8.56 (s, 1 H, N<u>H</u>C(=S)NHCH); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 26.3 (CHC(<u>C</u>H$_3$)$_3$), 26.8 (CHC(<u>C</u>H$_3$)$_3$), 33.8 (CH<u>C</u>(CH$_3$)$_3$), 34.8 ((CH<u>C</u>(CH$_3$)$_3$), 51.6 (NHCH<u>C</u>H$_A$H$_B$N$_3$), 57.0 (NH<u>C</u>HCH$_A$H$_B$N$_3$), 62.0 (NHC(=O)NH<u>C</u>H), 115.6 (spt, J_{FC} = 3.8 Hz, Ar<u>C</u>H), 118.5 (Ar<u>C</u>H), 121.1 (q, J_{FC} = 272.8 Hz, ArC<u>C</u>F$_3$), 132.1 (q, J_{FC} = 33.4 Hz, Ar<u>C</u>CF$_3$), 140.6 (Ar<u>C</u>), 155.4 (NH<u>C</u>(=O)NH), 172.7 (CH<u>C</u>(=O)NH); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm -63.3; **HRMS** (ESI+): calcd. for $C_{21}H_{28}F_6N_6NaO_2$ $[M+Na]^+$ 533.2070, found 533.2068.

8.2.10.6 Synthesis and characterisation of 396

<u>*N*-[(Anthracen-9-ylmethoxy)carbonyl]-3-methyl-L-valine **396**</u>



According to a literature procedure,[307] to a solution of 4-nitrophenylchloroformate (2.2 g, 11 mmol, 1.1 eq) in CH_2Cl_2 (14 mL) at rt was added pyridine (0.90 mL, 11 mmol, 1.1 eq) dropwise. The slurry was cooled to 0 °C and 9-anthracenemethanol (2.08 g, 10 mmol, 1.0 eq) was added portionwise. The reaction mixture was then allowed to warm to rt and stirring maintained overnight. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and

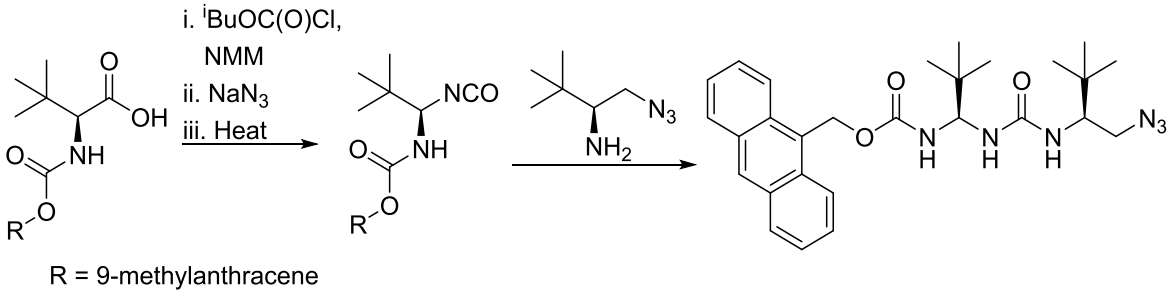
washed with 1 M HCl (20 mL), water (20 mL) and brine (20 mL) and dried ($MgSO_4$). The volatiles were removed *in vacuo* to afford a yellow solid in 60% yield (2.23g) which was used without further purification.

To a stirred solution of L-*tert*-Leucine (0.66 g, 5.0 mmol, 1.0 eq) in 10% aqueous Na_2CO_3 (13 mL) and DMF (10 mL) at 0 °C was slowly added the 4-nitrophenylcarbonate (1.87 g, 5.0 mmol, 1.0 eq) in DMF (15 mL). After stirring for one hour at this temperature, the reaction mixture was allowed to warm to rt overnight, diluted by the addition of H_2O (50 mL) and extracted with Et_2O (3 x 20 mL). The aqueous layer was cooled in an ice bath and acidified to pH 1 by the addition of concentrated HCl and then extracted with EtOAc (3 x 25 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to EtOAc] afforded the title compound **396** as a pale yellow solid in 60% yield (1.08 g).

MPT 153 – 154 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.00 (s, 9 H, C(C$\underline{H}_3$)$_3$), 4.27 (d, *J* = 10.0 Hz, 1 H, C$\underline{H}$NH), 5.31 (d, *J* = 10.0 Hz, 1 H, N$\underline{H}$CH), 6.13 (d, *J* = 12.5 Hz, 1 H, ArC$\underline{H}_A$H$_B$O), 6.20 (d, *J* = 12.5 Hz, 1 H, ArCH$_A$$\underline{H}_B$O), 7.44 - 7.61 (m, 4 H, Ar$\underline{H}$), 8.01 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}$), 8.37 (d, *J* = 8.5 Hz, 2 H, Ar$\underline{H}$), 8.49 (s, 1 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.6 (C($\underline{C}$H$_3$)$_3$), 34.7 ($\underline{C}$(CH$_3$)$_3$), 59.8 (Ar$\underline{C}$H$_A$H$_B$O), 62.4 ($\underline{C}$HNH), 124.1 (Ar$\underline{C}$H), 125.2 (Ar$\underline{C}$H), 126.4 (Ar$\underline{C}$), 126.8 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 131.2 (Ar$\underline{C}$), 131.5 (Ar$\underline{C}$), 156.6 (NH$\underline{C}$(=O)O), 176.4 ($\underline{C}$(=O)OH).

8.2.10.7 Synthesis and characterisation of 398

Anthracen-9-ylmethyl [(1*S*)-1-({[(2*S*)-1-azido-3,3-dimethylbutan-2-yl]carbamoyl}amino)-2,2-dimethylpropyl]carbamate **398**



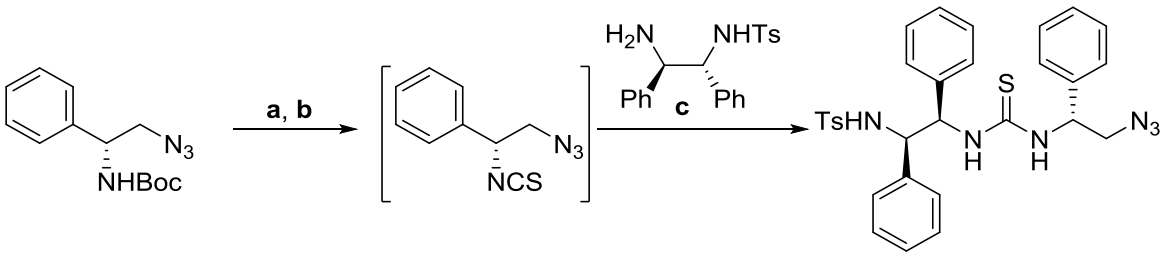
According to a modified literature procedure,[307] to a solution of **396** (365 mg, 1.0 mmol, 1.0 eq) in THF (4 mL) at -20 °C were added sequentially isobutyl chloroformate (130 µL, 1.0 mmol, 1.0 eq) and *N*-methylmorpholine (110 µL, 1.0 mmol, 1.0 eq) and stirring was maintained for 20 min. To the reaction mixture was added sodium azide (98 mg, 1.5 mmol, 1.5 eq) in H_2O (1.0 mL) and stirring was maintained for 30 min at -20 °C. The organic layer was then separated, the volatiles removed *in vacuo*, dissolved in CH_2Cl_2 (15 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to approximately 5 mL. The reaction mixture was heated to reflux for 2 h and then the reaction mixture was cooled to rt and the crude amino azide [obtained according to part I of General Procedure **I** using azide **125** (242 mg, 1.00 mmol, 1.00 eq)] as a solution in Et_2O (4 mL) was added dropwise. The reaction mixture was stirred at rt overnight and then the volatiles removed *in vacuo*. Purification by flash column chromatography [CH_2Cl_2/MeOH 9/1] and trituration with Et_2O afforded the title compound **398** as a colourless solid in 40% yield (200 mg).

MPT 268 – 270 °C; **IR** ν_{max}/cm^{-1} 3658, 3376, 2977, 2887, 2172, 1667, 1385, 1259, 1004; **^{1}H NMR** (500 MHz, CD_2Cl_2) δ ppm 0.88 (s, 9 H, C(C$\underline{H}_3$)$_3$), 0.89 (s, 9 H, C(C$\underline{H}_3$)$_3$), 3.18 - 3.25 (m, 1 H, CHC$\underline{H}_A$H$_B$N$_3$), 3.33 - 3.42 (m, 1 H, CHCH$_A\underline{H}_B$N$_3$), 3.75 - 3.85 (m, 1 H,

C<u>H</u>C$H_A$$H_B$$N_3$), 4.81 (d, *J* = 8.5 Hz, 1 H, N<u>H</u>CHNH), 4.89 (t, *J* = 9.5 Hz,1 H, NHC<u>H</u>NH), 5.00 (d, *J* = 11.0 Hz, 1 H, NHCHN<u>H</u>), 5.83 (br. s, N<u>H</u>CHC$H_A$$H_B$$N_3$), 6.03 (d, *J* = 12.5 Hz, 1 H, ArC<u>H_A</u>H_BO), 6.08 (d, *J* = 12.5 Hz, 1 H, ArCH_A<u>H_B</u>O), 7.40 - 7.43 (m, 2 H, Ar<u>H</u>), 7.47 - 7.50 (m, 2 H, Ar<u>H</u>), 7.96 (d, *J* = 8.5 Hz, 2 H, Ar<u>H</u>), 8.25 (d, *J* = 8.5 Hz, 2 H, Ar<u>H</u>), 8.44 (s, 1 H, Ar<u>H</u>); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ ppm 25.8 (C(<u>C</u>H_3)$_3$), 27.0 (C(<u>C</u>H_3)$_3$), 34.7 (<u>C</u>(CH_3)$_3$), 35.9 (<u>C</u>(CH_3)$_3$), 53.0 (CH<u>C</u>$H_A$$H_B$$N_3$), 58.9 (<u>C</u>HC$H_A$$H_B$$N_3$), 60.4 (Ar<u>C</u>$H_A$$H_B$O), 67.4 (NH<u>C</u>HNH), 124.4 (Ar<u>C</u>H), 125.7 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>), 127.2 (Ar<u>C</u>H), 129.6 (Ar<u>C</u>H), 129.7 (Ar<u>C</u>H), 131.5 (Ar<u>C</u>), 131.9 (Ar<u>C</u>), 157.8 (<u>C</u>=O), 157.9 (<u>C</u>=O); **HRMS** (ESI+): calcd. for $C_{28}H_{36}N_6NaO_3$ $[M+Na]^+$ 527.2741, found 527.2742.

8.2.10.8 Synthesis and characterisation of 401

<u>*N*-[(1*R*,2*R*)-2-({[(1*R*)-2-azido-1-phenylethyl]carbamothioyl}amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide **401**</u>



To **121** (105 mg, 0.40 mmol, 1.0 eq) at 0 °C was added TFA (0.4 mL) dropwise. The reaction mixture was allowed to warm to rt and stirring was maintained for 1 h whereupon the volatiles were removed under a stream of nitrogen. To the resultant oil was added CH_2Cl_2 (4 mL) and sat. aq $NaHCO_3$ (4 mL) and the biphasic mixture was stirred for 20 min. Stirring was stopped and thiophosgene (31 μL, 0.40 mmol, 1.00 eq) was added to the organic layer. 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 10 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered and the volatiles removed *in vacuo* to

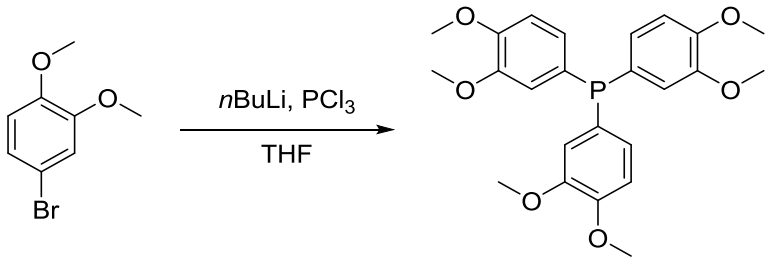
afford the crude isothiocyanate. To a solution of the isothiocyanate in THF (1.3 mL) was added (1*R*,2*R*)-*N*-(p-toluenesulfonyl)-1,2-diphenylethylenediamine (150 mg, 0.40 mmol, 1.0 eq) and stirring maintained for 14 h whereupon the volatiles were removed *in vacuo*. Purification by flash column chromatography [initial column: petroleum ether to petroleum ether: EtOAc 1:1 and second purification: petroleum ether to petroleum ether:Et_2O 1:1] and second afforded the title compound **401** as an amorphous pale yellow solid in 53% yield (120 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.26 (s, 3H), 3.77 (br s, 2H), 4.45 (br s, 1H), 4.56 - 4.70 (m, 1H), 5.45 - 5.75 (m, 1H), 6.55 - 6.84 (m, 2H), 6.88 - 7.11 (m, 9H), 7.35 - 7.61 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 21.3, 55.5, 62.6, 63.1, 63.2, 126.8, 126.9, 127.4, 127.4, 127.5, 127.6, 128.0, 129.1, 129.2, 136.6, 136.9, 137.1, 137.4, 137.9, 142.8, 142.9[xli]; **HRMS** (ESI+): calcd. for $C_{30}H_{31}N_6O_3S_2$ $[M+Na]^+$ 571.1944, found 571.1943.

8.2.11 Synthesis of Trivalent Phosphines

8.2.11.1 Synthesis and characterisation of 440

Tris(3,4-dimethoxyphenyl)phosphane **440**



According to a literature procedure,[308] to a solution of 4-bromoveratrole (2.1 mL, 15 mmol, 1.0 eq) in THF (20 mL) at -78 °C was added 2.5 M *n*BuLi in hexanes (5.9 mL, 15 mmol, 1.0 eq) dropwise over 30 minutes. To the reaction mixture was added freshly distilled phosphorous trichloride (0.430 mL, 4.92 mmol, 0.33 eq) in THF (10 mL)

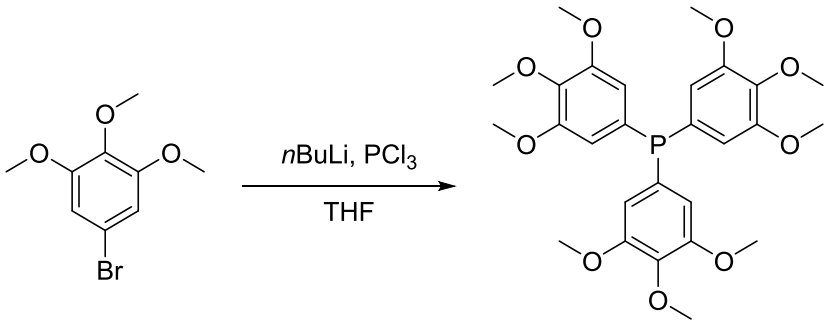
[xli] Quarterary carbon CS not found in spectrum.

dropwise maintaining the temperature below -50 °C. The reaction mixture was warmed to room temperature over one hour and stirring was maintained for 10 h whereupon the reaction mixture was quenched by the addition of 10% aq NH_4Cl (20 mL). The volatiles were removed *in vacuo* and the mixture diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organics were washed (brine) and dried ($MgSO_4$) and volatiles removed *in vacuo* to afford an orange oil. The crude reaction mixture was purified by recrystallisation [refluxing EtOH] to obtain the title compound **440** as a colourless solid (763 mg, 12% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.77 (s, 9 H), 3.88 (s, 9 H), 6.79 - 6.91 (m, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 55.8, 55.8, 111.2 (d, J_{PC} = 8.0 Hz), 116.1 (d, J_{PC} = 24.8 Hz), 126.5 (d, J_{PC} = 17.6 Hz), 129.0 (d, J_{PC} = 8.0 Hz), 148.9 (d, J_{PC} = 9.6 Hz), 149.6; **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm –4.90; **MP** 125 - 126 ˚C, **IR** ν_{max}/cm^{-1} 1587, 1504, 1452, 1392, 1313, 1249, 1232, 1177, 1139, 1097, 1023, 862, 843, 818, 805, 761, **HRMS** (ESI+): calcd. for $C_{24}H_{28}O_6P$ $[M+H]^+$ 443.1618, found 443.1606. Data is consistent with that given in the literature.[308]

8.2.11.2 Synthesis and characterisation of 441

Tris(3,4,5-trimethoxyphenyl)phosphane **441**



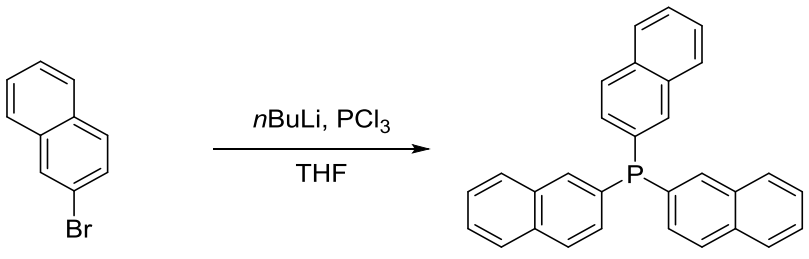
To a solution of 5-bromo-1,2,3-trimethoxybenzene (1.70 g, 6.90 mmol, 1.0 eq) in THF (10 mL) at -78 °C was added 2.5 M *n*BuLi in hexanes (2.76 mL, 6.90 mmol, 1.0 eq)

dropwise over 30 minutes. To the reaction mixture was added freshly distilled phosphorous trichloride (0.20 mL, 2.3 mmol, 0.33 eq) in THF (5.0 mL) dropwise maintaining the temperature below -50 °C. The reaction mixture was warmed to room temperature over one hour and stirring was maintained for 10 hours whereupon the reaction mixture was quenched by the addition of 10% aq NH_4Cl (20 mL). The volatiles were removed *in vacuo* and the mixture diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were washed (brine) and dried ($MgSO_4$) and volatiles removed *in vacuo* to afford an orange oil. The crude reaction mixture was purified by recrystallisation [refluxing EtOH] to obtain the title compound **441** as a colourless solid (717 mg, 20% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.75 (s, 18 H), 3.86 (s, 9 H), 6.57 (d, J = 8.1 Hz, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 56.2, 60.9, 110.5 (d, J_{PC} = 22.4 Hz), 132.0 (d, J_{PC} = 11.2 Hz), 138.8, 153.3 (d, J_{PC} = 8.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 2.37; **MP** 136 - 137 ˚C; **IR** ν_{max}/cm^{-1} 2359, 2164, 2011, 1573, 1499, 1467, 1399 1304, 1239, 1126, 999, 826, 772; **HRMS** (ESI+): calcd. for $C_{27}H_{34}O_9P$ $[M+H]^+$ 533.1935, found 533.1930.

8.2.11.3 Synthesis and characterisation of 442

Trinaphthalen-2-ylphosphane **442**



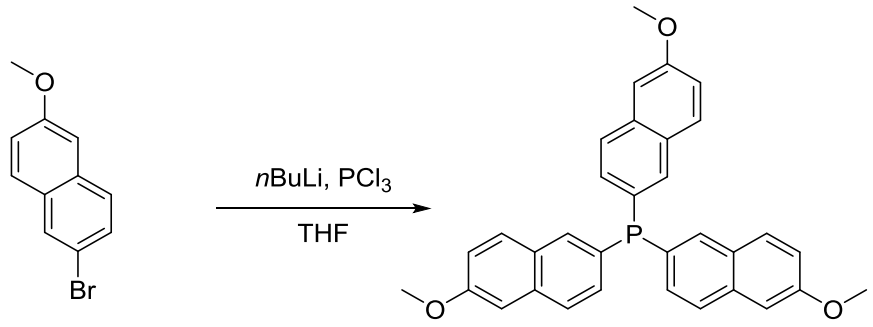
To a solution of 2-bromonaphthalene (1.4 g, 6.9 mmol, 1.0 eq) in THF (10 mL) at -78 °C was added 2.5 M *n*BuLi in hexanes (2.8 mL, 6.9 mmol, 1.0 eq) dropwise over 30 minutes. To the reaction mixture was added a solution of phosphorous trichloride (0.20 mL,

2.3 mmol, 0.33 eq) in THF (5 mL) dropwise maintaining the temperature below -50 °C. The reaction mixture was warmed to room temperature over one hour and stirring was maintained for 10 h whereupon the reaction mixture was quenched by the addition of 10% aq NH_4Cl (10 mL). The volatiles were removed *in vacuo* and the mixture diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed (brine) and dried ($MgSO_4$) and volatiles removed *in vacuo*. The crude material was purified by trituration in hot EtOH and filtered to obtain the title compound as a colourless solid in 90% purity (643 mg, 68% yield). An analytical sample was obtained by flash column chromatography [petroleum ether to petroleum ether/Et_2O 1/1] to afford the title compound **442** as a colourless solid.

MP 223 - 225 °C; **IR** ν_{max}/cm^{-1} 2978, 2360, 2035, 1974, 1585, 1494, 817, 743, 642; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.43 - 7.57 (m, 9 H, ArH), 7.74 (d, *J* = 8.0 Hz, 3 H, ArH), 7.83 ('t', *J* = 9.0 Hz, 6 H, ArH), 7.91 (d, *J* = 9.0 Hz, 3 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 126.5 (ArCH), 126.9 (ArCH), 127.9 (ArCH), 128.2 (d, J_{PC} = 6.4 Hz, ArC), 128.3 (ArCH), 130.3 (d, *J* = 17.5 Hz, ArCH), 133.5 (d, J_{PC} = 8.7 Hz, ArC), 133.6 (ArCH), 134.5 (d, *J* = 22.3 Hz, ArCH), 134.6 (d, J_{PC} = 11.1 Hz, ArCP); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm -3.74; **HRMS** (ESI+): calcd. for $C_{30}H_{22}P$ $[M+H]^+$ 413.1454, found 413.1455.

8.2.11.4 Synthesis and characterisation of 443

Tris(6-methoxynaphthalen-2-yl)phosphane **443**



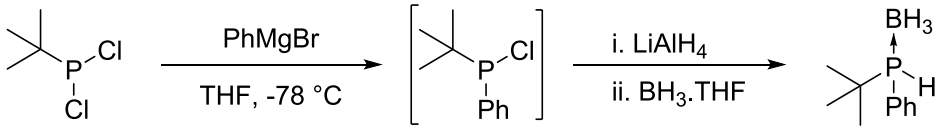
To a solution of 2-bromo-6-methoxynaphthalene (1.64 g, 6.9 mmol, 1.0 eq) in THF (10 mL) at -78 °C was added 2.5 M *n*BuLi in hexanes (2.8 mL, 6.9 mmol, 1.0 eq) dropwise over 30 minutes. To the reaction mixture was added a solution of phosphorous trichloride (0.20 mL, 2.3 mmol, 0.33 eq) in THF (5 mL) dropwise maintaining the temperature below -50 °C. The reaction mixture was warmed to room temperature over one hour and stirring was maintained for 10 h whereupon the reaction mixture was quenched by the addition of 10% aq NH_4Cl (10 mL). The volatiles were removed *in vacuo* and the mixture diluted with water (10 mL) and extracted with CH_2Cl_2 (3x 20 mL). The combined organics were washed (brine) and dried ($MgSO_4$) and volatiles removed *in vacuo*. The crude material was purified by trituration in hot EtOH and filtered to obtain 1.27 g of crude phosphine. Purification by flash column chromatography [CH_2Cl_2] afforded the title compound **443** as a colourless solid in 30% yield (350 mg).

MP 101 – 102 °C; **IR** ν_{max}/cm^{-1} 3052, 3005, 2933, 1622, 1588, 1469, 1386, 1262, 1212, 1161, 1030, 853, 759; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 3.93 (s, 9 H, OC$\underline{H}_3$), 7.10 - 7.16 (m, 6 H, ArC$\underline{H}$), 7.44 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 3 H, ArC$\underline{H}$), 7.60 - 7.66 (m, 3 H, ArC$\underline{H}$), 7.71 (d, *J* = 8.5 Hz, 3 H, ArC$\underline{H}$), 7.76 - 7.85 (m, 3 H, ArC$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 55.5 (O$\underline{C}H_3$), 105.8 (Ar$\underline{C}$H), 119.2 (Ar$\underline{C}$H), 127.1 (d, J_{PC} = 7.2 Hz, Ar$\underline{C}$H), 129.0 (d, J_{PC} = 8.7 Hz, Ar$\underline{C}$), 129.8 (Ar$\underline{C}$H), 130.9 (d, J_{PC} = 17.5 Hz, Ar$\underline{C}$H), 132.2 (d, J_{PC}

= 9.5 Hz, Ar<u>C</u>), 134.1 (d, J_{PC} = 23.1 Hz, Ar<u>C</u>H), 134.8 (Ar<u>C</u>), 158.5 (Ar<u>C</u>OCH$_3$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm -4.84; **HRMS** (ESI+): calcd. for $C_{33}H_{28}O_3P$ $[M+H]^+$ 503.1771, found 503.1772.

8.2.11.5 Synthesis and characterisation of 422

<u>*tert*-Butylphenylphosphine borane **422**</u>



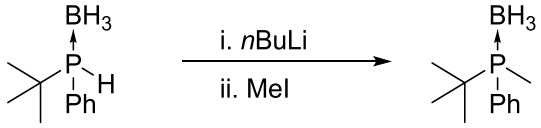
To a 1.0 M in Et_2O *tert*-butyldichlorophosphine solution (14.0 mL, 14.0 mmol, 1.00 eq) in THF (40 mL) at -78 °C was added dropwise 1.0 M in THF phenylmagnesium bromide solution (14.0 mL, 14.0 mmol, 1.0 eq) and the reaction mixture was allowed to warm to rt over one hour. The reaction mixture was then cooled to 0 °C and 1.0 M $LiAlH_4$ in Et_2O (14.0 mL, 14.0 mmol, 1.0 eq) was added dropwise followed by the addition of 1.0 M in THF BH_3•THF complex (16.0 mL, 16.0 mmol, 1.14 eq). The reaction mixture was allowed to warm to rt and stirring maintained overnight. The reaction mixture was carefully poured into a mixture of concentrated HCl (10 mL), ice (30 g), and CH_2Cl_2 (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [petroleum ether to Et_2O] afforded the title compound **422** as a colourless oil in 64% yield (1.62 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.20 - 1.00 (br m, 3 H, B<u>H</u>$_3$), 1.18 (d, J_{PH} = 14.9 Hz, 9 H, C(C<u>H</u>$_3$)$_3$), 5.09 (dq, J_{PH} = 363.5, J_{HH} = 6.6 Hz, 1 H, P<u>H</u>), 7.41 - 7.50 (m, 2 H, Ar<u>H</u>), 7.50 - 7.56 (m, 1 H, Ar<u>H</u>), 7.60 - 7.71 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.6 (d, J_{PC} = 2.4 Hz, C(<u>C</u>H$_3$)$_3$), 28.5 (d, J_{PC} = 32.6 Hz, <u>C</u>(CH$_3$)$_3$), 124.9 (d, J_{PC} = 51.7 Hz, Ar<u>C</u>), 128.7 (d, J_{PC} =9.5 Hz, Ar<u>C</u>H), 131.7 (d, J_{PC} = 2.4 Hz, Ar<u>C</u>H), 134.0 (d, J_{PC} = 7.2 Hz,

ArCH); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 30.1 (q, J_{PB} = 92 Hz). Data is consistent with that given in the literature.[309,310]

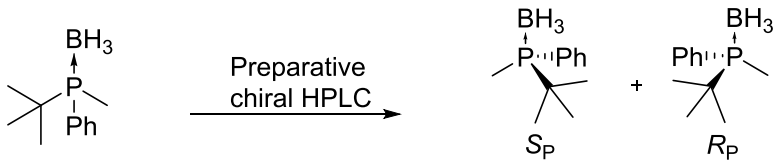
8.2.11.6 Synthesis and characterisation of 423

(±)-*tert*-Butylmethylphenylphosphine borane **423**



According to a modified literature procedure,[311] to a solution of **422** (1.42 g, 7.89 mmol, 1.00 eq) in Et_2O (60 mL) at -78 °C was added 2.5 M *n*BuLi in hexanes (3.47 mL, 8.69 mmol, 1.10 eq) dropwise and the reaction mixture was allowed to warm to room temperature over one hour. The reaction mixture was then cooled to -78 °C, methyl iodide (0.737 mL, 11.8 mmol, 1.50 eq) was added dropwise and then the reaction mixture allowed to warm to rt and stirring maintained overnight. The reaction mixture was quenched by the addition of 1 M HCl (10 mL) and the aqueous phase extracted with Et_2O (3 x 20 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to petroleum ether/Et_2O 4/1] afforded the title compound **423** as a colourless solid in 91% yield (1.40 g). **MP** 80 - 82 °C [lit. 81 - 82 °C][312]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.22 - 0.91 (br m, 3 H, BH_3), 1.09 (d, J_{PH} = 13.9 Hz, 9 H, $C(CH_3)_3$), 1.56 (d, J_{PH} = 9.5 Hz, 3 H, PCH_3), 7.39 - 7.55 (m, 3 H, ArH), 7.61 - 7.81 (m, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 5.3 (d, J_{PC} = 37.4 Hz, PCH_3), 25.2 (d, J_{PC} = 2.4 Hz, $PC(CH_3)_3$), 28.6 (d, J_{PC} = 33.4 Hz, $PC(CH_3)_3$), 127.7 (d, J_{PC} = 50.9 Hz, ArC), 128.3 (d, J_{PC} = 9.5 Hz, ArCH), 131.2 (d, J_{PC} = 2.4 Hz, ArCH), 132.9 (d, J_{PC} = 7.9 Hz, ArCH); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 25.0 (q, J_{BP} = 60.0 Hz). Data is consistent with that given in the literature.[282,313]

8.2.11.7 Separation of the enantiomers of 423



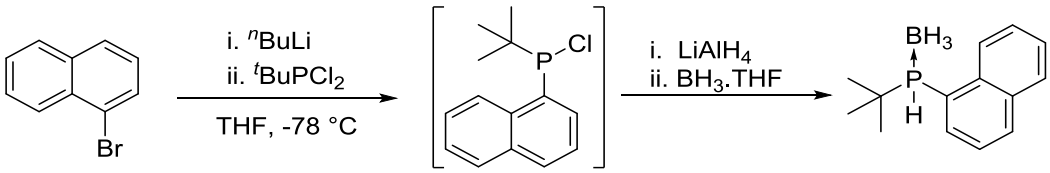
(±)-**423** (30 mg) was dissolved in hexane: *i*PrOH 1:1 and injected onto a preparative Chiralpak-AS column (99:1 hexane: *i*PrOH, 22 mL/min) and fractions collected every 30 seconds. The enantiomeric excess of each fraction was determined by analytical HPLC (AS-H, 95:5 hexane: *i*PrOH, 1 mL/min) and only fractions with ee greater than 99% were retained.

9.78 min: (S_P)-**423** (6.0 mg); $\mathbf{[\alpha]_D^{20}}$ = +15.1 (c = 0.17, $CHCl_3$).

12.21 min: (R_P)-**423** (6.5 mg); $\mathbf{[\alpha]_D^{24}}$ = -13.9 (c = 0.54, $CHCl_3$), [lit. for (R_P)-**423** $[\alpha]_D^{25}$ -15.0, c = 0.3][282].

8.2.11.8 Synthesis and characterisation of 444

<u>*tert*-Butyl-1-naphtylphosphine borane **444**</u>



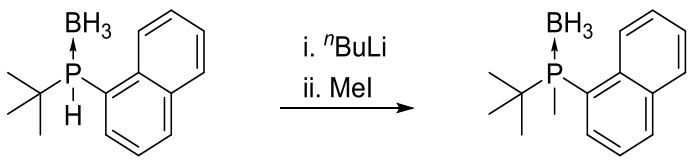
To a solution of 1-bromonaphthalene (0.98 mL, 7.0 mmol, 1.0 eq) in THF (20 mL) at -78 °C was added dropwise 2.5 M in hexanes nBuLi (2.8 mL, 7.0 mmol, 1.0 eq) and left to stir for one hour. The solution was then transferred *via* cannula to a solution of 1.0 M ^{t}butyldichlorophosphine in Et_2O (7.0 mL, 7.0 mmol, 1.0 eq) at -78 °C and the reaction mixture was allowed to warm to rt over one hour. The reaction mixture was then cooled to 0 °C and 1.0 M $LiAlH_4$ in Et_2O (7.0 mL, 7.0 mmol, 1.0 eq) was added dropwise followed by the addition of 1.0 M in THF BH_3·THF complex (8.0 mL, 8.0 mmol, 1.14 eq). The

reaction mixture was allowed to warm to rt and stirring maintained overnight. The reaction mixture was carefully poured into a mixture of concentrated HCl (5 mL), ice (15 g), and CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum Ether to Et_2O] afforded the title compound **444** as an amorphous colourless solid in 67% yield (1.18 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.20 - 1.01 (br. m, 3 H, B$\underline{H}_3$), 1.11 (d, J_{PH} = 14.9 Hz, 9 H, PC(C$\underline{H}_3$)$_3$), 5.70 (dq, J_{PH} = 365.6 Hz, J_{HH} = 6.1 Hz, 1 H, P$\underline{H}$), 7.37 - 7.56 (m, 3 H, Ar$\underline{H}$), 7.80 (d, J = 8.1 Hz, 1 H, Ar$\underline{H}$), 7.84 - 7.97 (m, 2 H, Ar$\underline{H}$), 8.19 (d, J = 8.3 Hz, 1 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 27.3 (d, J_{PC} = 3.2 Hz, PC($\underline{C}H_3$)$_3$), 30.2 (d, J_{PC} = 31.8 Hz, P$\underline{C}$(CH$_3$)$_3$), 122.5 (d, J_{PC} = 46.1 Hz, Ar$\underline{C}$), 125.0 (d, J_{PC} = 11.9 Hz, Ar$\underline{C}$H), 125.8 (d, J_{PC} = 4.0 Hz, Ar$\underline{C}$H), 126.4 (Ar$\underline{C}$H), 127.3 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 132.7 (d, J_{PC} = 3.2 Hz, Ar$\underline{C}$H), 133.6 (d, J_{PC} = 6.4 Hz, Ar$\underline{C}$), 134.0 (d, J_{PC} =4.0 Hz, Ar$\underline{C}$), 135.6 (d, J_{PC} =11.1 Hz, Ar$\underline{C}$H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 13.3 (br. s). Data is consistent with that given in the literature.[282]

8.2.11.9 Synthesis and characterisation of 445

(±)-*tert*-Butylmethyl-1-naphtylphosphine borane **445**

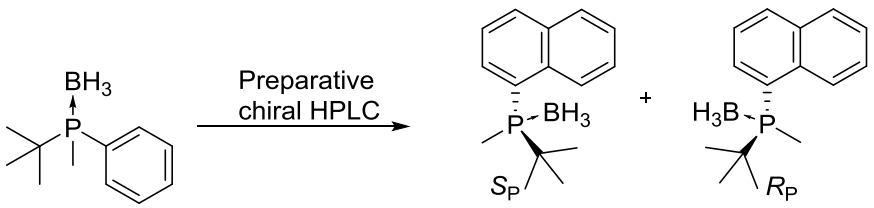


To a solution of **444** (800 mg, 3.17 mmol, 1.0 eq) in Et_2O (23 mL) at -78 °C was added 2.5 M *n*BuLi in hexanes (1.39 mL, 3.49 mmol, 1.10 eq) dropwise and the reaction mixture was allowed to warm to room temperature over one hour. The reaction mixture was then

cooled to -78 °C, methyl iodide (0.296 mL, 4.76 mmol, 1.50 eq) was added dropwise and then the reaction mixture allowed to warm to rt and stirring maintained overnight. The reaction mixture was quenched by the addition of 1 M HCl (5 mL) and the aqueous phase extracted with Et_2O (3 x 15 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [petroleum ether to petroleum ether/Et_2O 4/1] afforded the title compound **445** as a colourless solid in 76% yield (590 mg).

MPT 131 - 133 °C [lit. 144 - 146 °C for (*R*)- **445**][282]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 0.53 - 1.58 (m, 3 H, B$\underline{H}_3$), 1.19 (d, J_{PH} = 14.2 Hz, 9 H, PC(C$\underline{H}_3$)$_3$), 1.82 (d, J_{PH} = 9.0 Hz, 3 H, PC$\underline{H}_3$), 7.47 - 7.66 (m, 3 H, Ar$\underline{H}$), 7.77 - 7.85 (m, 1 H, Ar$\underline{H}$), 7.90 (d, *J* = 8.1 Hz, 1 H, Ar$\underline{H}$), 8.02 (d, *J* = 8.1 Hz, 1 H, Ar$\underline{H}$), 8.94 (d, *J* = 8.6 Hz, 2 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 9.1 (d, J_{PC} =39.7 Hz, P$\underline{C}$H$_3$), 25.9 (d, J_{PC} = 3.2 Hz, PC($\underline{C}$H$_3$)$_3$), 30.7 (d, J_{PC} = 31.8 Hz, P$\underline{C}$(CH$_3$)$_3$), 124.4 (d, J_{PC} = 9.5 Hz, Ar$\underline{C}$H), 125.2 (d, J_{PC} = 44.5 Hz, Ar$\underline{C}$), 126.4 (Ar$\underline{C}$H), 126.7 (Ar$\underline{C}$H), 128.3 (d, J_{PC} = 5.6 Hz, Ar$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 132.6 (d, J_{PC} = 2.4 Hz, Ar$\underline{C}$H), 133.6 (d, J_{PC} = 4.0 Hz, Ar$\underline{C}$H), 134.0 (d, J_{PC} = 7.2 Hz, Ar$\underline{C}$), 135.5 (d, J_{PC} = 11.1 Hz, Ar$\underline{C}$); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 23.9 (br. q, J_{BP} = 66.5 Hz). Data is consistent with that given in the literature.[282]

8.2.11.10 Separation of enantiomers of 445



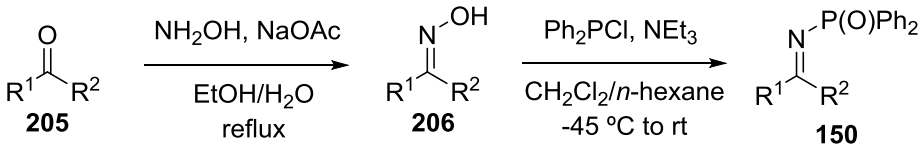
(±)-**445** (9 mg) was dissolved in *i*PrOH 1:1 and injected onto a preparative Chiralpak-AS column (99.5:0.5 hexane: *i*PrOH, 22 mL/min) and fractions collected every 30 seconds. The enantiomeric excess of each fraction was determined by analytical HPLC (AS-H, 95:5

hexane: *i*PrOH, 1 mL/min) and only fractions with ee greater than 99% were retained. The peak maxima were obtained at 10.66 min (S_P)-**445** (3.0 mg) and 17.61 min (R_P)-**445** (3.0 mg).

8.3 Ketimine Nitro-Mannich Reaction

8.3.1 General Procedures

General Procedure III **for the Synthesis of Diphenylphosphinoyl Ketimines**



To a solution of $NH_2OH{\cdot}HCl$ (1.5 equiv.) and NaOAc (1.5 equiv.) in EtOH/H_2O (1:1, 1.8 M) was added the corresponding ketone **205** (1.0 eq) at room temperature, and then refluxed for 8 hours. After cooling to room temperature, the reaction mixture was stored at - 20 °C for 24 hours. The precipitated oxime was filtered, washed with ethanol at 0 ˚C, vacuum dried and used directly without further purification. To a solution of oxime (1.0 equiv.) in dichloromethane/*n*-hexane (1: 1, 0.3 M) under inert atmosphere at -45 °C was added triethylamine (1.1 eq) and stirred for 10 min. Subsequently, chlorodiphenylphosphine (1.1 eq.) was added dropwise over 20 minutes by syringe pump. After stirring at -45 °C for one hour and room temperature for 16 h, the solvents were removed under reduced pressure (temperature of water bath below 20 °C). The crude reaction mixture was dissolved in CH_2Cl_2 and washed with water (2 x), then brine and dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [petrol/EtOAc mixtures, or as specified in the individual experiment] yielded the desired ketimines **150**.

General Procedure IV **for the Ketimine Nitro-Mannich Catalyst Optimisation Studies**

To a stirred solution of the catalyst precursors (0.020 mmol) in Et_2O (0.1 mL) in a closed vial was added triphenylphosphine (5.2 mg, 0.020 mmol, 1 eq) and stirred at rt for 24 h. The catalyst formation was confirmed by LRMS and TLC, the volatiles removed under nitrogen stream and to the crude mixture was added ketimine **150a** (64 mg, 0.20 mmol) and $MeNO_2$ (0.215 mL, 4.00 mmol). The reaction was stirred at rt for 24 h and quenched by the addition of 0.05 mL of a 1 M acetic acid solution in CH_2Cl_2 and stirred at rt for 10 min. After evaporation of the solvents, the conversion was measured by ^1H NMR and the ee was determined on an analytical sample obtained by flash column chromatography (PE/EtOAc).

General Procedure V **for the Enantioselective Ketimine Nitro-Mannich Addition of Nitromethane to Ketimines at -15 ºC**

To a stirred suspension of ketimine **150** (0.200 mmol) in $MeNO_2$ (0.215 mL, 4.00 mmol) at **-15 ºC**, catalyst **145** (0.020 mmol) was added and the reaction mixture was stirred at **-15 ºC** in a closed vial until disappearance of starting material by TLC or for a maximum of 96 h. The reaction was quenched by addition of 0.05 mL of a 1 M acetic acid solution in CH_2Cl_2 and stirred at rt for 10 min. After evaporation of the solvents the crude reaction mixture was purified by flash column chromatography.

General Procedure VI **for the Enantioselective Ketimine Nitro-Mannich Addition of Nitromethane to Ketimines at 0 ºC**

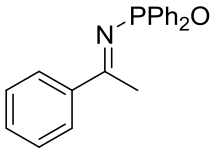
To a stirred suspension of ketimine **150** (0.200 mmol) in $MeNO_2$ (0.215 mL, 4.00 mmol) at **0 ºC**, catalyst **145** (0.020 mmol) was added and the reaction mixture was stirred at **0 ºC** in a closed vial until disappearance of starting material by TLC or for a maximum of 48 h. The reaction was quenched by addition of 0.05 mL of a 1 M acetic acid solution in CH_2Cl_2

and stirred at rt for 10 min. After evaporation of the solvents the crude reaction mixture was purified by flash column chromatography.

8.3.2 Synthesis and Characterisation of Ketimines

8.3.2.1 Synthesis and Characterisation of 150a

P,*P*-Diphenyl-*N*-[(1*E*)-1-phenylethylidene]phosphinic amide **150a**



A solution of acetophenone (29.0 mL, 250 mmol, 1.0 eq), hydroxylamine hydrochloride (24.0 g, 375 mmol, 1.5 eq) and sodium acetate (31.0 g, 375 mmol, 1.5 eq) in 1:1 water: EtOH (200 mL) was refluxed for 14 h. The reaction mixture was cooled and volatiles removed *in vacuo* and the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organics were washed with brine (30 mL), dried ($MgSO_4$). The crude product was purified by distillation [7 mBar, 115 °C] (lit.[314] bp 20 Torr, 119 °C) to afford the oxime as a colourless solid in 89% yield (30.2 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.32 (s, 3H), 7.32 - 7.51 (m, 3H), 7.55 - 7.78 (m, 2H); **MP** 58- 59 ˚C (lit. 58 ˚C)[315]. Data is consistent with that given in the literature.[316]

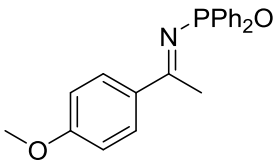
According to a modified literature procedure,[317] to a solution of acetophenone oxime (14.2 g, 105 mmol, 1.0 eq) in 1:1 CH_2Cl_2: Hex (314 mL) was added triethylamine (16.1 mL, 116 mmol, 1.5 eq). The reaction mixture was cooled to -45 °C and chlorodiphenylphosphine (21.4 mL, 115.7 mmol, 1.1 eq) was added dropwise over 2 hours using a syringe pump such that the temperature did not exceed -45 °C. The reaction mixture was allowed to slowly warm to room temperature and stirring was maintained for 12 h whereupon the reaction mixture was filtered and the filter cake washed with 1:1 Et_2O: CH_2Cl_2 (180 mL). The volatiles of the filtrate were removed *in vacuo*, the crude product was triturated with Et_2O (40 mL) for 2 hours and the reaction mixture filtered. Purification

of the crude material by flash column chromatography [300 g silica gel, 1:1 Petrol: EtOAc then 1:3 Petrol: EtOAc] afforded the title compound **150a** as an off white solid (17.9 g, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.95 (d, J = 2.0 Hz, 3H), 7.35 - 7.53 (m, 9H), 7.95 - 8.10 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 22.7 (d, J_{PC} = 12.8 Hz), 127.6, 128.1 (d, J_{PC} = 12.0 Hz), 128.3, 131.1 (d, J_{PC} = 3.2 Hz), 131.3 (d, J_{PC} = 9.6 Hz), 132.2, 134.5 (d, J_{PC} = 131.0 Hz), 139.1 (d, J_{PC} = 23.2 Hz), 181.2 (d, J_{PC} = 8.0 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 18.9; **MP** 130 - 132 ˚C (lit. 128 - 130 ˚C)[318]. Data is consistent with that given in the literature.[319]

8.3.2.2 Synthesis and characterisation of 150e

N-[(1*E*)-1-(4-Methoxyphenyl)ethylidene]-*P*,*P*-diphenylphosphinic amide **150e**

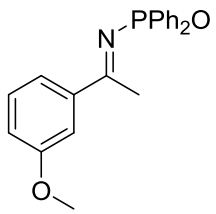


Synthesised according to General Procedure **III**, on a 4.42 mmol scale of the oxime to afford the title compound **150e** as an off-white solid (852 mg, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.93 (d, J = 1.9 Hz, 3H), 3.89 (s, 3H), 6.97 (d, J = 9.0 Hz, 2H), 7.36 - 7.56 (m, 6H), 7.91 - 8.02 (m, 4H), 8.07 - 8.13 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 22.8 (d, J_{PC} = 12.8 Hz), 55.4, 113.7, 128.3 (d, J_{PC} = 12.0 Hz), 130.1, 131.2 (d, J_{PC} = 2.4 Hz), 131.5 (d, J_{PC} = 9.6 Hz), 132.1 (d, J_{PC} = 24.8 Hz), 135.0 (d, J_{PC} = 131.0 Hz), 163.1, 180.5 (d, J_{PC} = 7.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 19.8; **MP** 120 - 122 ˚C. Data is consistent with that given in the literature.[317]

8.3.2.3 Synthesis and characterisation of 150f

N-[(1*E*)-1-(3-Methoxyphenyl)ethylidene]-*P*,*P*-diphenylphosphinic amide **150f**

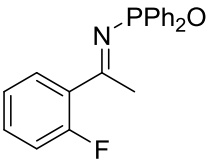


Synthesised according to General Procedure **III**, on a 8.78 mmol scale of the oxime to afford the title compound **150f** as a colourless amorphous solid after purification by flash column chromatography and then trituration with Et_2O (1.90g, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.95 (d, *J* = 2.0 Hz, 3H), 3.87 (s, 3H), 7.05 - 7.12 (m, 1H), 7.34 - 7.49 (m, 7H), 7.61 - 7.69 (m, 2H), 7.93 - 8.05 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 23.0 (d, J_{PC} = 12.8 Hz), 55.3, 113.3, 117.6, 120.4, 128.3 (d, J_{PC} = 12.8 Hz), 129.4, 131.3 (d, J_{PC} = 3.2 Hz), 131.4 (d, J_{PC} = 8.8 Hz), 134.6 (d, J_{PC} = 131.0 Hz), 140.8 (d, J_{PC} = 24.0 Hz), 159.5, 181.2 (d, J_{PC} = 8.0 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 20.1. Data is consistent with that given in the literature.[317]

8.3.2.4 Synthesis and characterisation of 150h

N-[(1*E*)-1-(2-fluorophenyl)ethylidene]-*P*,*P*-diphenylphosphinic amide **150h**



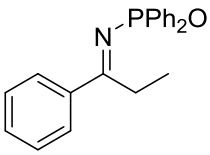
Synthesised according to General Procedure **III**, on a 9.80 mmol scale of the oxime to afford after flash column chromatography and trituration (Et_2O) the title compound **150h** as a colourless solid (1.77 g, 42% yield).

MPT 98-100 °C; **IR** ν_{max}/cm^{-1} 1640, 1483, 1200, 1122; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 2.97 (dd, *J* = 4.0, 2.0 Hz, 3H), 7.11 (dd, *J* = 11.1, 8.6 Hz, 1H), 7.22 ('t', *J* = 7.6 Hz, 1H), 7.37 - 7.53 (m, 7H), 7.89 (td, *J* = 7.7, 1.8 Hz, 1H), 7.94 - 8.04 (m, 4H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 27.2 (dd, J_{PC} =12.8, J_{FC} = 7.2 Hz), 116.7 (d, J_{FC} = 23.2 Hz), 124.2 (d, J_{FC} = 4.0 Hz), 128.4 (d, J_{PC} = 12.0 Hz), 128.5 - 128.7 (m, 1C), 130.3 (d, J_{FC} = 2.4 Hz), 131.4 (d, J_{PC} = 2.4 Hz), 131.5 (d, J_{PC} = 9.6 Hz), 133.3 (d, J_{FC} = 8.8 Hz), 134.2 (d, J_{PC} = 130.2 Hz), 161.5 (d, J_{FC} = 254.9 Hz), 180.9 (dd, J_{PC} = 7.2, J_{FC} = 2.4 Hz); **^{31}P NMR**

(162 MHz, $CDCl_3$) δ ppm 20.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ ppm - 110.0; **HRMS** (ESI+): calcd. for $C_{20}H_{17}FNNaOP$ $[M+Na]^+$ 360.0924, found 360.0915.

8.3.2.5 Synthesis and characterisation of 150m

P,*P*-Diphenyl-*N*-[(1*E*)-1-phenylpropylidene]phosphinic amide **150m**

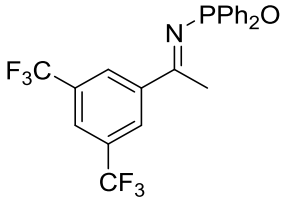


Synthesised according to General Procedure **III**, on a 10.1 mmol scale of the oxime to afford after trituration (Et_2O) the title compound **150m** as a colourless solid (1.72 g, 54% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm 1.22 (t, J = 7.7 Hz, 3H), 3.44 (qd, J_{HH} = 7.7 Hz, J_{PH} = 1.5 Hz, 2H), 7.38 – 7.60 (m, 9H), 7.94 – 8.10 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 13.3, 29.3 (d, J_{PC} = 11.9 Hz), 128.1, 128.5, (d, J_{PC} = 12.7 Hz), 128.7, 131.4 (d, J_{PC} = 2.4 Hz), 131.7 (d, J_{PC} = 8.7 Hz), 132.4, 135.1 (d, J_{PC} = 131.1 Hz), 138.1 (d, J_{PC} = 12.7 Hz), 186.8 (d, J_{PC} = 7.2 Hz); **MP** 98-100 °C. Data is consistent with that given in the literature.[317]

8.3.2.6 Synthesis and characterisation of 150q

P,*P*-Diphenyl-*N*-[1-(3,5-bis(trifluoromethyl)phenyl)ethylidene]phosphinic amide **150q**



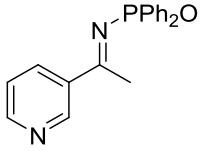
Synthesised according to General Procedure **III**, on a 3.69 mmol scale of the oxime and purification by flash column chromatography [CH_2Cl_2 then 10:1 CH_2Cl_2: Et_2O] afforded the title compound **150q** as a colourless solid (917 mg, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.05 (d, J = 2.0 Hz, 3H), 7.42 - 7.59 (m, 6H), 7.90 - 8.01 (m, 4H), 8.05 (s, 1H), 8.46 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 178.1 (d, J_{PC} = 7.1 Hz), 141.3 (d, J_{PC} = 24.6 Hz), 133.5 (d, J_{PC} = 130.9 Hz), 132.1 (q, J_{FC} = 33.8 Hz), 131.9 (d, J_{PC} = 2.5 Hz), 131.5 (d, J_{PC} = 9.3 Hz), 128.6 (d, J_{PC} = 12.7 Hz), 127.7 (br s),

125.3–125.6 (m, 1C), 123.0 (q, J_{FC} = 272.8 Hz), 22.9 (d, J_{PC} = 11.8 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 21.5; **MP** 120 - 121 °C; **IR** ν_{max}/cm^{-1} 1649, 1438, 1382, 1279, 1245, 1184, 1134, 746, 727, 695; **HRMS** (ESI+): calcd. for $C_{22}H_{17}F_6NOP$ $[M+H]^+$ 456.0946, found 456.0924.

8.3.2.7 Synthesis and characterisation of 150r

P,P-Diphenyl-*N*-[(1*E*)-1-(pyridin-3-yl)ethylidene]phosphinic amide **150r**

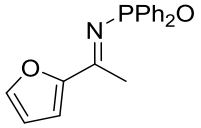


Synthesised according to General Procedure **III**, on a 7.35 mmol scale of the oxime to afford the title compound **150r** as an off-white solid (900 mg, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.98 (d, *J* = 1.3 Hz, 3H), 7.31 - 7.59 (m, 7H), 7.86 - 8.09 (m, 4H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.75 (d, *J* = 4.0 Hz, 1H), 9.30 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) ppm 22.8 (d, J_{PC} = 12.0 Hz), 123.3, 128.5 (d, J_{PC} = 12.8 Hz), 131.5 (d, J_{PC} = 9.6 Hz), 131.6 (d, J_{PC} = 2.4 Hz), 134.1 (d, J_{PC} = 131.0 Hz), 134.5, 135.0, 149.4, 152.7, 179.4 (d, J_{PC} = 7.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 19.5; **MP** 136-137 ˚C. Data consistent with that given in the literature.[317]

8.3.2.8 Synthesis and characterisation of 150s

N-[(1*E*)-1-(2-Furyl)ethylidene]-*P,P*-diphenylphosphinic amide **150s**



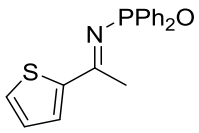
Synthesised according to General Procedure **III**, on a 7.99 mmol scale of the oxime to afford the title compound **150s** as a colourless solid (1.40g, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.80 (d, *J* = 1.5 Hz, 3H), 6.46 - 6.62 (m, 1H), 7.24 (d, *J* = 3.3 Hz, 1H), 7.35 - 7.52 (m, 6H), 7.62 (br s, 1H), 7.83 - 8.07 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 22.2 (d, J_{PC} = 12.8 Hz), 112.6, 116.5, 128.4 (d, J_{PC} = 12.8 Hz),

131.3 (d, J_{PC} = 2.4 Hz), 131.6 (d, J_{PC} = 9.6 Hz), 134.8 (d, J_{PC} = 131.0 Hz), 146.5, 154.4 (d, J_{PC} = 29.6 Hz), 170.2 (d, J_{PC} = 4.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 19.7; **MP** 167 – 170 ˚C. Data consistent with that given in the literature.[317]

8.3.2.9 Synthesis and characterisation of 150t

<u>*P*,*P*-Diphenyl-*N*-[(1*E*)-1-(2-thienyl)ethylidene]phosphinic amide **150t**</u>



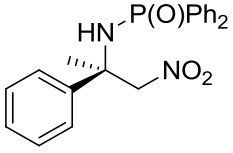
Synthesised according to General Procedure **III**, on a 7.09 mmol scale of the oxime to afford the title compound **150t** as pale yellow solid (820 mg, 37% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ ppm (d, *J* = 2.0 Hz, 3H), 7.11 (ddd, *J* = 4.9, 3.9, 0.9 Hz, 1H), 7.35 - 7.51 (m, 6H), 7.56 - 7.67 (m, 2H), 7.86 - 8.11 (m, 4H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ ppm 22.8 (d, J_{PC} = 11.8 Hz), 128.3, 128.3 (d, J_{PC} = 12.3 Hz), 131.2 – 131.6 (m, 3C), 133.3, 134.8 (d, J_{PC} = 130.8 Hz), 147.5 (d, J_{PC} = 24.6 Hz), 174.5 (d, J_{PC} = 5.9 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 18.3; **HRMS** (ESI+): calcd. for $C_{18}H_{16}NNaOPS$ $[M+Na]^+$ 348.0582, found 348.0574.

8.3.3 Ketimine nitro-Mannich methodology

8.3.3.1 Synthesis and characterisation of 152a

<u>*N*-[(2*R*)-1-Nitro-2-phenylpropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152a**</u>



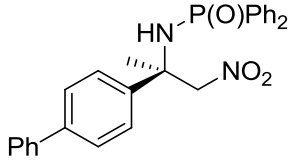
Obtained according to General Procedure **V**, using ketimine **150a** (63.8 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column

chromatography (PE/EtOAc 1:1) to yield compound **152a** (65 mg, 86%) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/iso-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 8.09 min, t (major) = 20.25 min (95%).

$[\alpha]_D^{24}$ = - 22.5 (c = 0.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.56 (s, 3H), 4.50 (d, *J* = 4.4 Hz, 1H), 5.06 (d, *J* = 13.4 Hz, 1H), 5.46 (d, *J* = 13.4 Hz, 1H), 7.28 - 7.31 (m, 1H), 7.35 - 7.40 (m, 2H), 7.42 - 7.57 (m, 8H), 7.81 - 7.87 (m, 2H), 8.00 - 8.05 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 27.2 (d, J_{CP} = 3.8 Hz), 59.8 (d, J_{CP} = 2.9 Hz), 84.3, 124.6, 127.8, 128.6 (d, J_{CP} = 13.3 Hz), 128.8 (d, J_{CP} = 12.4 Hz), 128.9, 131.0 (d, J_{CP} = 9.5 Hz), 131.9 (d, J_{CP} = 2.8 Hz), 132.0 (d, J_{CP} = 2.8 Hz), 132.2 (d, J_{CP} = 9.5 Hz), 133.7 (d, J_{CP} = 131.6 Hz), 133.9 (d, J_{CP} = 125.8 Hz), 143.1 (d, J_{CP} = 7.6 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.9; **IR** ν_{max}/cm^{-1} 3190, 1546, 1438, 1188, 1121, 1108; **MP** 161 - 163 °C; **HRMS** (ESI+): calcd. for $C_{21}H_{21}N_2NaO_3P$ $[M+Na]^+$ 403.1182, found 403.1169. Spectroscopic data are consistent with those given in the literature.[152]

8.3.3.2 Synthesis and characterisation of 152c

N-[(2*R*)-2-(Biphenyl-4-yl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152c**



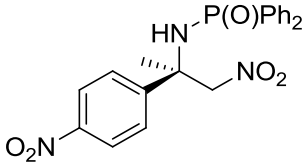
Obtained according to General Procedure **VI**, using ketimine **150c** (79.0 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 1:1) to yield compound **152c** (84 mg, 92%) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak AD, hexane/*iso*-propanol 80:20, λ 240 nm, 1.0 mL/min): t (major) = 17.03 min, t (minor) = 23.58 (90%).

$[\alpha]_D^{24}$ = - 43.2 (c = 1.13, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.61 (s, 3H), 4.55 (d, *J* = 4.5 Hz, 1H), 5.11 (d, *J* = 13.4 Hz, 1H), 5.47 (d, *J* = 13.4 Hz, 1H), 7.32 - 7.40 (m, 1H), 7.41 - 7.62 (m, 14H), 7.85 (d, *J* = 12.4 Hz, 1H), 7.87 (d, *J* = 12.4 Hz, 1H), 8.03 (d, *J* =

12.1 Hz, 1H), 8.04 (d, *J* = 12.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 27.2 (d, J_{CP} = 3.2 Hz), 59.7 (d, J_{CP} = 2.4 Hz), 88.4 (d, J_{CP} = 1.6 Hz), 125.3, 127.1, 127.6, 128.7 (d, J_{CP} = 11.2 Hz), 128.8 (d, J_{CP} = 11.2 Hz), 128.8, 131.1 (d, J_{CP} = 9.6 Hz), 132.0 ('t', J_{CP} = 3.2 Hz), 132.2 (d, J_{CP} = 9.6 Hz), 133.7 (d, J_{CP} = 131.0 Hz), 134.0 (d, J_{CP} = 126.2 Hz), 140.2, 140.8, 141.9 (d, J_{CP} = 8.0 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.7; **IR** ν_{max}/cm^{-1} 3141, 1547, 1439, 1413, 1372, 1186, 1119, 1107, 1009; **MP** 120 - 122 ˚C; **HRMS** (ESI+): calcd. for $C_{27}H_{25}N_2NaO_3P$ $[M+Na]^+$ 479.1495, found 479.1492.

8.3.3.3 Synthesis and characterisation of 152d

<u>*N*-[(2*R*)-1-Nitro-2-(4-nitrophenyl)-propan-2-yl]-*P*,*P*-diphenylphosphinic amide **152d**</u>



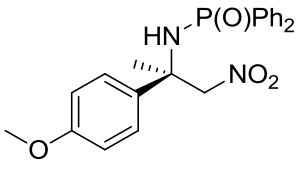
Obtained according to General Procedure **V**, using ketimine **150d** (72.8 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 1:1) to yield compound **152d** (78 mg, 92%) as a pale yellow solid. The ee was determined by HPLC analysis (Chiralpak IA, hexane/*iso*-propanol 80:20, λ 240 nm, 1.0 mL/min): t (major) = 27.39 min, t (minor) = 35.83 min (86%).

$[\alpha]_D^{24}$ = - 36.9 (c = 1.06, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.57 (s, 3H), 4.60 (d, *J* = 4.3 Hz, 1H), 5.10 (d, *J* = 13.6 Hz, 1H), 5.45 (d, *J* = 13.6 Hz, 1H), 7.42 - 7.58 (m, 6H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.77 - 7.85 (m, 2H), 7.93 - 8.00 (m, 2H), 8.18 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.9 (d, J_{CP} = 4.0 Hz), 59.8 (d, J_{CP} = 1.6 Hz), 83.9 (d, J_{CP} = 1.6 Hz), 124.0, 126.1, 128.8 (d, J_{CP} = 6.4 Hz), 128.9 (d, J_{CP} = 6.4 Hz), 131.1 (d, J_{CP} = 9.6 Hz), 131.9 (d, J_{CP} = 9.6 Hz), 132.3 (d, J_{CP} = 3.2 Hz), 133.1 (d, J_{CP} = 130.2 Hz), 133.4 (d, J_{CP} = 126.2 Hz), 147.3, 150.2 (d, J_{CP} = 6.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 23.1; **IR** ν_{max}/cm^{-1} 3176, 1733, 1550, 1519, 1438, 1349, 1247, 1186, 1121;

MP 138 - 142 °C; **HRMS** (ESI+): calcd. for $C_{21}H_{20}N_3NaO_5P$ $[M+Na]^+$ 448.1033, found 448.1018.

8.3.3.4 Synthesis and characterisation of 152e

N-[(2*R*)-2-(4-Methoxyphenyl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152e**

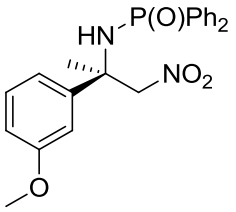


Obtained according to General Procedure **VI**, using ketimine **150e** (69.8 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 1:1) to yield compound **152e** (78 mg, 95%) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 10.64 min, t (major) = 16.78 min (91%).

$[\alpha]_D^{24}$ = - 33.0 (c = 1.04, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.55 (s, 3H), 3.78 (s, 3H), 4.44 (d, *J* = 4.3 Hz, 1H), 5.03 (d, *J* = 13.1 Hz, 1H), 5.38 (d, *J* = 13.1 Hz, 1H), 6.75 - 6.99 (m, 2H), 7.34 - 7.60 (m, 8H), 7.74 - 7.91 (m, 2H), 7.92 - 8.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 27.2 (d, J_{CP} = 4.0 Hz), 55.3, 59.5 (d, J_{CP} = 2.4 Hz), 84.6 (d, J_{CP} = 1.6 Hz), 114.1, 126.1, 128.6 (d, J_{CP} = 11.2 Hz), 128.7 (d, J_{CP} = 10.4 Hz), 131.1 (d, J_{CP} = 9.6 Hz), 131.9 ('t', J_{CP} = 3.2 Hz), 132.1 (d, J_{CP} = 9.6 Hz), 133.8 (d, J_{CP} = 131.8 Hz), 134.0 (d, J_{CP} = 126.2 Hz), 134.8 (d, J_{CP} = 7.2 Hz), 159.0 (d, J_{CP} = 0.8 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.5; **IR** ν_{max}/cm^{-1} 3180, 1544, 1510, 1247, 1194, 1179, 1120, 1016; **MP** 148 - 151 ˚C; **HRMS** (ESI+): calcd. for $C_{22}H_{23}N_2NaO_4P$ $[M+Na]^+$ 433.1288, found 433.1270.

8.3.3.5 Synthesis and characterisation of 152f

N-[(2*R*)-2-(3-Methoxyphenyl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152f**

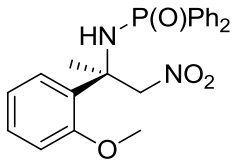


Obtained according to General Procedure **VI**, using ketimine **150f** (69.8 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 1:1) to yield compound **152f** (72 mg, 88%) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 10.57 min, t (major) = 18.19 min (91%).

$[\alpha]_D^{24}$ = - 27.4 (c = 1.15, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.54 (s, 3H), 3.82 (s, 3H), 4.50 (d, *J* = 4.3 Hz, 1H), 5.04 (d, *J* = 13.5 Hz, 1H), 5.47 (d, *J* = 13.5 Hz, 1H), 6.81 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.05 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.11 (t, *J* = 2.0 Hz, 1H), 7.24 - 7.34 (m, 1H), 7.41 - 7.59 (m, 6H), 7.77 - 7.88 (m, 2H), 7.96 - 8.09 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 27.2 (d, J_{CP} = 3.7 Hz), 55.3, 59.8 (d, J_{CP} = 2.8 Hz), 84.2 (br s), 111.7, 112.3, 116.7, 128.6 (d, J_{CP} = 12.9 Hz), 128.8 (d, J_{CP} = 12.0 Hz), 130.0, 131.0 (d, J_{CP} = 9.2 Hz), 132.0 (d, J_{CP} = 2.8 Hz), 132.0 (d, J_{CP} = 2.8 Hz), 132.2 (d, J_{CP} = 10.2 Hz), 133.7 (d, J_{CP} = 132.2 Hz), 134.0 (d, J_{CP} = 125.8 Hz), 144.9 (d, J_{CP} = 8.3 Hz), 159.9; **^{31}P NMR** (202 MHz, $CDCl_3$) δ ppm 24.0; **IR** ν_{max}/cm^{-1} 3190, 1549, 1538, 1258, 1183, 1120, 1108; **MP** 116 - 118 ˚C; **HRMS** (ESI+): calcd. for $C_{22}H_{23}N_2NaO_4P$ $[M+Na]^+$ 433.1288, found 433.1276.

8.3.3.6 Synthesis and characterisation of 152g

N-[(2*R*)-2-(2-Methoxyphenyl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152g**

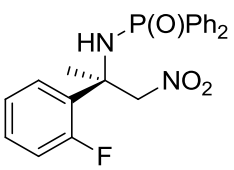


Obtained according to General Procedure **VI**, using ketimine **150g** (69.8 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 1:1) to yield compound **152g** (51 mg, 62%) as a colourless foam. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 8.37 min, t (major) = 15.33 min (93%).

$[\alpha]_D^{23}$ = - 31.0 (c = 0.89, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.75 (s, 3H), 3.83 (s, 3H), 5.00 (d, *J* = 5.8 Hz, 1H), 5.23 (d, *J* = 11.6 Hz, 1H), 5.35 (d, *J* = 11.6 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.97 - 7.06 (m, 1H), 7.25 - 7.36 (m, 1H), 7.38 - 7.56 (m, 7H), 7.77 - 7.97 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 23.0 (d, J_{CP} = 3.2 Hz), 55.4, 59.5 (d, J_{CP} = 2.4 Hz), 84.3 (d, J_{CP} = 1.6 Hz), 111.8, 121.4, 127.3, 128.5 (d, J_{CP} = 12.8 Hz), 128.7 (d, J_{CP} = 12.8 Hz), 129.5 (d, J_{CP} = 6.4 Hz), 129.7, 131.0 (d, J_{CP} = 9.6 Hz), 131.8 (d, J_{CP} = 2.4 Hz), 131.9 (d, J_{CP} = 2.4 Hz), 132.1 (d, J_{CP} = 9.6 Hz), 134.1 (d, J_{CP} = 131.8 Hz), 134.5 (d, J_{CP} = 126.2 Hz), 156.4; **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 21.7; **IR** ν_{max}/cm^{-1} 2924, 1543, 1492, 1461, 1436, 1374, 1236, 1198, 1188, 1119; **MP** 56 - 58 ˚C; **HRMS** (ESI+): calcd. for $C_{22}H_{23}N_2NaO_4P$ $[M+Na]^+$ 433.1288, found 433.1273.

8.3.3.7 Synthesis and characterisation of 152h

N-[(2*R*)-2-(2-Fluorophenyl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152h**



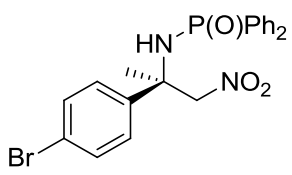
Obtained according to General Procedure **V**, using ketimine **150h** (67.4 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 3:1) to yield compound **152h** (71 mg, 89%) as a colourless solid. The ee was

determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 6.98 min, t (major) = 15.44 min (94%).

$[\alpha]_D^{23}$ = - 37.1 (c = 1.14, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.69 (s, 3H), 4.50 (d, *J* = 4.1 Hz, 1H), 5.25 (d, *J* = 12.9 Hz, 1H), 5.31 (dd, *J* = 12.9, 0.9 Hz, 1H), 7.04 (ddd, *J* = 12.9, 8.2, 0.9 Hz, 1H), 7.20 (td, *J* = 7.6, 0.9 Hz, 1H), 7.28 - 7.34 (m, 1H), 7.43 - 7.56 (m, 6H), 7.71 (td, *J* = 8.2, 1.4 Hz, 1H), 7.81 - 7.89 (m, 2H), 7.93 - 8.01 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 23.8 ('t', $J_{CP} = J_{CF}$ = 2.9 Hz), 58.8 - 58.9 (m), 84.3 (dd, J_{CF} = 7.6, J_{CP} = 1.9 Hz), 116.7 (d, J_{CF} = 23.8 Hz), 124.8 (d, J_{CF} = 2.9 Hz), 127.9 (d, J_{CF} = 2.9 Hz), 128.7 (d, J_{CP} = 13.4 Hz), 128.8 (d, J_{CP} = 12.4 Hz), 129.3 (dd, J_{CF} = 10.5, J_{CP} = 6.7 Hz), 130.2 (d, J_{CF} = 8.6 Hz), 131.1 (d, J_{CP} = 9.5 Hz), 132.0 (d, J_{CP} = 2.9 Hz), 132.0 (d, J_{CP} = 9.5 Hz), 132.1 (d, J_{CP} = 2.9 Hz), 133.6 (d, J_{CP} = 130.7 Hz), 134.0 (d, J_{CP} = 126.8 Hz), 159.6 (d, J_{CF} = 245.1 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.2; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ ppm -112.2; **IR** ν_{max}/cm^{-1} 3158, 1548, 1483, 1439, 1373, 1279, 1259, 1181, 1107, 1070, 1019; **MP** 120 - 126 °C; **HRMS** (ESI+): calcd. for $C_{21}H_{20}FN_2NaO_3P$ $[M+Na]^+$ 421.1088, found 421.1081.

8.3.3.8 Synthesis and characterisation of 152k

<u>*N*-[(2*R*)-2-(4-Bromophenyl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152k**</u>

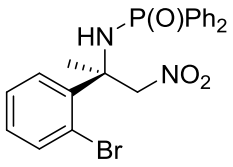


Obtained according to General Procedure **V**, using ketimine **150k** (79.4 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 1:1) to yield compound **152k** (77 mg, 84%) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 9.15 min, t (major) = 15.56 min (90%).

$[\alpha]_D^{24}$ = - 35.0 (c = 0.75, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.53 (s, 3H), 4.49 (d, *J* = 4.3 Hz, 1H), 5.02 (d, *J* = 13.4 Hz, 1H), 5.38 (d, *J* = 13.4 Hz, 1H), 7.33 - 7.61 (m, 10H), 7.80 (d, *J* = 12.4 Hz, 1H), 7.82 (d, *J* = 12.4 Hz, 1H), 7.96 (d, *J* = 12.1 Hz, 1H), 7.98 (d, *J* = 12.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 27.0 (d, J_{CP} = 3.2 Hz), 59.6 (d, J_{CP} = 1.6 Hz), 84.1 (d, J_{CP} = 1.6 Hz), 122.0, 126.7, 128.7 (d, J_{CP} = 8.8 Hz), 128.8 (d, J_{CP} = 8.8 Hz), 131.1 (d, J_{CP} = 9.6 Hz), 132.0 - 132.1 (m), 133.5 (d, J_{CP} = 131.0 Hz), 133.8 (d, J_{CP} = 126.2 Hz), 142.1 (d, J_{CP} = 7.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.7; **IR** ν_{max}/cm^{-1} 3158, 2925, 1545, 1439, 1397, 1373, 1253, 1184, 1150, 1110, 1084, 1007; **MP** 162 - 164 °C; **HRMS** (ESI+): calcd. for $C_{21}H_{20}{}^{79}BrN_2NaO_3P$ $[M+Na]^+$ 481.0287, found 481.0297; calcd. for $C_{21}H_{20}{}^{81}BrN_2NaO_3P$ $[M+Na]^+$ 483.0268, found 483.0276.

8.3.3.9 Synthesis and characterisation of 152l

N-[(2*R*)-2-(2-bromophenyl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152l**



To a solution of ketimine **150l** (65 mg, 0.20 mmol) in nitromethane (0.22 mL, 4.0 mmol) was added catalyst **145** (13 mg, 0.020 mmol) at room temperature. The reaction mixture was quenched after 60 h and the ^{1}H NMR conversion for compound **152l** was 35%. The crude reaction mixture was purified by flash column chromatography (Pet/EtOAc 1:1) to yield an analytical sample of compound **152l** as a colourless oil.[xlii] The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 10.14 min., t (major) = 28.40 min (ee 83%).

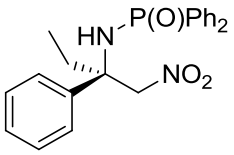
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.89 (s, 3H), 4.87 (d, *J* = 5.3 Hz, 1H), 5.33 (d, *J* = 12.4 Hz, 1H), 5.69 (d, *J* = 12.4 Hz, 1H), 7.11 - 7.21 (m, 1H), 7.30 - 7.56 (m, 7H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.80 - 8.01 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$)

[xlii] It was not possible to separate starting material from product by flash column chromatography and the NMR data reported is that of the racemate where the reaction did go to full conversion.

δ ppm 23.3 (d, J_{PC} = 4.0 Hz), 60.4 (d, J_{PC} = 2.4 Hz), 82.8 (d, J_{PC} = 2.4 Hz), 120.2, 128.1, 128.5 (d, J_{PC} =12.8 Hz), 128.7 (d, J_{PC} =12.8 Hz), 129.0, 129.8, 131.0 (d, J_{PC} = 10.4 Hz), 131.8 (d, J_{PC} = 9.6 Hz), 131.8 (d, J_{PC} = 3.2 Hz), 132.0 (d, J_{PC} = 2.4 Hz), 133.5 (d, J_{PC} = 130.2 Hz), 133.9 (d, J_{PC} = 127.0 Hz), 135.9, 139.7 (d, J_{PC} = 5.6 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 21.6; **IR** ν_{max}/cm^{-1} 3180, 1739, 1547, 1460, 1438, 1422, 1371, 1276, 1250, 1371, 1276, 1250, 1189, 1157, 1108, 1012, 998, 904, 834, 760, 745, 727, 700, 661, 642; **HRMS** (ESI+): calcd. for $C_{21}H_{20}{}^{79}BrN_2NaO_3P$ $[M+Na]^+$ 481.0287, found 481.0301; calcd. for $C_{21}H_{20}{}^{81}BrN_2NaO_3P$ $[M+Na]^+$ 483.0268, found 483.0281.

8.3.3.10 Synthesis and characterization of 152m

<u>*N*-[(2*R*)-1-Nitro-2-phenylbutan-2-yl]-*P*,*P*-diphenylphosphinic amide **152m**</u>



Obtained according to General Procedure **VI**, using ketimine 150**m** (66.6 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 1:1) to yield compound **152m** (75 mg, 95%) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 6.49 min, t (major) = 19.20 min (92%).

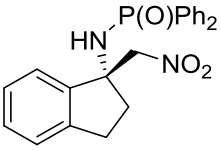
$[\alpha]_D^{23}$ = - 4.3 (c = 1.05, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 0.46 (t, *J* = 7.4 Hz, 3H), 2.00 (q, *J* = 7.4 Hz, 2H), 4.33 (d, *J* = 4.7 Hz, 1H), 5.28 (d, *J* = 13.6 Hz, 1H), 5.55 (d, *J* = 13.6 Hz, 1H), 7.21 - 7.27 (m, 1H), 7.29 - 7.35 (m, 2H), 7.39 - 7.57 (m, 8H), 7.75 - 7.83 (m, 2H), 7.98 - 8.07 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 8.5, 32.2 (d, J_{CP} = 3.8 Hz), 63.7 (d, J_{CP} = 2.8 Hz), 81.3, 125.8, 127.8, 128.5 (d, J_{CP} = 8.6 Hz), 128.6, 128.7 (d, J_{CP} = 8.6 Hz), 131.1 (d, J_{CP} = 9.5 Hz), 131.9 (d, J_{CP} = 2.9 Hz), 131.9 (d, J_{CP} = 2.9 Hz), 132.1 (d, J_{CP} = 9.5 Hz), 133.8 (d, J_{CP} = 131.6 Hz), 133.9 (d, J_{CP} = 125.9 Hz), 140.4 (d, J_{CP} = 7.6 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.8; **IR** ν_{max}/cm^{-1} 3189, 1548, 1437, 1378,

1243, 1187, 1122, 1107; **MP** 133 - 137 °C; **HRMS** (ESI+): calcd. for $C_{22}H_{23}N_2NaO_3P$ $[M+Na]^+$ 417.1339, found 417.1322.

8.3.3.11 Synthesis and characterisation of 152o

N-[(1*R*)-1-(nitromethyl)-2,3-dihydro-1H-inden-1-yl]-*P*,*P*-diphenylphosphinic amide **152o**

To a solution of ketimine **150o** (66 mg, 0.20 mmol) in nitromethane (0.22 mL, 4.0 mmol)



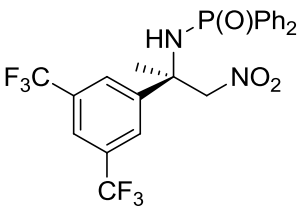
was added catalyst **145** (13 mg, 0.020 mmol) at room temperature. The reaction mixture was quenched after 4 h and the ^{1}H NMR conversion for compound **152o** was 32%. The crude reaction mixture was purified by flash column chromatography (Pet/EtOAc 1:1) to yield an analytical sample of compound **152o** as a colourless solid[xliii]. The ee was determined by HPLC analysis (Chiralpak AD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 14.38 min., t (major) = 21.07 min (ee 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.29 – 2.37 (m, 1H), 2.41 – 2.48 (m, 1H), 2.87 (ddd, J = 16.0, 7.9, 3.7 Hz, 1H), 3.11 ('dt', J = 15.8, 7.9, 1H), 4.09 (d, J = 6.4 Hz, 1H), 4.88 (d, J = 12.5 Hz, 1H), 5.55 (d, J = 12.2 Hz, 1H), 6.92 – 6.96 (m, 1H), 7.05 – 7.11 (m, 2H), 7.25 – 7.44 (m, 6H), 7.48 – 7.52 (m, 1H), 7.58 – 7.64 (m, 2H), 7.70 – 7.76 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 29.9, 39.7 (d, J_{PC} = 5.7 Hz), 66.2 (d, J_{PC} = 2.9 Hz), 83.7, 124.9, 125.0, 126.5, 128.2 (d, J_{PC} = 13.4 Hz), 128.7 (d, J_{PC} = 12.4 Hz), 129.4, 131.4 (d, J_{PC} = 10.5 Hz), 131.4, (d, J_{PC} = 2.9 Hz), 131.6 (d, J_{PC} = 10.5 Hz), 132.0 (d, J_{PC} = 3.2 Hz), 132.8 (d, J_{PC} = 130.7 Hz), 134.0 (d, J_{PC} = 125.9 Hz), 140.4 (d, J_{PC} = 3.8 Hz), 143.6; **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.5; **IR** ν_{max}/cm^{-1} 3136, 1544, 1437, 1380, 1185, 1124, 1019, 996, 748, 725, 695; **HRMS** (ESI+): calcd. for $C_{22}H_{21}N_2NaO_3P$ $[M+Na]^+$ 415.1182, found 415.1182.

[xliii] It was not possible to separate starting material from the product by flash column chromatography and the NMR data reported is that of the racemate where the reaction did go to full conversion.

8.3.3.12 Synthesis and characterization of 152q

N-{(2*R*)-2-[3,5-Bis(trifluoromethyl)phenyl]-1-nitropropan-2-yl}-*P*,*P*-diphenylphosphinic amide **152q**

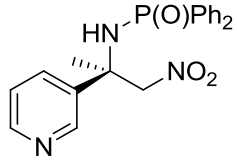


Obtained according to General Procedure **V**, using ketimine **150q** (91.0 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/EtOAc 3:1) to yield compound **152q** (98 mg, 95%) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak AD-H, hexane/*iso*-propanol 95:5, λ 220 nm, 1.0 mL/min): t (major) = 12.04 min, t (minor) = 14.73 min (90%).

$[\alpha]_D^{24}$ = - 19.8 (c = 0.88, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.65 (s, 3H), 4.47 (d, *J* = 4.4 Hz, 1H), 5.14 (d, *J* = 13.6 Hz, 1H), 5.43 (d, *J* = 13.6 Hz, 1H), 7.42 - 7.61 (m, 6H), 7.75 - 7.85 (m, 3H), 7.92 (dd, *J* = 12.3, 1.6 Hz, 1H), 7.94 (d, *J* = 12.3 Hz, 1H), 7.99 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 27.0 (d, J_{CP} = 3.7 Hz), 59.6 (d, J_{CP} = 1.8 Hz), 83.7 (d, J_{CP} = 1.8 Hz), 122.1 - 122.2 (m), 123.0 (q, J_{CF} = 272.8 Hz), 125.4 - 125.6 (m), 128.9 (d, J_{CP} = 12.9 Hz), 128.9 (d, J_{CP} = 12.0 Hz), 131.1 (d, J_{CP} = 10.2 Hz), 131.8 (d, J_{CP} = 9.2 Hz), 132.2 (q, J_{CF} = 33.3 Hz), 132.3 - 132.4 (m), 133.0 (d, J_{CP} = 129.5 Hz), 133.1 (d, J_{CP} = 126.7 Hz), 145.6 (d, J_{CP} = 6.5 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 23.4; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ ppm - 62.8; **IR** ν_{max}/cm^{-1} 2925, 1553, 1439, 1371, 1277, 1177, 1129; **MP** 68 - 70 °C; **HRMS** (ESI+): calcd. for $C_{23}H_{19}F_6N_2NaO_3P$ $[M+Na]^+$ 539.0930, found 539.0931.

8.3.3.13 Synthesis and characterisation of 152r

N-[(2*R*)-2-(Pyridin-3-yl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152r**

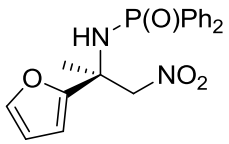


Obtained according to General Procedure **VI**, using ketimine **150r** (64.0 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (CH_2Cl_2/MeOH 9:1) to yield compound **152r** (74 mg, 97%) as a pale yellow solid. The ee was determined by HPLC analysis (Chiralpak AD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (major) = 15.32 min, t (minor) = 18.29 min (82%).

$[\alpha]_D^{23}$ = - 17.8 (c = 0.80, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.56 (s, 3H), 4.57 (d, *J* = 4.3 Hz, 1H), 5.06 (d, *J* = 13.4 Hz, 1H), 5.40 (d, *J* = 13.4 Hz, 1H), 7.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.38 - 7.57 (m, 6H), 7.74 - 7.88 (m, 3H), 7.91 - 8.02 (m, 2H), 8.48 (br s, 1H), 8.81 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 27.0 (d, J_{CP} = 3.2 Hz), 58.6 (d, J_{CP} = 1.6 Hz), 83.8 (d, J_{CP} = 1.6 Hz), 123.3, 128.6 (d, J_{CP} = 7.2 Hz), 128.8 (d, J_{CP} = 7.2 Hz), 131.0 (d, J_{CP} = 10.4 Hz), 131.9 (d, J_{CP} = 9.6 Hz), 132.1 ('t', J_{CP} = 3.2 Hz), 132.7, 133.3 (d, J_{CP} = 131.0 Hz), 133.5 (d, J_{CP} = 126.2 Hz), 138.4 - 138.5 (m), 146.7, 149.1; **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.8; **IR** ν_{max}/cm^{-1} 3158, 1545, 1438, 1416, 1374, 1272, 1184, 1121, 1107; **MP** 70 - 72 °C; **HRMS** (ESI+): calcd. for $C_{20}H_{20}N_3NaO_3P$ $[M+Na]^+$ 404.1134, found 404.1120.

8.3.3.14 Synthesis and characterisation of 152s

N-[(2*S*)-2-(2-Furyl)-1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152s**

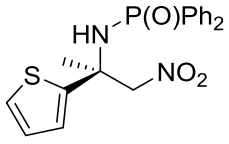


Obtained according to General Procedure **VI**, using ketimine **150s** (61.8 mg, 0.200 mmol) and nitromethane (0.215 mL, 4.00 mmol). The crude reaction mixture was purified by flash column chromatography (PE/ EtOAc 1:1) to yield compound **152s** (72 mg, 97%) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 7.19 min, t (major) = 9.51 min (84%).

$[\alpha]_D^{24}$ = - 13.2 (c = 1.14, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.67 (s, 3H), 4.21 (d, *J* = 6.1 Hz, 1H), 5.05 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 6.22 - 6.23 (m, 1H), 6.32 (d, *J* = 2.8 Hz, 1H), 7.21 - 7.24 (m, 1H), 7.36 - 7.56 (m, 6H), 7.72 - 7.82 (m, 2H), 7.83 - 7.94 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 23.7 (d, J_{CP} = 4.0 Hz), 56.0 (d, J_{CP} = 1.6 Hz), 83.5 (d, J_{CP} = 2.4 Hz), 107.3, 110.5, 128.5 (d, J_{CP} = 6.4 Hz), 128.6 (d, J_{CP} = 6.4 Hz), 131.3 (d, J_{CP} = 10.4 Hz), 131.9 - 132.0 (m), 132.0 (d, J_{CP} = 10.4 Hz), 133.3 (d, J_{CP} = 131.0 Hz), 133.4 (d, J_{CP} = 127.0 Hz), 142.4, 153.6 (d, J_{CP} = 7.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 22.1; **IR** ν_{max}/cm^{-1} 3178, 1548, 1436, 1373, 1242, 1183, 1163, 1122, 1107, 1009; **MP** 98 - 100 °C; **HRMS** (ESI+): calcd. for $C_{19}H_{19}N_2NaO_4P$ $[M+Na]^+$ 393.0975, found 393.0964.

8.3.3.15 Synthesis and characterization of 152t

N-[(2*S*)-2-(2-Thienyl)1-nitropropan-2-yl]-*P*,*P*-diphenylphosphinic amide **152t**

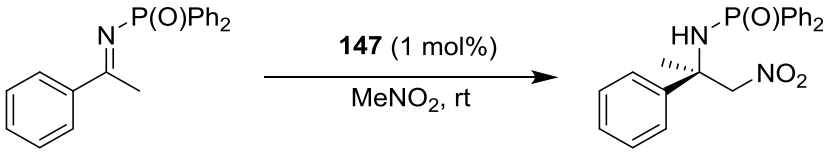


Obtained according to a modified General Procedure **VI**, using ketimine **150t** (65 mg, 0.20 mmol). ^{1}H NMR conversion for compound **152t** was 60% and the crude reaction mixture was purified by flash column chromatography (Pet/EtOAc 1:1) to yield a pure analytical sample of compound **152t** as a

colourless solid. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 7.47 min., t (major) = 20.48 min (ee 73%).

$[\alpha]_D^{24}$ = - 3.87 (c = 0.77, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.65 (s, 3H), 4.63 (d, *J* = 4.4 Hz, 1H), 5.02 (d, *J* = 12.9 Hz, 1H), 5.38 (d, *J* = 12.9 Hz, 1H), 6.92 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.97 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.21 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.39 - 7.58 (m, 6H), 7.75 - 7.86 (m, 2H), 7.97 - 8.08 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 28.3 (d, J_{PC} = 3.8 Hz), 58.3 (d, J_{PC} = 1.9 Hz), 84.6, 123.3, 124.8, 127.4, 128.6 (d, J_{PC} = 9.5 Hz), 128.7 (d, J_{PC} = 10.5 Hz), 131.0 (d, J_{PC} = 9.5 Hz), 132.0 ('t', J_{PC} = 2.9 Hz), 132.2 (d, J_{PC} = 9.5 Hz), 133.5 (d, J_{PC} = 125.9 Hz), 133.6 (d, J_{PC} = 130.6 Hz), 148.1 (d, J_{PC} = 8.6 Hz); **^{31}P NMR** (202.5 MHz, $CDCl_3$) δ ppm 23.7; **IR** ν_{max}/cm^{-1} 3150, 1543, 1438, 1374, 1262, 1185, 1107, 997, 904, 854, 723; **MP** 133 - 136 °C; **HRMS** (ESI+): calcd. for $C_{19}H_{19}N_2NaO_3PS$ $[M+Na]^+$ 409.0746, found 409.0743.

8.3.3.16 Preparative synthesis of 152a



To ketimine **150a** (10.0 g, 31.3 mmol) and catalyst **147** (231 mg, 0.313 mmol) under argon was added nitromethane *via* syringe (16.8 mL, 313 mmol) at rt (21 - 22 ˚C). Stirring was maintained for 21 h (an aliquot taken after 20 h showed 98% conversion by ^{1}H NMR analysis and an ee of 86%) and the reaction mixture was quenched by the addition of 1 M AcOH in CH_2Cl_2 (3.13 mL, 3.13 mmol). Stirring was maintained for 30 minutes, the volatiles were removed *in vacuo*, and propan-2-ol (50 mL) was added and removed *in vacuo* to afford a crude yellow solid. To the crude material was added propan-2-ol

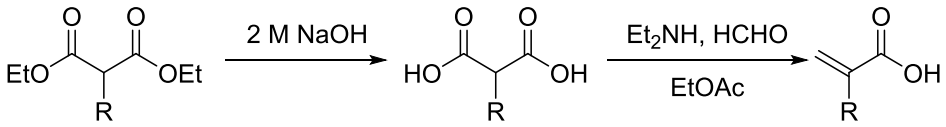
(100 mL) and the mixture was heated to reflux. The resulting solution was slowly cooled to rt and crystallization allowed to occur over 18 h. The precipitate was filtered, washed with cold propan-2-ol (20 mL) and dried *in vacuo* to afford the title compound **152a** (8.33 g, 70% yield) as a colourless solid. The ee was determined by HPLC analysis (Chiralpak OD-H, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 8.01 min, t (major) = 21.12 min (98%).[xliv]

$[\alpha]_D^{24}$ = - 25.7 (c = 1.02, $CHCl_3$); **MP** 134 - 137 ˚C. All spectroscopic data were identical to those reported in section 8.3.2.1.

8.4 Sulfa-Michael Addition of Alkyl Thiols to α,β-Unsaturated Esters

8.4.1 General Procedures

General Procedure VII **Synthesis of α-Alkyl Substituted α,β-Unsaturated Acids**

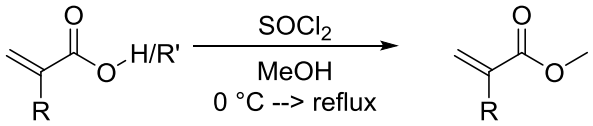


According to a modified literature procedure,[225] to the substituted malonate (synthesised by the treatment of diethylmalonate with NaH and the corresponding alkyl bromide in DMF) was added 2 M NaOH (2.67 eq), and the resulting mixture was stirred vigorously and refluxed for 2 h. The resulting solution was cooled to rt and extracted with hexane (2x) and the aqueous layer was then acidified to pH 1 with aq HCl. The resulting solution was then extracted with EtOAc (3x), the combined organics washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo* to afford the corresponding diacid which was used crude in the next step.

[xliv] The product was further recrystallised using 32 mL of refluxing propan-2-ol to give 7.50 g (90% yield and 63% overall yield) of **152a** in 99.7% ee.

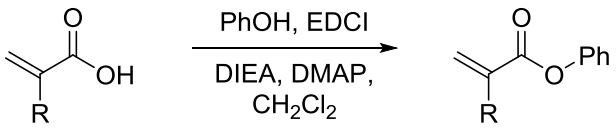
The crude diacid was dissolved in EtOAc (0.75 M) and the resulting solution was cooled to 0 °C, followed by the dropwise addition of diethylamine (1.01 eq) and subsequent addition of *p*-formaldehyde (1.5 eq). The resulting suspension was refluxed for 2 hours and then the reaction mixture was cooled to 0 °C, diluted with H_2O (0.6 mL/mmol diacid) and acidified to pH 1 with concentrated HCl. The aqueous layer was then extracted with EtOAc (3x) and the combined organics washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo* to afford the crude acid which was purified by FCC (petroleum ether/Et_2O).

General Procedure VIII **for the Synthesis of α-Substituted α,β-Unsaturated Methyl esters**



To a solution of MeOH (0.5 M) at 0 °C was added thionyl chloride (2.20 eq) dropwise followed by the acid or ester (1.00 eq). The reaction mixture was refluxed for 2 h for the acids or 16 h for the esters, then cooled to 0 °C, diluted with pentane (5mL/mmol), and aq K_2CO_3 was added until pH to 9-10. The aqueous layer was then extracted with pentane (2 x 5 mL/mmol), the combined organics were washed with brine, dried ($MgSO_4$) and the volatiles were removed under a stream of nitrogen to afford the crude methyl ester as an oil which was purified as specified for the individual compound.

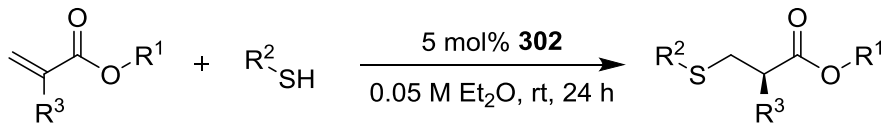
General Procedure IX **for the Synthesis of α-Substituted α,β-Unsaturated Phenolic Esters**



To a solution of the α-substituted α,β-unsaturated acid in CH_2Cl_2 (0.3 M) was added PhOH (1 eq), DIEA (1 eq), DMAP (0.2 eq) followed by EDCI (1 eq) at room temperature and

stirring was maintained overnight, whereupon the volatiles were removed *in vacuo*. The crude mixtures were purified by FCC (Petroleum ether/Et_2O = 19/1) to afford the desired phenolic ester.

General Procedure X **for the Sulfa-Michael Addition of Thiols to α-Substituted, α,β-Unsaturated Esters**

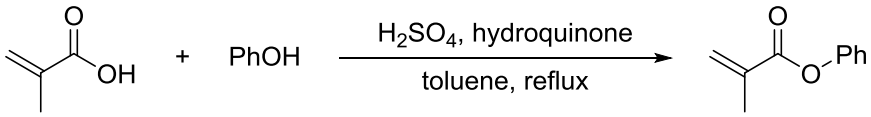


Azide **306** (4.8 mg, 0.010 mmol, 0.05 eq) and tris(4-methoxyphenyl)phosphine (3.5 mg, 0.010 mmol, 0.05 eq) were stirred in diethyl ether (0.2 mL) in a sealed vial at room temperature for 24 h. The *in situ* generated catalyst was then transferred with washings (3.8 mL Et_2O) to a flask containing the *α-substituted, α,β-unsaturated ester* **287** (0.40 or 1.0 mmol, 2.0 eq or 5.0 eq), and the desired *thiol* **286** (0.20 mmol, 1.0 eq) was then added *via* syringe. The reaction mixture was stirred for 24 h and then 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 flash column chromatography to afford the product **288**.

8.4.2 Synthesis and Characterisation of α-Substituted α,β-Unsaturated Esters

8.4.2.1 Synthesis and characterisation of 287e

Phenyl methacrylate **287e**



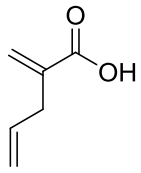
According to a modified literature procedure,[320] to a 2 L flask were charged sequentially phenol (111 g, 1.18 mol, 1.0 eq), toluene (1.0 L), methacrylic acid (100 mL, 1.18 mol, 1.0 eq), concentrated sulfuric acid (4.05 mL, 76 mmol, 0.06 eq) and hydroquinone (1.30 g,

11.8 mmol, 0.01 eq). The reaction mixture was placed under a nitrogen atmosphere, a Dean-Stark apparatus added and the reaction mixture refluxed for 7 days with occasional removal of H_2O. The reaction mixture was cooled and diluted with water (400 mL) and the organic layer collected. The aqueous layer and suspension of polymeric material were extracted with CH_2Cl_2 (3 x 200 mL) and the combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo* to afford 155 g of crude product. Purification[xlv] by flash column chromatography [1 kg silica, tube size 500 mL, petroleum Ether (1 column volume), petroleum ether/Et_2O 49/1 (1 column volume) then petroleum ether/Et_2O 19/1 (3 column volumes)] afforded the title compound **287e** as a colourless solid[xlvi] (86 g, 45% yield).

^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.08 ('t', *J* = 1.5 Hz, 3 H, C$\underline{H}_3$), 5.77 ('quin', *J* = 1.5 Hz, 1 H, C$\underline{H}_A$H$_B$C), 6.36 (t, *J* = 1.5 Hz, 1 H, CH$_A\underline{H}_B$C), 7.07 - 7.19 (m, 2 H, Ar$\underline{H}$), 7.19 - 7.32 (m, 1 H, Ar$\underline{H}$), 7.34 - 7.50 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 18.3 ($\underline{C}H_3$), 121.6 (Ar$\underline{C}$H), 125.6 (Ar$\underline{C}$H), 127.1 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 135.8 (CH$_A$H$_B\underline{C}$), 150.9 (Ar$\underline{C}$), 165.7 ($\underline{C}$=O). Data is consistent with that given in the literature.[320]

Synthesis and characterisation of 309a

2-Methylidenepent-4-enoic acid **309a**



Synthesised according to General Procedure **VII** from 1,3-diethyl 2-(prop-2-en-1-yl)propanedioate on a 62.4 mmol scale to afford the title compound **309a** as a colourless oil in 68% yield over two steps (4.17 g).

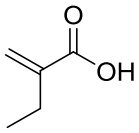
^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.01 - 3.11 (m, 2 H, CH$_A$H$_B$C$\underline{H}_2$), 5.08 - 5.11 (m, 1 H, C$\underline{H}_A$H$_B$CH), 5.11 - 5.16 (m, 1 H, CH$_A\underline{H}_B$CH), 5.71 ('q', *J* = 1.0 Hz, 1 H, C$\underline{H}_A$H$_B$C),

[xlv] Purification by vacuum distillation using a Vigreux condenser was attempted but yielded mixed distillates of methacrylic acid, phenol and phenyl methacrylate due to their similar boiling points (163 °C, 182 °C and 195 °C respectively).
[xlvi] Melting point less than 20 °C

5.80 - 5.96 (m, 1 H, $CH_AH_BC\underline{H}$), 6.36 (d, *J* = 1.0 Hz, 1 H, $CH_A\underline{H_B}C$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm) 35.8 ($\underline{C}H_2$), 117.0 ($\underline{C}H_AH_BCH$), 128.1 ($\underline{C}H_AH_BC$), 135.1 ($CH_AH_B\underline{C}H$), 138.9 ($CH_AH_B\underline{C}$), 172.7 ($\underline{C}$=O). Data consistent with that given in the literature.[321]

8.4.2.2 Synthesis and characterisation of 309b

2-Methylidenebutanoic acid **309b**

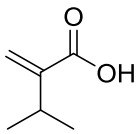


Synthesised according to General Procedure **VII** from 1,3-diethyl 2-ethylpropanedioate on a 55.4 mmol scale to afford the title compound **309b** as a colourless oil in 76% yield over two steps (4.20 g).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.10 (t, *J* = 7.5 Hz, 3 H, $CH_2C\underline{H_3}$), 2.33 (q, *J* = 7.5 Hz, 2 H, $C\underline{H_2}CH_3$), 5.66 (s, 1 H, $C\underline{H_A}H_BC$), 6.29 (s, 1 H $CH_A\underline{H_B}C$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 12.8 ($CH_2\underline{C}H_3$), 24.5 ($\underline{C}H_2CH_3$), 126.2 ($\underline{C}H_AH_BC$), 141.8 ($CH_AH_B\underline{C}$), 173.3 ($\underline{C}$=O). Data consistent with that given in the literature.[322]

8.4.2.3 Synthesis and characterisation of 309c

3-Methyl-2-methylidenebutanoic acid **309c**

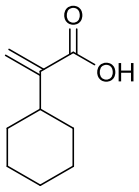


Synthesised according to General Procedure **VII** from 1,3-diethyl 2-(propan-2-yl)propanedioate on a 54.4 mmol scale to afford the title compound **309c** as a colourless oil in 61% yield over two steps (3.80 g).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.12 (d, *J* = 7.0 Hz, 6 H, $CH(C\underline{H_3})_2$), 2.81 (spt, *J* = 7.0 Hz, 1 H, $C\underline{H}(CH_3)_2$), 5.66 (s, 1 H, $C\underline{H_A}H_BC$), 6.30 (s, 1 H, $CH_A\underline{H_B}C$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 21.8 ($CH(\underline{C}H_3)_2$), 29.0 ($\underline{C}H(CH_3)_2$), 124.2 ($\underline{C}H_AH_BC$), 146.3 ($CH_AH_B\underline{C}$),173.0 ($\underline{C}$=O). Data consistent with that given in the literature.[323]

8.4.2.4 Synthesis and characterisation of 309d

2-Cyclohexylprop-2-enoic acid **309d**

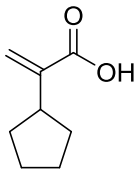


Synthesised according to General Procedure **VII** from 1,3-diethyl 2-cyclohexylpropanedioate on a 14.5 mmol scale to afford the title compound **309d** as a colourless oil in 19% yield over two steps (417 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.07 - 1.25 (m, 3 H, 3 of $C_6\underline{H}_{11}$), 1.27 - 1.46 (m, 2 H, 2 of $C_6\underline{H}_{11}$), 1.64 - 1.95 (m, 5 H, 5 of $C_6\underline{H}_{11}$), 2.38 - 2.50 (m, 1 H, $CH_2C\underline{H}CH_2$), 5.60 (s, 1 H, $C\underline{H}_AH_BC$), 6.28 ('s', 1 H, $CH_A\underline{H}_BC$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 26.3, 26.7, 32.6 ($\underline{C}H_2\underline{C}H_2\underline{C}H_2CH$), 38.9 ($CH_2\underline{C}HCH_2$), 124.8 ($\underline{C}H_AH_BC$), 145.7 ($CH_AH_B\underline{C}$), 172.8 ($\underline{C}$=O). Data consistent with that given in the literature.[264]

8.4.2.5 Synthesis and characterisation of 309e

2-Cyclopentylprop-2-enoic acid **309e**

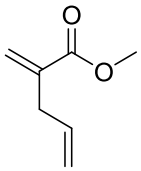


Synthesised according to General Procedure **VII** from 1,3-diethyl 2-cyclopentylpropanedioate on a 6.58 mmol scale to afford the title compound **309e** as a colourless oil in 49% yield over two steps (449 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm); 1.36 - 1.50 (m, 2 H, $C\underline{H}_AH_BCHC\underline{H}_AH_B$), 1.56 - 1.78 (m, 4 H, $C\underline{H}_2CH_2CHCH_2C\underline{H}_2$), 1.89 - 2.00 (m, 2 H, $CH_A\underline{H}_BCHCH_A\underline{H}_B$), 2.86 (quin, J = 8.5 Hz, 1 H, $CH_2C\underline{H}CH_2$), 5.67 ('t', J = 1.5 Hz, 1 H, $C\underline{H}_AH_BC$), 6.29 ('s', 1 H, $CH_A\underline{H}_BC$), 11.50 (br. s, 1 H, O$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm) 24.9 ($\underline{C}H_2CH_2CHCH_2\underline{C}H_2$), 31.9 ($\underline{C}H_2CH\underline{C}H_2$), 41.0 ($CH_2\underline{C}HCH_2$), 124.3 ($\underline{C}H_AH_BC$), 143.8 ($CH_AH_B\underline{C}$), 173.3 ($\underline{C}$=O). Data is consistent with that given in the literature.[324]

8.4.2.6 Synthesis and characterisation of 287g

Methyl 2-methylidenepent-4-enoate **287g**

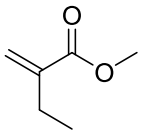


Synthesised according to General Procedure VIII on a 8.9 mmol scale of acid **309a** to afford the crude product **287g** in 54% yield (612 mg) as a colourless oil which was used without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.02 (d, *J* = 6.5 Hz, 2 H, $CH_AH_BCHC\underline{H}_2$), 3.71 (s, 3 H, $OC\underline{H}_3$), 5.03 ('s', 1 H, $C\underline{H}_AH_BCHCH_2$), 5.06 (dd, *J* = 6.5, 1.5 Hz, 1 H, $CH_A\underline{H}_BCHCH_2$), 5.53 (d, *J* = 1.5 Hz, 1 H, $C\underline{H}_AH_BC$), 5.73 - 5.89 (m, 1 H, $CH_AH_BC\underline{H}CH_2$), 6.15 ('s', 1 H, $CH_A\underline{H}_BC$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 35.7 ($CH_AH_BCH\underline{C}H_2$), 51.7 ($O\underline{C}H_3$), 116.7 ($\underline{C}H_AH_BCHCH_2$), 125.3 ($\underline{C}H_AH_BC$), 134.9 ($CH_AH_B\underline{C}HCH_2$), 138.8 ($CH_AH_B\underline{C}$), 167.2 ($\underline{C}$=O). Data is consistent with that given in the literature.[325]

8.4.2.7 Synthesis and characterisation of 287h

Methyl 2-methylidenebutanoate **287h**

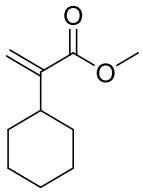


Synthesised according to General Procedure VIII on a 6.0 mmol scale of acid **309b** to afford the crude product **287h** in 50% yield (340 mg) as a colourless oil which was used without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.07 (t, *J* = 7.5 Hz, 3 H, $CH_2C\underline{H}_3$), 2.32 (q, *J* = 7.5 Hz, 2 H, $C\underline{H}_2CH_3$), 3.75 (s, 3 H, $OC\underline{H}_3$), 5.53 (d, *J* = 1.0 Hz, 1 H, $C\underline{H}_AH_BC$), 6.13 ('s', 1 H, $CH_A\underline{H}_BC$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 12.8 ($CH_2\underline{C}H_3$), 24.9 ($\underline{C}H_2CH_3$), 51.9 ($O\underline{C}H_3$), 123.7 ($\underline{C}H_AH_BC$), 142.3 ($CH_AH_B\underline{C}$), 168.0 ($\underline{C}$=O). Data is consistent with that given in the literature.[326]

8.4.2.8 Synthesis and characterisation of 287i

Methyl 2-cyclohexylprop-2-enoate **287i**

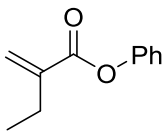


Synthesised according to General Procedure VIII on a 4.7 mmol scale of acid **309d** to afford the crude product **287i** in 50% yield (340 mg) as a colourless oil which was used without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.07 - 1.45 (m, 5 H, 5 of $C_6\underline{H}_{11}$), 1.90 - 1.68 (m, 5 H, 5 of $C_6\underline{H}_{11}$), 2.41 - 2.53 (m, 1 H, $CH_2C\underline{H}CH_2$), 3.78 (s, 3 H, $OC\underline{H}_3$), 5.51 ('t', *J* = 1.0 Hz, 1 H, $C\underline{H}_AH_BC$), 6.13 (d, *J* = 1.0 Hz, 1 H, $CH_A\underline{H}_BC$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 26.4, 26.7, 32.7 (3 of $\underline{C}_6H_{11}$), 39.2 ($CH_2\underline{C}HCH_2$), 51.9 ($O\underline{C}H_3$), 122.3 ($\underline{C}H_AH_BC$), 146.5 ($CH_AH_B\underline{C}$), 168.2 ($\underline{C}$=O). Data is consistent with that given in the literature.[327]

8.4.2.9 Synthesis and characterisation of 287j

Phenyl 2-methylidenebutanoate **287j**

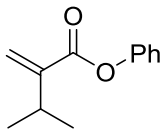


Synthesised according to General Procedure **IX** on a 3.00 mmol scale of acid **309b** to afford the title compound **287j** as a colourless oil in 75% yield (398 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (t, *J* = 7.5 Hz, 3 H, $CH_2C\underline{H}_3$), 2.46 (q, *J* = 7.5 Hz, 2 H, $C\underline{H}_2CH_3$), 5.73 (d, *J* = 1.0 Hz, 1 H, $C\underline{H}_AH_BC$), 6.40 ('s', 1 H, $CH_A\underline{H}_BC$), 7.13 (d, *J* = 8.0 Hz, 2 H, Ar$C\underline{H}$), 7.20 - 7.30 (m, 1 H, Ar$C\underline{H}$), 7.34 - 7.46 (m, 2 H, Ar$C\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 12.8 ($CH_2\underline{C}H_3$), 25.0 ($\underline{C}H_2CH_3$), 121.8 (Ar$\underline{C}$H), 125.5 ($\underline{C}H_AH_BC$), 125.8 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 141.9 ($CH_AH_B\underline{C}$), 151.0 (Ar$\underline{C}$), 165.9 ($\underline{C}$=O). Data consistent with that given in the literature.[328]

8.4.2.10 Synthesis and characterisation of 287k

Phenyl 3-methyl-2-methylidenebutanoate **287k**

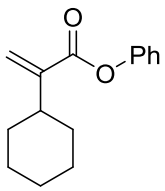


Synthesised according to General Procedure **IX** on a 4.38 mmol scale of acid **309c** to afford the title compound **287k** as a colourless oil in 98% yield (805 mg).

IR: 2955 (C-H), 1733 (C=O), 1498, 1197 (C-O), 1110; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.18 (d, *J* = 7.0 Hz, 6 H, $(C\underline{H}_3)_2CH$), 2.92 (sptd, *J* = 7.0, 1.0 Hz, 1 H, $(CH_3)_2C\underline{H}$), 5.72 ('t', *J* = 1.0 Hz, 1 H, $C\underline{H}_AH_BC$), 6.39 (br s, 1 H, $CH_A\underline{H}_BC$), 7.10 - 7.16 (m, 2 H, Ar$C\underline{H}$), 7.21 - 7.28 (m, 1 H, Ar$C\underline{H}$), 7.36 - 7.44 (m, 2 H, Ar$C\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 22.0 ($(\underline{C}H_3)_2CH$), 29.7 ($(CH_3)_2\underline{C}H$), 121.8 (Ar$\underline{C}$H), 123.8, ($\underline{C}H_AH_BC$), 125.8 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 146.8 ($CH_AH_B\underline{C}$), 151.1 (Ar$\underline{C}$), 166.0 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{14}NaO_2$) requires *m/z* 213.0886, found *m/z* 213.0883.

8.4.2.11 Synthesis and characterisation of 287l

Phenyl 2-cyclohexylprop-2-enoate **287l**



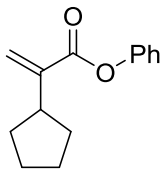
Synthesised according to General Procedure **IX** on a 1.95 mmol scale of acid **309d** to afford the title compound **287l** as a colourless solid in 75% yield (336 mg).

MP 27-29 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.14 - 1.47 (m, 5 H, 5 of $C_6\underline{H}_{11}$), 1.69 - 1.78 (m, 1 H, 1 of $C_6\underline{H}_{11}$), 1.78 - 1.87 (m, 2 H, 2 of $C_6\underline{H}_{11}$), 1.92 ('d', *J* = 12.0 Hz, 2 H, 2 of $C_6\underline{H}_{11}$), 2.51 – 2.61 (m, 1 H, $CH_2C\underline{H}CH_2$), 5.68 ('s', 1 H, $C\underline{H}_AH_BC$), 6.38 ('s', 1 H, $CH_A\underline{H}_BC$), 7.13 (d, *J* = 7.5 Hz, 2 H, Ar$\underline{H}$), 7.20 - 7.29 (m, 1 H, Ar$\underline{H}$), 7.36 - 7.45 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 26.3, 26.7, 32.7 (3 of $\underline{C}_6H_{11}$), 39.4

($CH_2\underline{C}HCH_2$), 121.8 (Ar<u>C</u>H), 124.1 ($\underline{C}H_AH_BC$), 125.8 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 146.0 ($CH_AH_B\underline{C}$), 151.1 (Ar<u>C</u>), 166.1 (<u>C</u>=O). Data consistent with that given in the literature.[329]

8.4.2.12 Synthesis and characterisation of 287m

Phenyl 2-cyclopentylprop-2-enoate **287m**

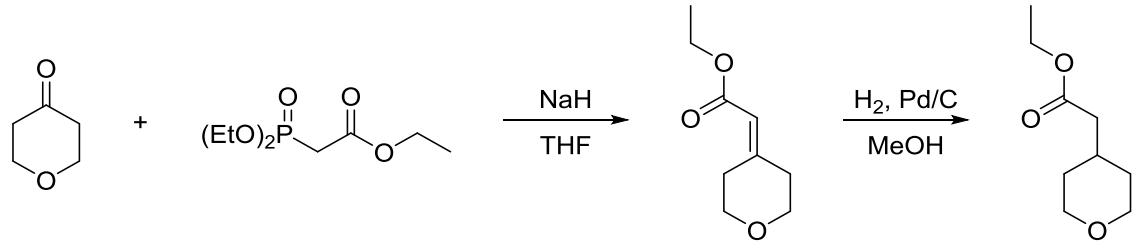


Synthesised according to General Procedure **IX** on a 2.85 mmol scale of acid **309e** to afford the title compound **287m** as a colourless oil in 89% yield (546 mg).

IR (film) ν_{max}/cm^{-1}: 2953 (C-H), 1734 (C=O), 1492, 1196 (C-O), 1110; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.42 - 1.56 (m, 2 H, 2 of $C_5\underline{H}_9$), 1.59 - 1.82 (m, 4 H, 4 of $C_5\underline{H}_9$), 1.94-2.10 (m, 2 H, 2 of $C_5\underline{H}_9$), 2.97 (quin, *J* = 8.5 Hz, 1 H, $CH_2C\underline{H}CH_2$), 5.73 ('s', 1 H, $C\underline{H}_AH_BC$), 6.37 ('s', 1 H, $CH_A\underline{H}_BC$), 7.13 (d, *J* = 8.0 Hz, 2 H, Ar<u>H</u>), 7.20 - 7.28 (m, 1 H, Ar<u>H</u>), 7.35 - 7.55 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 25.1 ($CHCH_2\underline{C}H_2$), 32.0 ($CH\underline{C}H_2$), 41.7 ($CH_2\underline{C}HCH_2$), 121.8 (Ar<u>C</u>H), 123.8 ($\underline{C}H_AH_BC$), 125.8 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 144.2 ($CH_AH_B\underline{C}$), 151.1 (Ar<u>C</u>), 166.2 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}NaO_2$) requires *m/z* 239.1043, found *m/z* 239.1038.

8.4.2.13 Synthesis and characterisation of 311

Ethyl 2-(oxan-4-yl)acetate **311**



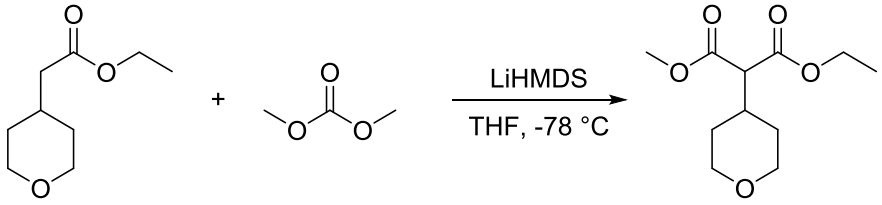
According to a literature procedure,[226] to a suspension of sodium hydride (60% in mineral oil, 0.88 g, 22 mmol, 1.1 eq) THF (67 mL) at 0 °C was added dropwise triethyl

phosphonoacetate (4.36 mL, 22 mmol, 1.1 eq). The reaction mixture was then stirred at rt for 30 min and then tetrahydropyran-4-one (1.85 mL, 20 mmol, 1.0 eq) was added dropwise. Stirring was maintained for 6 h, the reaction was cooled to 0 °C, quenched by the addition of H_2O (150 mL) and extracted with Et_2O (3 x 50 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 4/1 petroleum ether/EtOAc] yielded the α,β-unsaturated ester as a pale yellow oil (3.36 g, 99%). To the α,β-unsaturated ester (3.36 g, 20 mmol, 1.0 eq) in MeOH (133 mL) was added 10% Pd/C (0.34 g, 0.1 eq) and the reaction mixture placed under a hydrogen atmosphere for 4 h. The suspension was filtered through Celite® washing with CH_2Cl_2 and MeOH and the filtrate concentrated to yield the title compound **311** as a colourless oil (2.92 g, 85% yield over two steps).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.11 - 1.22 (m, 3 H, $OCH_2C\underline{H_3}$), 1.22 - 1.33 (m, 2 H, two of $OCH_2C\underline{H_2}CHC\underline{H_2}CH_2$), 1.56 (br. d, *J* = 13.0 Hz, 2 H, two of $OCH_2C\underline{H_2}CHC\underline{H_2}CH_2$), 1.88 - 2.00 (m, 1 H, $OCH_2CH_2C\underline{H}$), 2.13 - 2.18 (m, 2 H, $C(O_2CH_2CH_3)C\underline{H_2}CH$), 3.27 - 3.37 (m, 2 H, two of $OC\underline{H_2}CH_2CHCH_2C\underline{H_2}$), 3.82 - 3.90 (m, 2 H, two of $OC\underline{H_2}CH_2CHCH_2C\underline{H_2}$), 3.99 - 4.10 (m, 2 H, $OC\underline{H_2}CH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 14.2 ($OCH_2\underline{C}H_3$), 32.0 ($OCH_2CH_2\underline{C}H$), 32.6 ($OCH_2\underline{C}H_2CH$), 41.4 ($C(O_2CH_2CH_3)\underline{C}H_2CH$), 60.2 ($O\underline{C}H_2CH_3$), 67.7 ($O\underline{C}H_2CH_2CH$), 172.3 ($\underline{C}$=O). Data is consistent with that given in the literature.[226]

8.4.2.14 Synthesis and characterisation of 312

1-Ethyl 3-methyl 2-(oxan-4-yl)propanedioate **312**



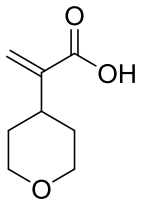
A solution of **311** (720 mg, 4.19 mmol, 1.00 eq) and dimethyl carbonate (0.46 mL, 5.44 mmol, 1.3 eq) in THF (18 mL) was added dropwise to 1.0 M LiHMDS in THF (9.2 mL, 9.2 mmol, 2.2 eq) at -78 °C over 5 min. The reaction mixture was allowed to stir at -78 °C for 30 min then allowed to warm to 0 °C over 2 h and remained at this temperature for 14 h whereupon it was quenched by the addition of glacial AcOH (1.29 mL, 22.6 mL, 5.4 eq) and Et_2O (25 mL). Vigorous stirring was maintained for 5 min and the insoluble solids were filtered off, washed with Et_2O (2 x 10 mL) and the filtrate concentrated *in vacuo*. Purification by flash column chromatography [Petroleum ether to petroleum ether/Et_2O 3/2] afforded the title compound **312** as a pale yellow oil (929 mg, 96% yield).

IR (film) ν_{max}/cm^{-1}: 2956, 2845, 1753, 1733, 1180, 1135, 1094; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.26 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.34 - 1.48 (m, 2 H, two of $OCH_2C\underline{H}_2CHC\underline{H}_2CH_2$), 1.56 - 1.71 (m, 2 H, two of $OCH_2C\underline{H}_2CHC\underline{H}_2CH_2$), 2.25 - 2.38 (m, 1 H, $OCH_2CH_2C\underline{H}CH$), 3.18 (d, *J* = 9.5 Hz, 1 H, $OCH_2CH_2CHC\underline{H}$), 3.41 (td, *J* = 12.0, 2.0 Hz, 2 H, two of $OC\underline{H}_2CH_2CHCH_2C\underline{H}_2$), 3.72 (s, 3 H, $OC\underline{H}_3$), 3.95 (dd, *J* = 11.5, 3.5 Hz, 2 H, two of $OC\underline{H}_2CH_2CHCH_2C\underline{H}_2$), 4.19 (q, *J* = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 14.2 ($OCH_2\underline{C}H_3$), 30.7 ($\underline{C}H_2CH_2OCH_2\underline{C}H_2CH$), 30.7 ($OCH_2\underline{C}H_2CHCH$), 35.3 ($OCH_2CH_2\underline{C}HCH$), 52.5 ($O\underline{C}H_3$), 57.7 ($OCH_2CH_2CH\underline{C}H$), 61.6 ($O\underline{C}H_2CH_3$), 67.7, 67.7 ($CH_2\underline{C}H_2O\underline{C}H_2CH_2CH$), 168.2 ($\underline{C}$=O), 168.8 ($\underline{C}$=O); **HRMS**

(ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{18}NaO_5$) requires *m/z* 253.1046, found *m/z* 253.1046.

8.4.2.15 Synthesis and characterisation of 313

2-(oxan-4-yl)prop-2-enoic acid **313**

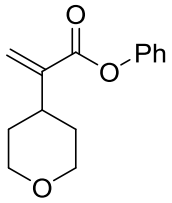


Synthesised according to General Procedure **VII** from **312** on a 6.21 mmol scale to afford the title compound **313** as a colourless solid in 47% yield over two steps (453 mg).

IR (film) ν_{max}/cm^{-1}: 2948, 2924, 2360, 1708, 1627, 1159, 1120, 863; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.53 (qd, *J* = 12.5, 4.0 Hz, 2 H, $CH_A\underline{H_B}CH_2OCH_2CH_A\underline{H_B}CH$), 1.73 ('d', *J* = 12.5 Hz, 2 H, $C\underline{H_A}H_BCH_2OCH_2C\underline{H_A}H_BCH$), 2.67 (tt, *J* = 12.5, 3.0 Hz, 1 H, $OCH_2CH_2C\underline{H}$), 3.48 (td, *J* = 12.0, 2.0 Hz, 2 H, $CH_2CH_A\underline{H_B}OCH_A\underline{H_B}CH_2CH$), 4.03 ('dd', *J* = 11.5, 4.0 Hz, 2 H, $CH_2C\underline{H_A}H_BOC\underline{H_A}H_BCH_2CH$), 5.62 ('s', 1 H, $CH_A\underline{H_B}C$), 6.33 ('s', 1 H, $C\underline{H_A}H_BC$), 11.34 (br. s., 1 H, $COO\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 32.0 ($OCH_2\underline{C}H_2CH$), 36.0 ($OCH_2CH_2\underline{C}H$), 68.1 ($O\underline{C}H_2CH_2$), 125.3 ($\underline{C}H_AH_BC$), 143.8 ($CH_AH_B\underline{C}$), 171.7 ($\underline{C}$=O); **MP** 58 - 60 °C; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_8H_{12}NaO_3$) requires *m/z* 179.0679, found *m/z* 179.0677.

8.4.2.16 Synthesis and characterisation of 287n

Phenyl 2-(oxan-4-yl)prop-2-enoate **287n**



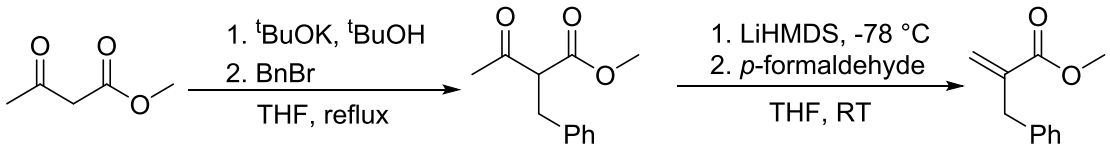
Synthesised according to General Procedure **IX** on a 1.92 mmol scale of acid **313** to afford the title compound **287n** as a colourless solid in 67% yield (300 mg).

IR (film) ν_{max}/cm^{-1}: 2917, 2847, 1729, 1193, 1121, 1091, 752; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.61 (qd, *J* = 12.5, 4.5 Hz, 2 H, $C\underline{H_A}H_BCH_2OCH_2C\underline{H_A}H_BCH$), 1.76 -

1.87 (m, 2 H, $CH_A\underline{H_B}CH_2OCH_2CH_A\underline{H_B}CH$), 2.80 (tt, *J* = 12.0, 3.0 Hz, 1 H, $OCH_2CH_2C\underline{H}$), 3.51 (td, *J* = 12.0, 2.0 Hz, 2 H, $CH_2C\underline{H_A}H_BOC\underline{H_A}H_BCH_2CH$), 4.05 (dd, *J* = 11.5, 4.5 Hz, 2 H, $CH_2CH_A\underline{H_B}OCH_A\underline{H_B}CH_2CH$), 5.73 ('s', 1 H, $C\underline{H_A}H_BC$), 6.47 ('s', 1 H, $CH_A\underline{H_B}C$), 7.08 - 7.16 (m, 2 H, Ar$\underline{H}$), 7.22 - 7.29 (m, 1 H, Ar$\underline{H}$), 7.35 - 7.47 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 32.2 ($OCH_2\underline{C}H_2CH$), 36.6 ($OCH_2CH_2\underline{C}H$), 68.2 ($O\underline{C}H_2CH_2$), 121.7 (Ar$\underline{C}$H), 125.0 ($\underline{C}H_AH_BC$), 125.9 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 144.0 ($CH_AH_B\underline{C}$), 150.9 (Ar$\underline{C}$), 165.5 ($\underline{C}$=O); **MP** 54 - 56 °C; **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}NaO_3$) requires *m/z* 255.0992, found *m/z* 255.0990.

8.4.2.17 Synthesis and characterisation of 287o

Methyl 2-benzylprop-2-enoate **287o**

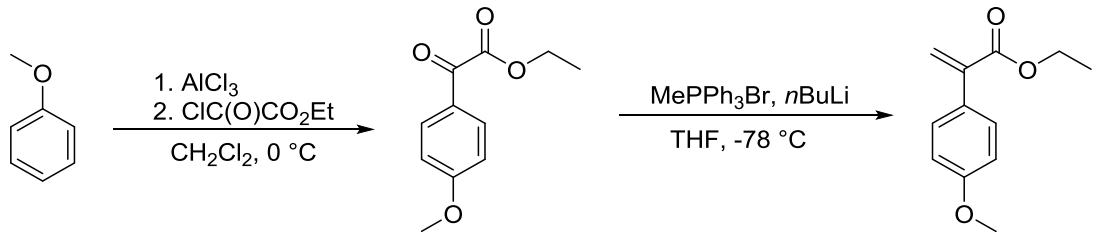


According to a literature procedure,[227] methyl 3-oxobutanoate (1.74 g, 15.0 mmol, 1.00 eq) and ^{t}BuOH (110 mg, 1.5 mmol, 0.10 eq) were added to a suspension of ^{t}BuOK (1.72 g, 15.3 mmol, 1.02 eq) in THF (40 mL) under a N_2 atmosphere at 0 °C, and the mixture was stirred for 30 min. Benzyl bromide (2.55 g, 14.9 mmol, 0.990 eq) was added and the mixture refluxed for 24 h. The reaction was quenched with water (30 mL) and a sat. aq. $NaHCO_3$ solution (30 mL) was added. The aqueous layer was extracted with *tert*-butyl methyl ether (25 mL) and washed with Et_2O (2 x 25 mL), the combined organic washed with brine (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether/EtOAc = 19/1) to yield methyl 2-benzyl-3-oxobutanoate as a colourless oil (2.26 g, 73% yield). LiHMDS (1.0 M in THF, 12.0 mL, 12 mmol, 1.1 eq) was added to a solution of methyl 2-benzyl-3-oxobutanoate (2.26 g, 11.0 mmol, 1.00 eq) in THF (80 mL) at –78 °C and stirred for

30 min. Paraformaldehyde (1.65 g, 55 mmol, 5.0 eq) was added to yield a suspension, which was warmed to rt and stirred for 5 h before filtering through Celite® and the volatiles removed *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether/EtOAc = 19/1) to yield the title compound **287o** as a colourless oil (1.50 g, 77% yield, 57% yield over two steps). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.48 (s, 2 H, PhC$\underline{H_2}$C), 3.57 (s, 3 H, OC$\underline{H_3}$), 5.31 (d, *J* = 1.5 Hz, 1 H, $\underline{H_A}H_B$C=C(Bn)C=O), 6.08 (m, 1 H, $H_A\underline{H_B}$C=C(Bn)C=O), 7.01 - 7.08 (m, 3 H, Ar$\underline{H}$), 7.10 - 7.18 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 38.1 (Ph$\underline{C}H_2$C), 51.9 (O$\underline{C}H_3$), 126.3, 126.4 (Ar$\underline{C}$H and $H_2\underline{C}$=C(Bn)C=O), 128.5 (Ar$\underline{C}$H), 129.1 (Ar$\underline{C}$H), 138.7, 140.1(Ar$\underline{C}$ and H_2C=$\underline{C}$(Bn)C=O), 167.4 ($\underline{C}$=O). All characterisation data agree with those published in the literature.[227]

8.4.2.18 Synthesis and characterisation of 317a

Ethyl 2-(4-methoxyphenyl)prop-2-enoate **317a**



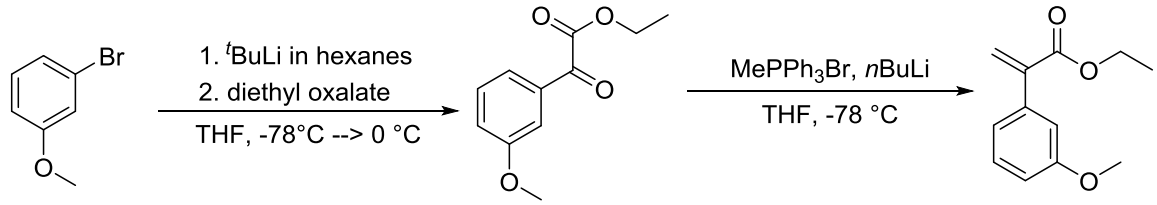
According to a literature procedure,[330] $AlCl_3$ (5.07 g, 38.0 mmol, 1.90 eq) was suspended in CH_2Cl_2 (27 mL) at 0 °C and ethyl chlorooxoacetate (4.24 mL, 38.0 mmol, 1.90 eq) was added dropwise over 15 min. The suspension became a yellow solution after stirring for 10 min and then anisole (2.17 mL, 20.0 mmol, 1.00 eq) was added dropwise over 10 min at 0 °C. Upon complete addition the reaction mixture was warmed to RT and stirring maintained for 14 h. The reaction was quenched by pouring into crushed ice (100 g) and 37% HCl (33 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the

combined organics were washed with 0.1 M NaOH (20 mL) then brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 4/1 petroleum ether/Et_2O] afforded the oxalate as a pale yellow oil (2.97 g, 71% yield). To a suspension of methyl-triphenylphosphonium bromide (5.11 g, 14.3 mmol, 1.00 eq) in THF (57 mL) at 0 °C was added 1.6 M ^{n}BuLi in hexanes (8.9 mL, 14.3 mmol, 1.00 eq) dropwise. Stirring was maintained for 1 h and the reaction mixture cooled to -78°C then a solution of the oxalate (2.97 g, 14.3 mmol, 1.00 eq) in THF (25 mL) was added dropwise and then the solution was allowed to warm to RT whereupon stirring was maintained for 14 h. The reaction mixture was quenched by the addition of sat. NH_4Cl (30 mL) and diluted with brine (30 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 40 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 9/1 petroleum ether/Et_2O] afforded the title compound **317a** as a pale yellow oil (1.70 g, 58% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.34 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 3.83 (s, 3 H, $OC\underline{H}_3$), 4.30 (q, *J* = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.84 (d, *J* = 0.5 Hz, 1 H, $C\underline{H}_AH_BC$), 6.26 (d, *J* = 0.5 Hz, 1 H, $CH_A\underline{H}_BC$), 6.88 - 6.92 (m, 2 H, Ar$\underline{H}$), 7.36 – 7.40 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 14.2 ($OCH_2\underline{C}H_3$), 55.3 ($ArCO\underline{C}H_3$), 61.1 ($O\underline{C}H_2CH_3$), 113.5 (Ar$\underline{C}$H), 125.0 ($\underline{C}H_AH_BC$), 129.2 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$H), 140.9 ($CH_AH_B\underline{C}$), 159.5 ($Ar\underline{C}OCH_3$), 167.1 ($\underline{C}$=O). Data is consistent with that given in the literature.[331]

8.4.2.19 Synthesis and characterisation of 317b

Ethyl 2-(3-methoxyphenyl)prop-2-enoate **317b**

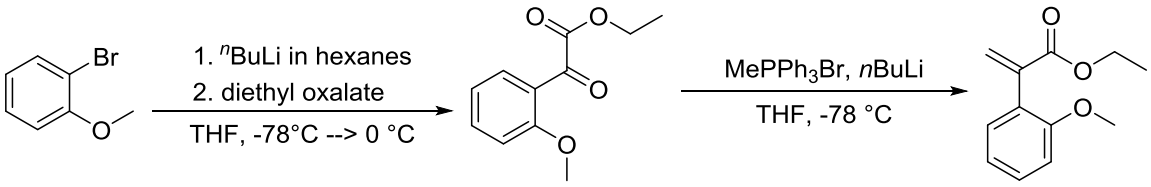


To a solution of 3-bromoanisole (1.27 mL, 10.0 mmol, 1.00 eq) in THF (40 mL) at -78 °C was added 1.67 M ^{t}BuLi in hexanes (12.0 mL, 20 mmol, 2.00 eq) dropwise. In a separate R.B.F. diethyl oxalate (1.36 mL, 10.0 mmol, 1.00 eq) in THF (48 mL) was cooled to -78 °C and the organolithium reagent was cannulated at low temperature dropwise to the dioxalate solution. The reaction mixture was warmed to RT over 2 h and stirring was maintained for 12 h whereupon it was quenched by the addition of sat. NH_4Cl (60 mL) and extracted with Et_2O (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 9/1 petroleum ether/Et_2O] afforded the oxalate as a yellow oil (1.16 g, 56% yield). To a suspension of methyl-triphenylphosphonium bromide (1.72 g, 4.81 mmol, 1.00 eq) in THF (19 mL) at -78 °C was added 1.8 M *n*BuLi in hexanes (2.70 mL, 4.81 mmol, 1.00 eq) dropwise. Stirring was maintained for 1 h and then a solution of the oxalate (1.00 g, 4.81 mmol, 1.00 eq) in THF (10 mL) was added dropwise and then the solution was allowed to warm to RT whereupon stirring was maintained for 14 h. The reaction mixture was quenched by the addition of 1 M HCl (15 mL) and diluted with brine (20 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 20 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 9/1 petroleum ether/Et_2O] afforded the title compound **317b** as a yellow oil (350 mg, 35% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.35 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 3.83 (s, 3 H, $ArOC\underline{H}_3$), 4.30 (q, *J* = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.90 (t, *J* = 1.0 Hz, 1 H, $C\underline{H}_AH_BC$), 6.35 (t, *J* = 1.0 Hz, 1 H, $CH_A\underline{H}_BC$), 6.94 - 6.87 (m, 1 H, Ar<u>H</u>), 6.97 - 7.04 (m, 2 H, Ar<u>H</u>), 7.25 - 7.31 (m, 1 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 14.2 ($OCH_2\underline{C}H_3$), 55.2 ($ArO\underline{C}H_3$), 61.1 ($O\underline{C}H_2CH_3$), 113.7 (Ar<u>C</u>H), 114.0 (Ar<u>C</u>H), 120.7 (Ar<u>C</u>H), 126.6 ($\underline{C}H_AH_BC$), 129.0 (Ar<u>C</u>H), 138.1 (Ar<u>C</u>), 141.4 ($CH_AH_B\underline{C}$), 159.2 (Ar<u>C</u>OCH_3), 166.7 (<u>C</u>=O). Data is consistent with that given in the literature.[332]

8.4.2.20 Synthesis and characterisation of 317c

<u>Ethyl 2-(2-methoxyphenyl)prop-2-enoate</u> **<u>317c</u>**



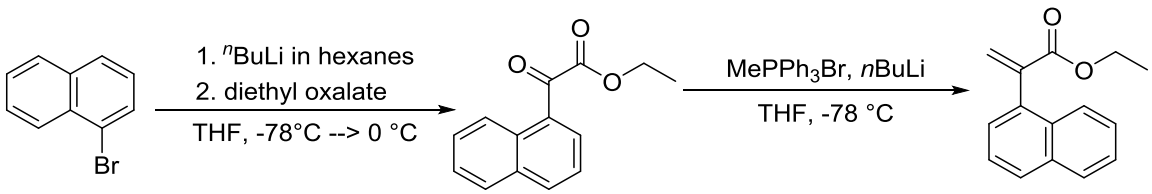
According to a modified procedure,[211] to a solution of 2-bromoanisole (1.49 mL, 12.0 mmol, 1.00 eq) in THF (48 mL) at -78 °C was added a solution of *n*BuLi (7.5 mL, 1.6 M in hexanes) dropwise and then the reaction mixture was warmed to 0 °C over 20 min and then cooled back to -78 °C. In a separate R.B.F. diethyl oxalate (1.63 mL, 12.0 mmol, 1.00 eq) in THF (48 mL) was cooled to -78 °C and the organolithium reagent was cannulated at low temperature dropwise to the oxalate. The reaction mixture was warmed to RT over 2 h and stirring was maintained for 12 h whereupon it was quenched by the addition of sat. NH_4Cl (60 mL) and extracted with Et_2O (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 9/1 petroleum ether/Et_2O] afforded the oxalate as a yellow oil (1.71 g, 68% yield). To a suspension of methyl-triphenylphosphonium bromide (3.07 g, 8.58 mmol, 1.05 eq) in THF (55 mL) at -

78 °C was added 1.24 M *n*BuLi in hexanes (6.60 mL, 8.17 mmol, 1.00 eq) dropwise. Stirring was maintained for 1 h and then a solution of the oxalate (1.70 g, 8.17 mmol) in THF (10 mL) was added dropwise and then the solution was allowed to warm to RT whereupon stirring was maintained for 14 h. The reaction mixture was quenched by the addition of 1 M HCl (20 mL) and diluted with brine (40 mL). The layers were separated and the aqueous layer extracted with Et_2O (2x 40 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 9/1 petroleum ether/Et_2O] afforded the title compound **317c** as a yellow oil (1.52 g, 90% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.28 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H_3}$), 3.80 (s, 3 H, $OC\underline{H_3}$), 4.25 (q, *J* = 7.0 Hz, 2 H, $C\underline{H_2}CH_3$), 5.74 (d, *J* = 1.5 Hz, 1 H, $C\underline{H_A}H_BC$), 6.28 (d, *J* = 1.5 Hz, 1 H, $CH_A\underline{H_B}C$), 6.90 (dd, *J* = 8.0, 1.0 Hz, 1 H, Ar<u>H</u>), 6.97 (td, *J* = 7.5, 1.0 Hz, 1 H, Ar<u>H</u>), 7.24 (dd, *J* = 7.5, 2.0 Hz, 1 H, Ar<u>H</u>), 7.34 (ddd, *J* = 8.5, 7.5, 2.0 Hz, 1 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 14.2 ($OCH_2\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 60.8 ($O\underline{C}H_2CH_3$), 110.6 (Ar<u>C</u>H), 120.6 (Ar<u>C</u>H), 126.0 ($\underline{C}H_AH_BC$), 127.1 (Ar<u>C</u>), 129.7 (Ar<u>C</u>H), 130.0 (Ar<u>C</u>H), 140.3 ($CH_AH_B\underline{C}$), 156.8 (Ar<u>C</u>OCH_3), 167.4 (<u>C</u>=O). Data is consistent with that given in the literature.[330]

8.4.2.21 Synthesis and characterisation of 317d

<u>Ethyl 2-(naphthalen-1-yl)prop-2-enoate</u> **<u>317d</u>**



To a solution of 1-bromonaphthalene (1.68 mL, 12.0 mmol, 1.00 eq) in THF (48 mL) at -78 °C was added 1.24 M *n*-BuLi in hexanes (9.8 mL, 12 mmol, 1.0 eq) dropwise. In a

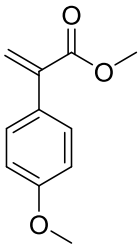
separate R.B.F. diethyl oxalate (1.63 mL, 12.0 mmol, 1.00 eq) in THF (48 mL) was cooled to -78 °C and the organolithium reagent was cannulated at low temperature dropwise to the dioxalate solution. The reaction mixture was warmed to RT over 2 h and stirring was maintained for 12 h whereupon it was quenched by the addition of sat. NH_4Cl (60 mL) and extracted with Et_2O (3 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 3/2 petroleum ether/Et_2O] afforded the oxalate as a yellow oil (1.66 g, 61% yield). To a suspension of methyl-triphenylphosphonium bromide (2.51 g, 7.02 mmol, 1.00 eq) in THF (28 mL) at -78 °C was added 2.5 M ^{n}BuLi in hexanes (2.80 mL, 7.0 mmol, 1.00 eq) dropwise. Stirring was maintained for 1 h and then a solution of the oxalate (1.60 g, 7.02 mmol, 1.00 eq) in THF (15 mL) was added dropwise and then the solution was allowed to warm to rt whereupon stirring was maintained for 14 h. The reaction mixture was quenched by the addition of 1 M HCl (20 mL) and diluted with brine (30 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 x 30 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to 9/1 petroleum ether/Et_2O] and subsequent crystallisation (neat) afforded the title compound **317d** as a colourless solid (400 mg, 25% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.22 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 4.23 (q, *J* = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$), 5.91 (d, *J* = 2.0 Hz, 1 H, $C\underline{H}_AH_BC$), 6.72 (d, *J* = 2.0 Hz, 1 H, $CH_A\underline{H}_BC$), 7.38 (dd, *J* = 7.0, 1.5 Hz, 1 H, Ar<u>H</u>), 7.44 - 7.52 (m, 3 H, Ar<u>H</u>), 7.72 - 7.78 (m, 1 H, Ar<u>H</u>), 7.84 - 7.91 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 14.1 ($OCH_2\underline{C}H_3$), 61.1 ($O\underline{C}H_2CH_3$), 125.2 (Ar<u>C</u>H), 125.3 (Ar<u>C</u>H), 125.8 (Ar<u>C</u>H), 126.1 (Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 129.6 ($\underline{C}H_AH_BC$), 131.8 (Ar<u>C</u>),

133.4 (Ar<u>C</u>), 135.4 (Ar<u>C</u>), 141.1 ($CH_AH_B\underline{C}$), 167.0 (<u>C</u>=O); **MPT** 49 – 51 °C [lit 52 – 53 °C].[333] Data is consistent with that given in the literature.[331]

8.4.2.22 Synthesis and characterisation of 287p

<u>Methyl 2-(4-methoxyphenyl)prop-2-enoate **287p**</u>

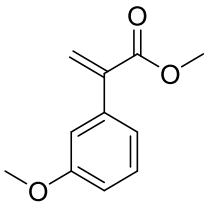


Synthesised according to General Procedure VIII on a 8.25 mmol scale of ethyl ester **317a** to afford, after reflux for 16 h, the crude product. Purification by flash column chromatography [Petroleum ether to petroleum ether/Et_2O 9/1] afforded the title compound **287p** in 78% yield (1.23 g) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.83 ('s', 6 H, ArOC<u>H</u>$_3$ and C(=O)OC<u>H</u>$_3$), 5.84 (d, *J* = 1.0 Hz, 1 H, $CH_A\underline{H_B}C$), 6.28 (d, *J* = 1.0 Hz, 1 H, $C\underline{H_A}H_BC$), 6.87 - 6.93 (m, 2 H, Ar<u>H</u>),7.34 - 7.42 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 52.1 (C(=O)O<u>C</u>H_3), 55.2 (ArCO<u>C</u>H_3), 113.5 (Ar<u>C</u>H), 125.4 ($\underline{C}H_AH_BC$), 129.1 (Ar<u>C</u>), 129.5 (Ar<u>C</u>H), 140.6 ($CH_AH_B\underline{C}$), 159.6 (Ar<u>C</u>OCH_3), 167.5 (<u>C</u>=O). Data is consistent with that given in the literature.[227]

8.4.2.23 Synthesis and characterisation of 287q

<u>Methyl 2-(3-methoxyphenyl)prop-2-enoate **287q**</u>



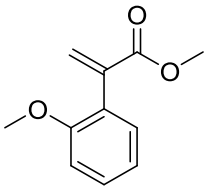
Synthesised according to General Procedure VIII on a 1.97 mmol scale of ethyl ester **317b** to afford, after reflux for 16 h, the crude product. Purification by flash column chromatography [Petroleum ether to 9/1 petroleum ether/Et_2O] afforded the title compound **287q** as a yellow oil (120 mg, 43% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.83 (s, 3 H, COOC<u>H</u>$_3$ or ArCOC<u>H</u>$_3$), 3.83 (s, 3 H, COOC<u>H</u>$_3$ or ArCOC<u>H</u>$_3$), 5.91 (d, *J* = 1.0 Hz, 1 H, $C\underline{H_A}H_BC$), 6.37 (d, *J* = 1.0 Hz, 1 H,

$CH_A\underline{H_B}C$), 6.90 (ddd, *J* = 8.5, 2.5, 1.0 Hz, 1 H, Ar<u>H</u>), 6.96 - 6.98 (m, 1 H, Ar<u>H</u>), 6.99 -7.03 (m, 1 H, Ar<u>H</u>), 7.26 - 7.31 (m, 1 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 52.2 ($COO\underline{C}H_3$), 55.2 ($ArCO\underline{C}H_3$), 113.7 (Ar<u>C</u>H), 114.0 (Ar<u>C</u>H), 120.7 (Ar<u>C</u>H), 127.0 ($\underline{C}H_AH_BC$), 129.1 (Ar<u>C</u>H), 138.0 (Ar<u>C</u>), 141.1 ($CH_AH_B\underline{C}$), 159.2 ($Ar\underline{C}OCH_3$), 167.2 (<u>C</u>=O). Data is consistent with that given in the literature.[228]

8.4.2.24 Synthesis and characterisation of 287r

<u>Methyl 2-(2-methoxyphenyl)prop-2-enoate **287r**</u>

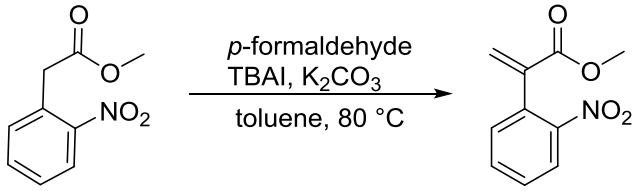


Synthesised according to General Procedure VIII on a 1.97 mmol scale of ethyl ester **317c** to afford, after reflux for 16 h, the title compound **287r** in 61% yield (234 mg) as a pale yellow oil which was used without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.76 (s, 3 H, C(=O)O$C\underline{H_3}$), 3.80 (s, 3 H, $ArCOC\underline{H_3}$), 5.74 (d, *J* = 1.5 Hz, 1 H, $C\underline{H_A}H_BC$), 6.29 (d, *J* = 1.5 Hz, 1 H, $CH_A\underline{H_B}C$), 6.90 (d, *J* = 8.5 Hz, 1 H, Ar<u>H</u>), 6.97 ('td', *J* = 7.5, 1.0 Hz, 1 H, Ar<u>H</u>), 7.22 (dd, *J* = 7.5, 1.5 Hz, 1 H, Ar<u>H</u>), 7.30 - 7.38 (m, 1 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 52.2 (C(=O)O$\underline{C}H_3$), 55.8 ($ArCO\underline{C}H_3$), 110.9 (Ar<u>C</u>H), 120.8 (Ar<u>C</u>H), 126.6 ($\underline{C}H_AH_BC$), 127.2 (Ar<u>C</u>), 130.0 (Ar<u>C</u>H), 130.2 (Ar<u>C</u>H), 140.0 ($CH_AH_B\underline{C}$), 157.0 ($Ar\underline{C}OCH_3$), 168.1 (<u>C</u>=O). Data is consistent with that given in the literature.[334]

8.4.2.25 Synthesis and characterisation of 287s

Methyl 2-(2-nitrophenyl)prop-2-enoate **287s**

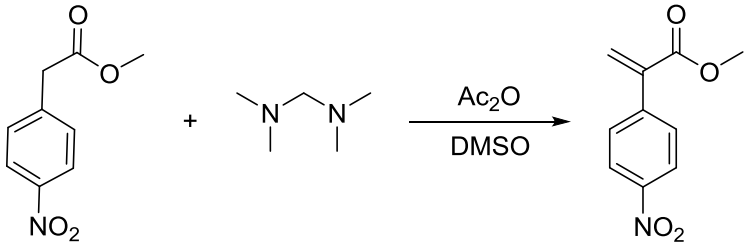


According to a literature procedure,[228] to a solution of methyl 2-(2-nitrophenyl)acetate (1.45 g, 7.43 mmol, 1.00 eq) in toluene (10 mL) were added paraformaldehyde (625 mg, 20.8 mmol, 2.80 eq), TBAI (110 mg, 0.30 mmol, 0.04 eq) and K_2CO_3 (3.08 g, 22.3 mmol, 3.00 eq). The resulting suspension was stirred at 80 °C for 24 h, cooled to room temperature and diluted with H_2O (10 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organics were washed (brine), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [petroleum ether to 4/1 petroleum ether/Et_2O] afforded the title compound **287s** as a pale yellow oil (818 mg, 53% yield).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.73 (s, 3 H, OC$\underline{H}_3$), 5.88 (d, *J* = 0.5 Hz, 1 H, $CH_A\underline{H}_BC$), 6.54 (d, *J* = 0.5 Hz, 1 H, $C\underline{H}_AH_BC$), 7.39 (dd, *J* = 8.0, 1.5 Hz, 1 H, Ar$\underline{H}$), 7.53 ('td', *J* = 8.0, 1.5 Hz, 1 H, Ar$\underline{H}$), 7.65 ('td', *J* = 8.0, 1.5 Hz, 1 H, Ar$\underline{H}$), 8.12 (dd, *J* = 8.0, 1.5 Hz, 1 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 52.5 (O$\underline{C}H_3$), 124.7 (Ar$\underline{C}$H), 127.7 ($\underline{C}H_AH_BC$), 129.5 (Ar$\underline{C}$H), 132.3 (Ar$\underline{C}$H), 133.1 (Ar$\underline{C}$), 133.8 (Ar$\underline{C}$H), 139.9 ($CH_AH_B\underline{C}$), 148.0 (Ar$\underline{C}$), 165.4 ($\underline{C}$=O). Data is consistent with that given in the literature.[228]

8.4.2.26 Synthesis and characterisation of 287t

Methyl 2-(4-nitrophenyl)prop-2-enoate **287t**



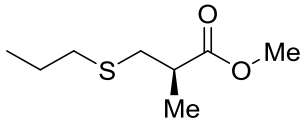
According to a literature procedure,[335] to a stirred solution of methyl 2-(4-nitrophenyl)acetate (1.50g, 7.68 mmol, 1.0 eq) in DMSO (8 mL) was added tetramethyldiaminomethane (1.57 mL, 11.5 mmol, 1.50 eq) followed by acetic anhydride (2.40 mL, 25.3 mmol, 3.3 eq) at RT and the mixture was stirred for 2 h. The reaction mixture was diluted with water (10 mL), extracted with ether (2 x 30 mL) and the volatiles removed *in vacuo*. Purification by flash column chromatography [petroleum ether to 4/1 petroleum ether/EtOAc] afforded the title compound **287t** as a colourless solid (552 mg, 35% yield).

MPT 189- 191 °C [lit. 110 °C][336]; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.84 (s, 3 H, OC$\underline{H}_3$), 6.04 (‘s’, 1 H, C$\underline{H}_A$H$_B$C), 6.54 (‘s’, 1 H, CH$_A\underline{H}_B$C), 7.54 - 7.65 (m, 2 H, Ar$\underline{H}$), 8.17 - 8.23 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 52.4 (O$\underline{C}$H$_3$), 123.2 (Ar$\underline{C}$H), 129.3 (Ar$\underline{C}$H), 129.6 ($\underline{C}$H$_A$H$_B$C), 139.4 (CH$_A$H$_B\underline{C}$), 143.0 (Ar$\underline{C}$), 147.4, (Ar$\underline{C}$), 165.9 ($\underline{C}$=O). Data is consistent with that given in the literature.[337]

8.4.3 Synthesis and Characterisation of α-Substituted, β-Mercaptoesters

8.4.3.1 Synthesis and characterisation of 288a

Methyl (2*R*)-2-methyl-3-(propylsulfanyl)propanoate **288a**

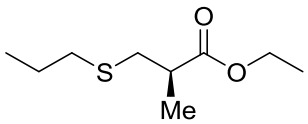


Methyl methacrylate (110 μL, 1.0 mmol, 5.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 49/1) to afford the title compound **288a** as a pale yellow oil in 97% yield (34 mg) and 94% ee [determined by HPLC, Chiralpak AD, hexane/isopropanol = 99/1, 1 mL/min, λ = 230 nm, t (major) = 5.32 min, t (minor) = 5.91 min].

$[\alpha]_D^{20}$ = +27.3 (*c* 1.09, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2962, 1736 (C=O), 1458, 1435, 1375, 1208 (C-O), 1161 (C-O), 986, 826; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.98 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.25 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)C=O$), 1.60 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.49 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.57 (dd, *J* = 13.0, 7.0 Hz, 1 H, $SC\underline{H}_AH_BCH(CH_3)$), 2.68 ('sxt', *J* = 7.0 Hz, 1 H, $C\underline{H}(CH_3)C=O$), 2.83 (dd, *J* = 13.0, 7.0 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 3.70 (s, 3 H, $OC\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.4 ($\underline{C}H_3CH_2CH_2S$), 16.8 ($CH(\underline{C}H_3)C=O$), 22.9 ($CH_3\underline{C}H_2CH_2S$), 34.7 ($CH_3CH_2\underline{C}H_2S$), 35.4 ($S\underline{C}H_2CH(CH_3)$), 40.2 ($\underline{C}H(CH_3)C=O$), 51.8 ($O\underline{C}H_3$), 175.7 ($\underline{C}=O$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_8H_{16}NaO_2S$) requires *m/z* 199.0763, found *m/z* 199.0758.

8.4.3.2 Synthesis and characterisation of 288b

Ethyl (2*R*)-2-methyl-3-(propylsulfanyl)propanoate **288b**



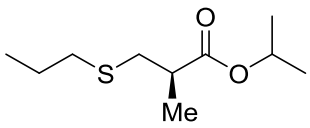
Ethyl methacrylate (124 μL, 1.00 mmol, 5.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to

General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288b** as a colourless oil in 87% yield (33 mg) and 92% 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℃ ramp 1 ℃/min to 90 ℃ then 90 ℃ t (minor) = 62.70 min, t (major) = 63.21 min].

$[\alpha]_D^{24}$ = +15.8 (*c* 0.66, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2964, 1732 (C=O), 1458, 1375, 1340, 1204, 1159 (C-O), 1117, 1030, 862; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.98 ppm (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.25 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)C=O$), 1.27 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.60 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.50 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.56 (dd, *J* = 12.5, 7.0 Hz, 1 H, $SC\underline{H}_AH_BCH(CH_3)$), 2.65 ('sxt', *J* = 7.0 Hz, 1 H, $C\underline{H}(CH_3)C=O$), 2.83 (dd, *J* = 12.5, 7.0 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 4.16 (q, *J* = 7.0 Hz, 2 H, $OC\underline{H}_2CH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.4 ($\underline{C}H_3CH_2CH_2S$), 14.2 ($OCH_2\underline{C}H_3$), 16.8 ($CH(\underline{C}H_3)C=O$), 22.9 ($CH_3\underline{C}H_2CH_2S$), 34.7 ($CH_3CH_2\underline{C}H_2S$), 35.4 ($S\underline{C}H_2CH(CH_3)$), 40.3 ($\underline{C}H(CH_3)C=O$), 60.5 ($O\underline{C}H_2CH_3$), 175.2 ($\underline{C}=O$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_9H_{18}NaO_2S$) requires *m/z* 213.0920, found *m/z* 213.0916.

8.4.3.3 Synthesis and characterisation of 288c

Propan-2-yl (2*R*)-2-methyl-3-(propylsulfanyl)propanoate **288c**

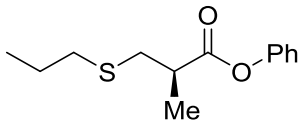


Isopropyl methacrylate (144 µL, 1.00 mmol, 5.0 eq) was reacted with 1-propanethiol (18 µL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288c** as a colourless oil in 71% yield (29 mg) and 93% ee [determined by HPLC, Chiralcel OD, hexane/isopropanol = 99.5/0.5, 1 mL/min, λ = 220 nm, t (minor) = 6.32 min, t (major) = 7.25 min].

[α]$_D^{23}$ = +22.3 (*c* 0.39, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2972, 1731 (C=O), 1457, 1375, 1208, 1169 (C-O), 1109; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.98 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.28 - 1.20 (m, 9 H, $CH(C\underline{H}_3)C=O$ and $OCH(C\underline{H}_3)_2$), 1.60 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_3S$), 2.45 - 2.67 (m, 4 H, $SC\underline{H}_AH_BCH(CH_3)$, $C\underline{H}(CH_3)C=O$ and $CH_3CH_2C\underline{H}_2S$), 2.78 - 2.85 (m, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 5.02 (spt, *J* = 6.5 Hz, 1 H, $OC\underline{H}(CH_3)_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.9 ($\underline{C}H_3CH_2CH_2S$), 17.3 ($CH(\underline{C}H_3)C=O$), 22.2 (one of $CH(\underline{C}H_3)_2$), 22.3 (one of $OCH(\underline{C}H_3)_2$), 23.4 ($CH_3\underline{C}H_2CH_2S$), 35.1 ($CH_3CH_2\underline{C}H_2S$), 35.9 ($S\underline{C}H_2CH(CH_3)$), 40.9 ($\underline{C}H(CH_3)C=O$), 68.3 ($O\underline{C}H(CH_3)_2$), 175.3 ($\underline{C}=O$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{20}NaO_2S$) requires *m/z* 227.1076, found *m/z* 227.1074.

8.4.3.4 Synthesis and characterisation of 288e

Phenyl (2*R*)-2-methyl-3-(propylsulfanyl)propanoate **288e**



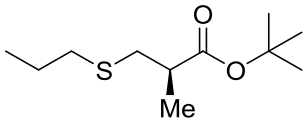
Phenyl methacrylate **287e** (65 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 49/1) to afford the title compound **288e** as a colourless oil in >99% yield (48 mg) and 95% ee [determined by HPLC, Chiralpak AD, hexane/isopropanol = 99/1, 1 mL/min, λ = 230 nm, t (major) = 7.13 min, t (minor) = 7.64 min].

[α]$_D^{20}$ = +44.2 (*c* 0.65, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2963, 1757 (C=O), 1594, 1493, 1457, 1192 (C-O), 1162, 1136 (C-O), 748, 690; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.00 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.40 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)C=O$), 1.64 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.57 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.68 - 2.77 (m, 1 H, $SC\underline{H}_AH_BCH(CH_3)$), 2.88 - 2.99 (m, 2 H, $SCH_A\underline{H}_BCH(CH_3)$ and $C\underline{H}(CH_3)C=O$), 7.08 - 7.13 (m, 2 H, Ar$\underline{H}$), 7.20 - 7.27 (m, 1 H, Ar$\underline{H}$), 7.35 - 7.41 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$,

100 MHz) δ (ppm): 13.4 ($\underline{C}H_3CH_2CH_2SH$), 16.9 ($CH(\underline{C}H_3)C=O$), 22.9 ($CH_3\underline{C}H_2CH_2SH$), 34.7 ($CH_3CH_2\underline{C}H_2SH$), 35.4 ($S\underline{C}H_2CH(CH_3)$), 40.5 ($\underline{C}H(CH_3)C=O$), 121.5 (Ar$\underline{C}$H), 125.8 (Ar$\underline{C}$H), 129.4 (Ar$\underline{C}$H), 150.7 (Ar$\underline{C}$), 173.7 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{18}NaO_2S$) requires *m/z* 261.0920, found *m/z* 261.0908.

8.4.3.5 Synthesis and characterisation of 288f

<u>*tert*-Butyl (2*R*)-2-methyl-3-(propylsulfanyl)propanoate **288f**</u>

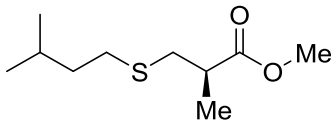


tert-Butyl methacrylate (163 µL, 1.00 mmol, 5.0 eq) was reacted with 1-propanethiol (18 µL, 0.20 mmol, 1.0 eq) according to General Procedure **X** stirring for 48 h. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288f** as a colourless oil in 37% yield (16 mg) and 96% 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 ℃ ramp 1 ℃/min to 90 ℃ then 90 ℃ t (major) = 81.36 min, t (minor) = 82.60 min].

$[\alpha]_D^{23}$ = +19.2 (*c* 0.63, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2969, 1728 (C=O), 1458, 1367, 1252, 1148 (C-O), 848; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.99 ppm (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.21 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)C=O$), 1.46 (s, 9 H, $OC(C\underline{H}_3)_3$), 1.61 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.47 - 2.60 (m, 4 H, $SC\underline{H}_A\underline{H}_BCH(CH_3)$, $C\underline{H}(CH_3)C=O$ and $CH_3CH_2C\underline{H}_2S$), 2.77 – 2.83 (m, 1 H, $SCH_A\underline{H}_BCH(CH_3)$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.4 ($\underline{C}H_3CH_2CH_2S$), 16.9 ($CH(\underline{C}H_3)C=O$), 22.9 ($CH_3\underline{C}H_2CH_2S$), 28.0 ($OC(\underline{C}H_3)_3$), 34.7 ($CH_3CH_2\underline{C}H_2S$), 35.6 ($S\underline{C}H_2CH(CH_3)$), 41.1 ($\underline{C}H(CH_3)C=O$), 80.4 ($O\underline{C}(CH_3)_3$), 174.6 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{22}NaO_2S$) requires *m/z* 241.1233, found *m/z* 241.1240.

8.4.3.6 Synthesis and characterisation of 288i

Methyl (2*R*)-2-methyl-3-[(3-methylbutyl)sulfanyl]propanoate **288i**

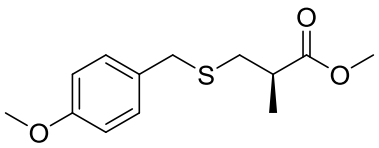


Methyl methacrylate (0.107 mL, 1.00 mmol, 5.0 eq) was reacted with isopentylmercaptan (25 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether to petroleum ether/Et_2O 49/1) to afford the title compound **288i** as a colourless oil in 86% yield (35 mg) and 92% ee [determined by GC, Supelco β-dex^{TM} 325, 30 m, 0.25 mm, 0.25 μm, carrier gas He (flow rate 40 cm/s); column temperature 80 ℃ ramp 1 ℃/min to 120 ℃ then 10 ℃/min to 220 ℃, t (minor) = 89.56 min, t (major) = 90.27 min].

$[\alpha]_D^{25}$ = +14.2 (*c* 0.51, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2955, 1740 (C=O), 1460, 1163 (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.88 (d, *J* = 6.5 Hz, 6 H, $CH(C\underline{H}_3)_2$), 1.24 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)C{=}O$), 1.38 - 1.50 (m, 2 H, $C\underline{H}_2CH_2S$), 1.58 - 1.72 (m, 1 H, $C\underline{H}(CH_3)_2$), 2.45 - 2.53 (m, 2 H, $CH_2C\underline{H}_2S$), 2.56 (dd, *J* = 13.0, 7.0 Hz, 1 H, $SC\underline{H}_AH_BCH(CH_3)$), 2.67 ('sxt', *J* = 7.0 Hz, 1 H, $C\underline{H}(CH_3)C{=}O$), 2.82 (dd, *J* = 13.0, 7.0 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 3.69 (s, 3 H, $OC\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 16.8 ($CH(\underline{C}H_3)C{=}O$), 22.2 ($CH(\underline{C}H_3)_2$), 27.4 ($\underline{C}H(CH_3)_2$), 30.6 ($S\underline{C}H_2CH(CH_3)$), 35.4 ($CH_2\underline{C}H_2S$), 38.5 ($\underline{C}H_2CH_2S$), 40.1 ($\underline{C}H(CH_3)C{=}O$), 51.8 ($O\underline{C}H_3$), 175.7 ($\underline{C}{=}O$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{20}NaO_2S$) requires *m/z* 227.1076, found *m/z* 227.1072.

8.4.3.7 Synthesis and characterisation of 288l

Methyl (2*R*)-3-[(4-methoxybenzyl)sulfanyl]-2-methylpropanoate **288l**

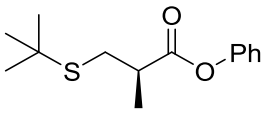


Methyl methacrylate (110 μL, 1.0 mmol, 5.0 eq) was reacted with 4-methoxybenzyl mercaptan (28 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 4/1) to afford the title compound **288l** as a colourless oil in 89% yield (45 mg) and 89% ee [determined by HPLC, Chiralcel OD, hexane/isopropanol = 98/2, 1 mL/min, λ = 220 nm, t (minor) = 9.52 min, t (major) = 10.53 min].

$[\alpha]_D^{22}$ = +25.2 (*c* 1.00, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.21 (d, *J* = 7.0 Hz, 3 H, $SCH_AH_BCH(C\underline{H}_3)$), 2.46 (dd, *J* = 13.0, 7.0 Hz, 1 H, $SC\underline{H}_AH_BCH(CH_3)$), 2.65 ('sxt', *J* = 7.0 Hz, 1 H, $SCH_AH_BC\underline{H}(CH_3)$), 2.74 (dd, *J* = 13.0, 7.0 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 3.68 (s, 2 H, $ArC\underline{H}_2S$), 3.70 (s, 3 H, $C(O)C\underline{H}_3$), 3.81 (s, 3 H, $ArOC\underline{H}_3$), 6.82 - 6.89 (m, 2 H, Ar<u>H</u>), 7.20 - 7.26 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 16.9 ($SCH_AH_BCH(\underline{C}H_3)$), 34.4 ($S\underline{C}H_AH_BCH(CH_3)$), 36.0 ($Ar\underline{C}H_2S$), 39.8 ($SCH_AH_BC\underline{H}(CH_3)$), 51.8 ($C(O)\underline{C}H_3$), 55.3 ($ArO\underline{C}H_3$), 113.9 (Ar<u>C</u>H), 129.9 (Ar<u>C</u>H), 130.0 (Ar<u>C</u>), 158.6 (ArC), 175.6 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{18}NaO_3S$) requires *m/z* 277.0869, found *m/z* 277.0868.

8.4.3.8 Synthesis and characterisation of 288m

Phenyl (2*R*)-3-(*tert*-butylsulfanyl)-2-methylpropanoate **288m**



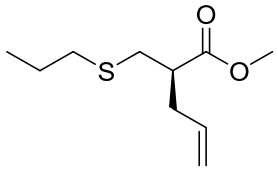
Ester **287e** (65 mg, 0.40 mmol, 2.0 eq) was reacted with *tert*-butyl mercaptan (23 μL, 0.20 mmol, 1.0 eq) according to a modified General Procedure **X** stirring at RT for 96 h. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288m** as a colourless oil

in 48% yield (24 mg) and 85% ee [determined by derivatization to the sulfone (according to 8.4.6.1) and analysis by HPLC, Chiralcel AS-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 25.62 min, t (major) = 27.29 min].

$[\alpha]_D^{23}$ = +24.7 (*c* 1.01, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2963, 1758, 1594, 1493, 1458, 1193, 1162, 1135; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.36 (s, 9 H, ($C\underline{H}_3)_3CS$), 1.41 (d, *J* = 7.0 Hz, 3 H, $SCH_AH_BCH(C\underline{H}_3)$), 2.74 (dd, *J* = 11.5, 7.0 Hz, 1 H, $SC\underline{H}_AH_BCH(CH_3)$), 2.90 ('sxt', *J* = 7.0 Hz, 1 H, $SCH_AH_BC\underline{H}(CH_3)$), 2.98 (dd, *J* = 11.5, 7.0 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 7.08 - 7.14 (m, 2 H, Ar<u>H</u>), 7.20 - 7.25 (m, 1 H, Ar<u>H</u>), 7.34 - 7.42 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 17.2 ($SCH_AH_BCH(\underline{C}H_3)$), 31.1 (($\underline{C}H_3)_3CS$), 31.8 ($S\underline{C}H_AH_BCH(CH_3)$), 40.7 ($SCH_AH_B\underline{C}H(CH_3)$), 42.5 (($CH_3)_3\underline{C}S$), 121.7 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 151.0 (Ar<u>C</u>), 173.9 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_2S$) requires *m/z* 275.1076, found *m/z* 275.1076.

8.4.3.9 Synthesis and characterisation of 288o

<u>Methyl (2*R*)-2-[(propylsulfanyl)methyl]pent-4-enoate **288o**</u>



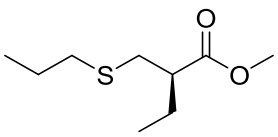
Ester **287g** (50 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether to petroleum ether/Et_2O 49/1) to afford the title compound **288o** as a colourless oil in 94% yield (38 mg) and 93% ee [determined by HPLC, Chiralpak AS-H, hexane/isopropanol = 99.5/0.5, 1 mL/min, λ = 220 nm, t (major) = 12.62 min, t (minor) = 14.42 min].

$[\alpha]_D^{24}$ = +23.0 (*c* 0.32, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2959, 1739 (C=O), 1438, 1218; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.95 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.57 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.31 - 2.41 (m, 2 H, $C\underline{H}_2CH{=}CH_2$), 2.46 (t, *J* = 7.5 Hz,

2 H, $CH_3CH_2C\underline{H_2}S$), 2.57 - 2.69 (m, 2 H, $SC\underline{H_A}H_BCH(CH_2CH=CH_2)$ and $C\underline{H}(CH_2CH=CH_2)C=O$), 2.70 - 2.80 (m, 1 H, $SCH_A\underline{H_B}CH(CH_2CH=CH_2)$), 3.67 (s, 3 H, $OC\underline{H_3}$), 4.97 - 5.12 (m, 2 H, $CH=C\underline{H_A}H_B$ and $CH=CH_A\underline{H_B}$), 5.70 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H, $C\underline{H}=CH_AH_B$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.3 ($\underline{C}H_3CH_2CH_2S$), 22.8 ($CH_3\underline{C}H_2CH_2S$), 33.2 ($S\underline{C}H_2CHC=O$), 34.5 ($SCH_3CH_2\underline{C}H_2S$), 35.8 ($\underline{C}H_2CH=CH_2$), 45.7 ($SCH_2\underline{C}HC=O$), 51.6 ($O\underline{C}H_3$), 117.4 ($CH=\underline{C}H_AH_B$), 134.5 ($\underline{C}H=CH_AH_B$), 174.5 ($\underline{C}=O$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{18}NaO_2S$) requires *m/z* 225.0920, found *m/z* 225.0916.

8.4.3.10 Synthesis and characterisation of 288p

Methyl (2*R*)-2-[(propylsulfanyl)methyl]butanoate **288p**



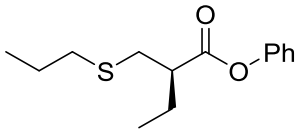
Ester **287h** (114 mg, 1.00 mmol, 5.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 49/1) to afford the title compound **288p** as a colourless oil in 47% yield (18 mg) and 92% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 99/1, 1 mL/min, λ = 230 nm, t (major) = 11.5 min, t (minor) = 12.6 min].

$[\alpha]_D^{20}$ = +27.1 (*c* 0.72, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2963, 1737, 1460, 1263, 1202, 1160, 797; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.92 ppm (t, *J* = 7.5 Hz, 3 H, $CH(CH_2C\underline{H_3})C=O$), 0.98 (t, *J* = 7.5 Hz, 3 H, $C\underline{H_3}CH_2CH_2S$), 1.55 - 1.63 (m, 2 H, $CH_3C\underline{H_2}CH_2S$), 1.63 - 1.71 (m, 2 H, $CH(C\underline{H_2}CH_3)C=O$), 2.49 (t, *J* = 7.5 Hz, 1 H, $CH_3CH_2C\underline{H_2}S$), 2.50 - 2.58 (m, 1 H, $C\underline{H}(CH_2CH_3)C=O$), 2.63 (dd, *J* = 13.0, 6.0 Hz, 1 H, $SC\underline{H_A}H_BCH(CH_2CH_3)$), 2.77 (dd, *J* = 13.0, 8.5 Hz, 1 H, $SCH_A\underline{H_B}CH(CH_2CH_3)$), 3.72 (s, 3 H, $OC\underline{H_3}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 11.6 ($CH(CH_2\underline{C}H_3)C=O$), 13.4

($\underline{C}H_3CH_2CH_2S$), 22.9 ($CH_3\underline{C}H_2CH_2S$), 25.1 ($CH(\underline{C}H_2CH_3)C=O$), 33.6 ($S\underline{C}H_2CH(CH_2CH_3)$), 34.6 ($CH_3CH_2\underline{C}H_2S$), 47.6 ($\underline{C}H(CH_2CH_3)C=O$), 51.6 ($O\underline{C}H_3$), 175.2 ($\underline{C}=O$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_9H_{18}NaO_2S$) requires *m/z* 213.0920, found *m/z* 213.0916.

8.4.3.11 Synthesis and characterisation of 288q

Phenyl (2*R*)-2-[(propylsulfanyl)methyl]butanoate **288q**

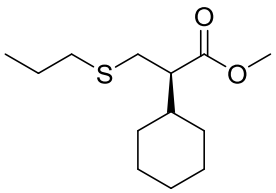


Ester **287j** (70 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 49/1) to afford the title compound **288q** as a colourless oil in 85% yield (43 mg) and 92% ee [determined by HPLC, Chiralcel AS-H, hexane/isopropanol = 98/2, 1 mL/min, λ = 220 nm, t (major) = 6.10 min, t (minor) = 6.43 min].

$[\alpha]_D^{24}$ = +40.7 (*c* 0.82, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2969, 1754 (C=O), 1457, 1197 (C-O), 1133 (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.00 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.06 (t, *J* = 7.5 Hz, 3 H, $CH(CH_2C\underline{H}_3)C=O$), 1.64 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 1.74 - 1.91 (m, 2 H, $CH(C\underline{H}_2CH_3)C=O$), 2.57 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.73 - 2.83 (m, 2 H, $SC\underline{H}_AH_BCH$ and $C\underline{H}(CH_2CH_3)C=O$), 2.84 - 2.95 (m, 1 H, $SCH_A\underline{H}_BCH$), 7.08 - 7.15 (m, 2 H, Ar$\underline{H}$), 7.20 - 7.26 (m, 1 H, Ar$\underline{H}$), 7.34 - 7.44 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 11.8 ($\underline{C}H_3CH_2CH_2S$), 13.6 ($CH(CH_2\underline{C}H_3)C=O$), 23.0 ($CH_3\underline{C}H_2CH_2S$), 25.4 ($CH(\underline{C}H_2CH_3)C=O$), 33.8 ($S\underline{C}H_2CH$), 34.7 ($CH_3CH_2\underline{C}H_2S$), 47.9 ($\underline{C}H(CH_2CH_3)C=O$), 121.8 (Ar$\underline{C}$H), 125.9 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 150.9 (Ar$\underline{C}$), 173.4 ($\underline{C}=O$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_2S$) requires *m/z* 275.1076, found *m/z* 275.1070.

8.4.3.12 Synthesis and characterisation of 288r

Methyl (2*R*)-2-cyclohexyl-3-(propylsulfanyl)propanoate **288r**

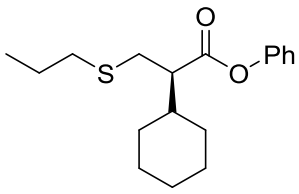


Ester **287i** (67 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) in MTBE (4.0 mL) at 55 °C for 24 h according to a modified General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288r** as a colourless oil in 39% yield (19 mg) and 85% ee [determined by HPLC, Chiralcel AS-H, hexane/isopropanol = 99.5/0.5, 1 mL/min, λ = 210 nm, t (major) = 9.98 min, t (minor) = 13.48 min].

$[\alpha]_D^{23}$ = +38.9 (*c* 0.48, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2927, 2853, 1737, 1157; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.90 - 1.01 (m, 4 H, $SCH_2CH_2C\underline{H}_3$ and one $C_6\underline{H}_{11}$), 1.01 - 1.32 (m, 5 H, 5 of $C_6\underline{H}_{11}$), 1.53 - 1.85 (m, 7 H, $SCH_2C\underline{H}_2CH_3$, $SCH_AH_BCHC\underline{H}$ and 4 of $C_6\underline{H}_{11}$), 2.38 - 2.52 (m, 3 H, $SC\underline{H}_2CH_2CH_3$ and $SCH_AH_BC\underline{H}$), 2.67 - 2.77 (m, 2 H, $SC\underline{H}_A\underline{H}_BCH$), 3.70 (s, 3 H, $OC\underline{H}_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.5 ($SCH_2CH_2\underline{C}H_3$), 22.9 ($SCH_2\underline{C}H_2CH_3$), 26.2, 26.2, 26.2, 30.7, 30.8 (5 of $\underline{C}_6H_{11}$), 31.5 ($S\underline{C}H_AH_BCHCH$), 34.5 ($S\underline{C}H_2CH_2CH_3$), 40.3 ($SCH_AH_BCH\underline{C}H$), 51.4 ($O\underline{C}H_3$), 52.5 ($SCH_AH_B\underline{C}HCH$), 174.8 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{24}NaO_2S$) requires *m/z* 267.1389, found *m/z* 267.1389.

8.4.3.13 Synthesis and characterisation of 288s

Phenyl (2*R*)-2-cyclohexyl-3-(propylsulfanyl)propanoate **288s**



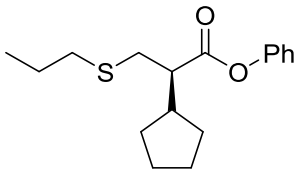
Ester **287l** (92 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 49/1) to afford the title compound **288s** as a colourless oil

in 93% yield (57 mg) and 85% ee [determined by HPLC, Chiralcel AD-H, hexane/isopropanol = 98/2, 1 mL/min, λ = 220 nm, t (major) = 9.91 min, t (minor) = 10.55 min].

$[\alpha]_D^{24}$ = +40.5 (*c* 0.50, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2928, 1740 (C=O), 1366, 1216 (C-O), 1129 (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.00 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.04 - 1.37 (m, 5 H, 5 of $C_6\underline{H}_{11}$), 1.55 - 1.84 (m, 7 H, $CH_3C\underline{H}_2CH_2S$ and 5 of $C_6\underline{H}_{11}$), 1.84 -1.96 (m, 1 H, one of $C_6\underline{H}_{11}$), 2.56 (t, *J* = 7.0 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.67 (ddd, *J* = 10.5, 7.5, 5.0 Hz, 1 H, $SCH_AH_BC\underline{H}$), 2.81 (dd, *J* = 13.0, 10.5 Hz, 1 H, $SC\underline{H}_AH_BCH$), 2.87 (dd, *J* = 13.0, 5.0 Hz, 1 H, $SCH_A\underline{H}_BCH$), 7.09 - 7.17 (m, 2 H, Ar<u>H</u>), 7.19 - 7.25 (m, 1 H, Ar<u>H</u>), 7.32 - 7.44 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.6 ($\underline{C}H_3CH_2CH_2S$), 23.0 ($CH_3\underline{C}H_2CH_2S$), 26.3, 26.3, 26.4, 30.9, 30.9 ($CH(\underline{C}H_2)_5$), 31.8 ($S\underline{C}H_AH_BCH$), 34.6 ($CH_3CH_2\underline{C}H_2S$), 40.6 ($SCH_AH_BCH\underline{C}H$), 52.6 ($SCH_AH_B\underline{C}H$), 121.9 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 150.9 (Ar<u>C</u>), 173.0 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}NaO_2S$) requires *m/z* 329.1546, found *m/z* 329.1538.

8.4.3.14 Synthesis and characterisation of 288t

<u>Phenyl (2*R*)-2-cyclopentyl-3-(propylsulfanyl)propanoate **288t**</u>

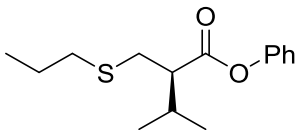


Ester **287m** (86 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 49/1) to afford the title compound **288t** as a colourless oil in 96% yield (56 mg) and 90% ee [determined by HPLC, Chiralcel AS-H, hexane/isopropanol = 99.5/0.5, 0.5 mL/min, λ = 210 nm, t (major) = 29.47 min, t (minor) = 35.51 min].

$[\alpha]_D^{24}$ = +53.8 (*c* 1.12, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2958, 1756 (C=O), 1493, 1194 (C-O), 1125 (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.00 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.18 - 1.33 (m, 1 H, $CH_AH_BCHC\underline{H}_AH_B$), 1.36 - 1.50 (m, 1 H, $C\underline{H}_AH_BCHCH_AH_B$), 1.55 - 1.76 (m, 6 H, $CH_3C\underline{H}_2CH_2S$ and $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.81 - 1.98 (m, 2 H, 2 of $CH_A\underline{H}_BCHCH_A\underline{H}_B$), 2.09 - 2.23 (m, 1 H, $SCH_AH_BCHC\underline{H}$), 2.57 (t, *J* = 7.0 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.63 - 2.72 (m, 1 H, $SCH_AH_BC\underline{H}$), 2.82 - 2.87 (m, 2 H, $SC\underline{H}_A\underline{H}_BCH$), 7.09 - 7.15 (m, 2 H, Ar$\underline{H}$), 7.19 - 7.25 (m, 1 H, Ar$\underline{H}$), 7.34 - 7.42 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.6 ($\underline{C}H_3CH_2CH_2S$), 23.0 ($CH_3\underline{C}H_2CH_2S$), 25.1 (one of $CH_2\underline{C}H_2\underline{C}H_2CH_2$), 25.2 (one of $CH_2\underline{C}H_2\underline{C}H_2CH_2$), 30.9 (one of $\underline{C}H_2CH\underline{C}H_2$), 31.0 (one of $\underline{C}H_2CH\underline{C}H_2$), 33.4 ($CH_3CH_2\underline{C}H_2S$), 34.6 ($S\underline{C}H_2CH$), 43.1 ($SCH_2CH\underline{C}H$), 52.2 ($SCH_2\underline{C}H$), 121.9 (Ar$\underline{C}$H), 125.9 (Ar$\underline{C}$H), 129.5 (Ar$\underline{C}$H), 151.0 (Ar$\underline{C}$), 173.2 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}NaO_2S$) requires *m/z* 315.1389, found *m/z* 315.1380.

8.4.3.15 Synthesis and characterisation of 288u

Phenyl (2*R*)-3-methyl-2-[(propylsulfanyl)methyl]butanoate **288u**



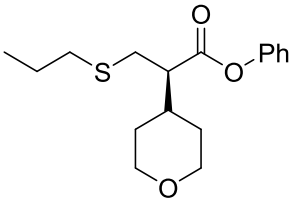
Ester **287k** (76 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 49/1) to afford the title compound **288u** as a colourless oil in 98% yield (52 mg) and 88% ee [determined by HPLC, Chiralcel OD, hexane/isopropanol = 99/1, 1 mL/min, λ = 220 nm, t (minor) = 7.60 min, t (major) = 8.03 min].

$[\alpha]_D^{24}$ = +52.8 (*c* 1.06, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2963, 1756 (C=O), 1492, 1194 (C-O), 1121 (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.01 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.08 (d, *J* = 7.0 Hz, 3 H, one of $C\underline{H}_3CHC\underline{H}_3$), 1.08 (d, *J* = 7.0 Hz, 3 H, one

of C<u>H</u>$_3$CHC<u>H</u>$_3$), 1.59 - 1.69 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$S), 2.03 - 2.15 (m, 1 H, CH$_3$C<u>H</u>CH$_3$), 2.57 (t, *J* = 7.5 Hz, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$S), 2.65 ('q', *J* = 7.5 Hz, 1 H, SCH$_A$H$_B$C<u>H</u>), 2.84 ('d', *J* = 7.5 Hz, 2 H, SC<u>H</u>$_A$H$_B$CH and SCH$_A$<u>H</u>$_B$CH), 7.09 - 7.16 (m, 2 H, Ar<u>H</u>), 7.21 - 7.25 (m, 1 H, Ar<u>H</u>), 7.34 - 7.43 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.6 (<u>C</u>H$_3$CH$_2$CH$_3$S), 20.4 (one of <u>C</u>H$_3$CH<u>C</u>H$_3$), 20.5 (one of <u>C</u>H$_3$CH<u>C</u>H$_3$), 23.0 (CH$_3$<u>C</u>H$_2$CH$_2$S), 31.1 (CH$_3$<u>C</u>HCH$_3$), 32.0 (S<u>C</u>H$_2$CH), 34.6 (CH$_3$CH$_2$<u>C</u>H$_2$S), 53.3 (SCH$_2$<u>C</u>H), 121.8 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 150.9 (Ar<u>C</u>), 172.9 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{22}NaO_2S$) requires *m/z* 289.1233, found *m/z* 289.1226.

8.4.3.16 Synthesis and characterisation of 288v

<u>Phenyl (2*R*)-2-(oxan-4-yl)-3-(propylsulfanyl)propanoate **288v**</u>



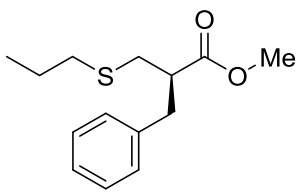
Ester **287n** (77 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 4/1) to afford the title compound 288**v** as a colourless oil in >99% yield (63 mg) and 54% ee [determined by HPLC, Chiralcel AD, hexane/isopropanol = 98/2, 1 mL/min, λ = 220 nm, t (minor) = 15.22 min, t (major) = 16.54 min].

$[\alpha]_D^{23}$ = +28.6 (*c* 0.92, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2959, 2933, 2844, 1754, 1492, 1193, 1129; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.01 (t, *J* = 7.5 Hz, 3 H, SCH$_2$CH$_2$C<u>H</u>$_3$), 1.41 - 1.57 (m, 1 H, CH$_A$H$_B$CH$_2$OCH$_2$C<u>H</u>$_A$H$_B$CH), 1.57 - 1.71 (m, 4 H, SCH$_2$C<u>H</u>$_2$CH$_3$ and two of C<u>H</u>$_A$H$_B$CH$_2$OCH$_2$CH$_A$<u>H</u>$_B$CH), 1.72 - 1.82 (m, 1 H, CH$_A$<u>H</u>$_B$CH$_2$OCH$_2$CH$_A$H$_B$CH), 2.01 ('tdt', *J* = 11.5, 7.5, 4.0 Hz, 1 H, SCH$_A$H$_B$CHC<u>H</u>), 2.57 (t, *J* = 7.5 Hz, 2 H, SC<u>H</u>$_2$CH$_2$CH$_3$), 2.67 - 2.76 (m, 1 H, SCH$_A$H$_B$C<u>H</u>CH), 2.77 - 2.94 (m, 2 H, SC<u>H</u>$_A$<u>H</u>$_B$CHCH), 3.35 - 3.49

(m, 2 H, $CH_2C\underline{H}_AH_BO C\underline{H}_AH_BCH_2CH$), 3.96 - 4.09 (m, 2 H, $CH_2CH_A\underline{H}_BOCH_A\underline{H}_BCH_2CH$), 7.09 - 7.16 (m, 2 H, Ar<u>H</u>), 7.20 - 7.29 (m, 1 H, Ar<u>H</u>), 7.34 - 7.45 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.4 ($SCH_2CH_2\underline{C}H_3$), 22.8 ($SCH_2\underline{C}H_2CH_3$), 30.6 ($OCH_2\underline{C}H_2$), 30.7 ($OCH_2\underline{C}H_2$), 31.3 ($S\underline{C}H_AH_BCHCH$), 34.5 ($S\underline{C}H_2CH_2CH_3$), 37.6 ($SCH_AH_BCH\underline{C}H$), 52.0 ($SCH_AH_B\underline{C}HCH$), 67.7 ($O\underline{C}H_2CH_2$), 67.8 ($O\underline{C}H_2CH_2$), 121.6 (Ar<u>C</u>H), 125.9 (Ar<u>C</u>H), 129.4 (Ar<u>C</u>H), 150.6 (Ar<u>C</u>), 172.3 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}NaO_3S$) requires *m/z* 331.1338, found *m/z* 331.1334.

8.4.3.17 Synthesis and characterisation of 288w

<u>Methyl (2*R*)-2-benzyl-3-(propylsulfanyl)propanoate **288w**</u>



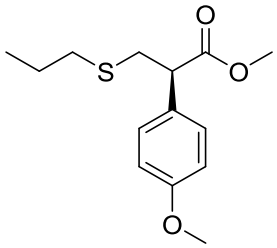
Methyl 2-benzylprop-2-enoate **287o** (70 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to a modified General Procedure **X** stirring for 48 h. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 49/1) to afford the title compound **288w** as a pale yellow oil in 99% yield (50 mg) and 86% ee [determined by HPLC, Chiralpak AD, hexane/isopropanol = 99/1, 1 mL/min, λ = 230 nm, t (major) = 7.36 min, t (minor) = 7.92 min].

$[\alpha]_D^{20}$ = +86.0 (*c* 1.01, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2959, 1735 (C=O), 1495, 1435, 1369, 1214 (C-O), 1162 (C-O), 1029, 745, 700; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.94 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.54 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.45 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.62 (dd, *J* = 13.0, 5.5 Hz, 1 H, either $SC\underline{H}_AH_BCH(CH_2Ph)$ or $CH(C\underline{H}_AH_BPh)C=O$), 2.76 (dd, *J* = 13.0, 8.0 Hz, 1 H, either $SCH_A\underline{H}_BCH(CH_2Ph)$ or $CH(CH_A\underline{H}_BPh)C=O$), 2.83 - 3.01 (m, 3 H, $C\underline{H}(CH_2Ph)C=O$ and either $CH(C\underline{H}_2Ph)C=O$ or $SC\underline{H}_2C(CH_2Ph)$), 3.62 (s, 3 H, $OC\underline{H}_3$), 7.12 - 7.23 (m, 3 H, Ar<u>H</u>), 7.24 - 7.30 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.4 ($\underline{C}H_3CH_2CH_2S$), 22.8 ($CH_3\underline{C}H_2CH_2S$),

33.2 (either S<u>C</u>H_2CH(CH_2Ph) or CH(<u>C</u>H_2Ph)C=O), 34.5 (CH_3CH_2<u>C</u>H_2S), 37.7 (either S<u>C</u>H_2CH(CH_2Ph) or CH(<u>C</u>H_2Ph)C=O), 48.0 (<u>C</u>H(CH_2Ph)C=O), 51.7 (O<u>C</u>H_3), 126.5 (Ar<u>C</u>H)), 128.5 (Ar<u>C</u>H), 128.8 (Ar<u>C</u>H), 138.5 (Ar<u>C</u>), 174.5 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_2S$) requires *m/z* 275.1076, found *m/z* 275.1075.

8.4.3.18 Synthesis and characterisation of 288y

<u>Methyl (2*R*)-2-(4-methoxyphenyl)-3-(propylsulfanyl)propanoate **288y**</u>

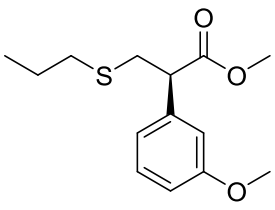


Ester **287p** (38.4 mg, 0.20 mmol, 1.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to a modified General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288y** as a colourless oil in 94% yield (49 mg) and 86% ee [determined by HPLC, Chiralcel OD-H, hexane/isopropanol = 99/1, 1 mL/min, λ = 220 nm, t (major) = 10.30 min, t (minor) = 12.39 min].

$[\alpha]_D^{23}$ = -48.4 (*c* 0.86, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2959, 1735 (C=O), 1511, 1250 (C-O), 1155 (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.96 (t, *J* = 7.5 Hz, 3 H, C<u>H$_3$</u>CH_2CH_2S), 1.58 ('sxt', *J* = 7.5 Hz, 2 H, CH_3C<u>H$_2$</u>CH_2S), 2.43 - 2.50 (m, 2 H, CH_3CH_2C<u>H$_2$</u>S), 2.82 (dd, *J* = 13.0, 6.5 Hz, 1 H, SC<u>H$_A$</u>H_BCH), 3.16 (1 H, dd, *J* = 13.0, 9.5 Hz, SCH_A<u>H$_B$</u>CH), 3.68 (3 H, s, C(=O)OC<u>H$_3$</u>), 3.74 (dd, *J* = 9.5, 6.5 Hz, 1 H, S$CH_A$$H_B$C<u>H</u>), 3.78 (s, 3 H, ArCOC<u>H$_3$</u>), 6.80 - 6.91 (m, 2 H, Ar<u>H</u>), 7.18 - 7.26 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.5 (<u>C</u>$H_3CH_2CH_2$S), 23.0 (CH_3<u>C</u>H_2CH_2S), 34.7 (CH_3CH_2<u>C</u>H_2S), 35.4 (S<u>C</u>$H_A$$H_B$CH), 51.4 (S$CH_A$$H_B$<u>C</u>H), 52.3 (C(=O)O<u>C</u>H_3), 55.3 (ArCO<u>C</u>H_3), 114.2 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 130.1 (Ar<u>C</u>), 159.2 (Ar<u>C</u>OCH_3), 173.6 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_3S$) requires *m/z* 291.1025, found *m/z* 291.1020.

8.4.3.19 Synthesis and characterisation of 288z

Methyl (2*R*)-2-(3-methoxyphenyl)-3-(propylsulfanyl)propanoate **288z**

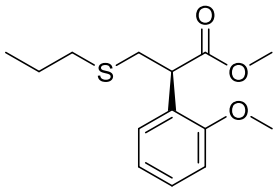


Ester **287q** (77 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288z** as a colourless oil in 94% yield (51 mg) and 75% ee [determined by HPLC, Chiralcel IB, hexane/isopropanol = 99/1, 1 mL/min, λ = 220 nm, t (major) = 7.41 min, t (minor) = 8.99 min].

$[\alpha]_D^{23}$ = -26.3 (*c* 1.11, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2955, 2837, 1734, 1600, 1258, 1157, 1047; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.96 (3 H, t, *J* = 7.5 Hz, C$\underline{H_3}$CH$_2$CH$_2$S), 1.53 - 1.65 (2 H, m, CH$_3$C$\underline{H_2}$CH$_2$S), 2.44 - 2.53 (2 H, m, CH$_3$CH$_2$C$\underline{H_2}$S), 2.84 (1 H, dd, *J* = 13.0, 6.0 Hz, SC$\underline{H_A}$H$_B$CH), 3.19 (1 H, dd, *J* = 13.0, 9.5 Hz, SCH$_A$$\underline{H_B}$CH), 3.70 (3 H, s, C(O)OC$\underline{H_3}$), 3.76 (1 H, dd, *J* = 9.5, 6.0 Hz, SCH$_A$H$_B$C$\underline{H}$), 3.80 (3 H, s, ArCOC$\underline{H_3}$), 6.78 - 6.93 (3 H, m, ArC$\underline{H}$), 7.20 - 7.30 (1 H, m, ArC$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.6 (C$\underline{H_3}$CH$_2$CH$_2$S), 23.0 (CH$_3$C$\underline{H_2}$CH$_2$S), 34.8 (CH$_3$CH$_2$C$\underline{H_2}$S), 35.3 (S$\underline{C}$H$_A$H$_B$CH), 52.4 (C(O)O$\underline{C}$H$_3$), 52.5 (SCH$_A$H$_B$$\underline{C}$H), 55.4 (ArCO$\underline{C}H_3$), 113.2 (Ar$\underline{C}$H), 113.6 (Ar$\underline{C}$H), 120.2 (Ar$\underline{C}$H), 129.9 (Ar$\underline{C}$H), 139.5 (Ar$\underline{C}$), 159.9 (Ar$\underline{C}OCH_3$), 173.2 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_3S$) requires *m/z* 291.1025, found *m/z* 291.1018.

8.4.3.20 Synthesis and characterisation of 288aa

Methyl (2*R*)-2-(2-methoxyphenyl)-3-(propylsulfanyl)propanoate **288aa**

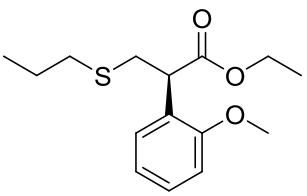


Ester **287r** (77 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288aa** as a colourless oil in 89% yield (47 mg) and 94% ee [determined by HPLC, Chiralcel IB, hexane/isopropanol = 99/1, 1 mL/min, λ = 220 nm, t (major) = 6.96 min, t (minor) = 7.65 min].

$[\alpha]_D^{23}$ = -67.2 (*c* 0.18, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2960, 1737 (C=O), 1494, 1247 (C-O), 1156 (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.97 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.60 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.50 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.80 (dd, *J* = 13.5, 6.0 Hz, 1 H, $SC\underline{H}_AH_BCH$), 3.14 (dd, *J* = 13.5, 9.0 Hz, 1 H, $SCH_A\underline{H}_BCH$), 3.70 (s, 3 H, $C(=O)OC\underline{H}_3$), 3.84 (s, 3 H, $ArOC\underline{H}_3$), 4.26 (dd, *J* = 9.0, 6.0 Hz, 1 H, $SCH_AH_BC\underline{H}$), 6.89 (d, *J* = 8.0 Hz, 1 H, Ar<u>H</u>), 6.94 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1 H, Ar<u>H</u>), 7.21 - 7.30 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.4 ($\underline{C}H_3CH_2CH_2S$), 22.8 ($CH_2\underline{C}H_2CH_3S$), 34.0 ($S\underline{C}H_2CH$), 34.4 ($CH_3CH_2\underline{C}H_2S$), 45.3 ($SCH_2\underline{C}H$), 52.0 ($C(=O)O\underline{C}H_3$), 55.5 ($ArO\underline{C}H_3$), 110.8 (Ar<u>C</u>H), 120.7 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>), 128.3 (Ar<u>C</u>H), 128.6 (Ar<u>C</u>H), 156.6 ($Ar\underline{C}OCH_3$), 173.6 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}NaO_3S$) requires *m/z* 291.1025, found *m/z* 291.1020.

8.4.3.21 Synthesis and characterisation of 288ab

Ethyl (2*R*)-2-(2-methoxyphenyl)-3-(propylsulfanyl)propanoate **288ab**

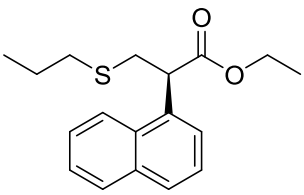


Ester **317c** (82 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288ab** as a colourless oil in 96% yield (54 mg) and 93% ee [determined by HPLC, Chiralcel IB, hexane/isopropanol = 98/2, 1 mL/min, λ = 230 nm, t (major) = 5.48 min, t (minor) = 5.88 min].

$[\alpha]_D^{23}$ = -45.6 (*c* 1.01, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2961, 2935, 1730, 1493, 1731, 1493, 1245, 1204, 1154, 1028, 754; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.89 (t, *J* = 7.5 Hz, 3 H, $SCH_2CH_2C\underline{H}_3$), 1.15 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.48 - 1.59 (m, 2 H, $SCH_2C\underline{H}_2CH_3$), 2.39 - 2.46 (m, 2 H, $SC\underline{H}_2CH_2CH_3$), 2.72 (dd, *J* = 13.5, 6.0 Hz, 1 H, $SC\underline{H}_AH_BCH$), 3.05 (dd, *J* = 13.5, 9.0 Hz, 1 H, $SCH_A\underline{H}_BCH$), 3.76 (s, 3 H, $ArOC\underline{H}_3$), 4.10 (q, *J* = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.15 (dd, *J* = 9.0, 6.0 Hz, 1 H, $SCH_AH_BC\underline{H}$), 6.80 (dd, *J* = 8.5, 1.0 Hz, 1 H, $Ar\underline{H}$), 6.85 (td, *J* = 7.5, 1.0 Hz, 1 H, $Ar\underline{H}$), 7.14 - 7.21 (m, 2 H, $Ar\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.5 ($SCH_2CH_2\underline{C}H_3$), 14.2 ($OCH_2\underline{C}H_3$), 22.9 ($SCH_2\underline{C}H_2CH_3$), 34.1 ($S\underline{C}H_AH_BCH$), 34.5 ($S\underline{C}H_2CH_2CH_3$), 45.6 ($SCH_2\underline{C}H$), 55.5 ($ArCO\underline{C}H_3$), 60.8 ($OC\underline{H}_2CH_3$), 110.7 ($Ar\underline{C}H$), 120.7 ($Ar\underline{C}H$), 126.8 ($Ar\underline{C}$), 128.3 ($Ar\underline{C}H$), 128.6 ($Ar\underline{C}H$), 156.7 ($Ar\underline{C}OCH_3$), 173.1 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{22}NaO_3S$) requires *m/z* 305.1182, found *m/z* 305.1182.

8.4.3.22 Synthesis and characterisation of 288ac

Ethyl (2*R*)-2-(naphthalen-1-yl)-3-(propylsulfanyl)propanoate **288ac**



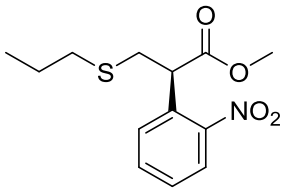
Ester **317d** (91 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288ac** and ester **317d** as a colourless oil as an inseparable mixture (100% conversion by ^{1}H NMR (105 mg)) and 74% ee [determined by HPLC, Chiralcel AD, hexane/isopropanol = 99/1, 1 mL/min, λ = 220 nm, t (minor) = 9.53 min, t (major) = 10.50 min].

IR (film) ν_{max}/cm^{-1}: 2961, 2931, 1731, 1195, 1150, 1032, 779; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm):[xlvii] 0.98 (t, *J* = 7.5 Hz, 3 H, $SCH_2CH_2C\underline{H}_3$), 1.20 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H}_3$), 1.62 ('sxt', *J* = 7.5 Hz, 2 H, $SCH_2C\underline{H}_2CH_3$), 2.48 - 2.63 (m, 2 H, $SC\underline{H}_2CH_2CH_3$), 2.97 (dd, *J* = 13.0, 5.0 Hz, 1 H, $SC\underline{H}_AH_BCH$), 3.39 (dd, *J* = 13.0, 10.0 Hz, 1 H, $SCH_A\underline{H}_BCH$), 4.15 (ddq, *J* = 7.5, 11.0, 7.0 Hz, 1 H, $OC\underline{H}_AH_BCH_3$), 4.23 (ddq, *J* = 7.5, 11.0, 7.0 Hz, 1 H, $OCH_A\underline{H}_BCH_3$), 4.64 (dd, *J* = 10.0, 5.0 Hz, 1 H, $SCH_AH_BC\underline{H}$), 7.41 - 7.63 (m, 4 H, Ar$\underline{H}$), 7.80 (d, *J* = 8.0 Hz, 1 H, Ar$\underline{H}$), 7.88 (d, *J* = 7.5 Hz, 1 H, Ar$\underline{H}$), 8.16 (d, *J* = 8.5 Hz, 1 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.5 ($SCH_2CH_2\underline{C}H_3$), 14.2 ($OCH_2\underline{C}H_3$), 23.1 ($SCH_2\underline{C}H_2CH_3$), 35.0 ($S\underline{C}H_2CH_2CH_3$), 35.1 ($S\underline{C}H_AH_BCH$), 48.0 ($SCH_AH_B\underline{C}H$), 61.3 ($O\underline{C}H_2CH_3$), 123.0 (Ar$\underline{C}$H), 124.9 (Ar$\underline{C}$H), 125.6 (Ar$\underline{C}$H), 125.9 (Ar$\underline{C}$H), 126.6 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 129.1 (Ar$\underline{C}$H), 131.4 (Ar$\underline{C}$), 134.1 (Ar$\underline{C}$), 134.5 (Ar$\underline{C}$), 173.1 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}NaO_2S$) requires *m/z* 325.1233, found *m/z* 325.1237.

[xlvii] NMR data is given for rac-**288ac**.

8.4.3.23 Synthesis and characterisation of 288ad

Methyl (2*R*)-2-(2-nitrophenyl)-3-(propylsulfanyl)propanoate **288ad**

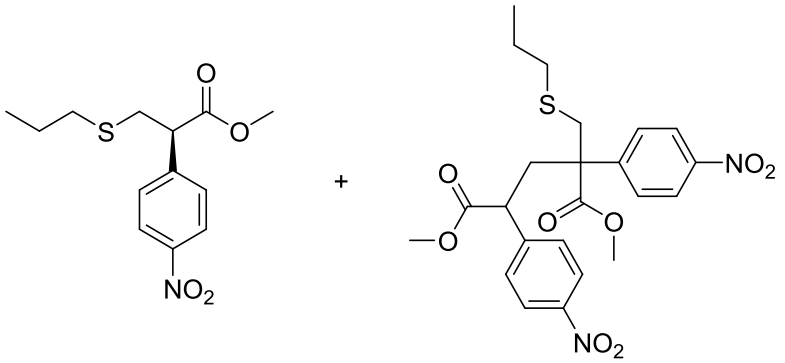


Methyl 2-(2-nitrophenyl)prop-2-enoate **287s** (63 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 19/1) to afford the title compound **288ad** as a colourless oil in 98% yield (56 mg) and 84% ee [determined by HPLC, Chiralcel IA, hexane/isopropanol = 98/2, 1 mL/min, λ = 220 nm, t (minor) = 10.20 min, t (major) = 10.96 min].

$[\alpha]_D^{25}$ = -137.3 (*c* 0.64, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 3016, 2970, 1739 (C=O), 1527 (NO_2), 1435 (C-O), 1368, 1216; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.18 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.54 - 1.63 (m, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.47 - 2.53 (m, 2 H, $CH_3CH_2C\underline{H}_2S$), 2.95 (dd, *J* = 13.5, 6.5 Hz, 1 H, $SC\underline{H}_ACH_BCH$), 3.24 (dd, *J* = 13.5, 8.0 Hz, 1 H, $SCH_A\underline{H}_BCH$), 3.69 (s, 3 H, $OC\underline{H}_3$), 4.46 (dd, *J* = 8.0, 6.5 Hz, 1 H, $SCH_AH_BC\underline{H}$), 7.38 - 7.49 (m, 1 H, Ar$\underline{H}$), 7.54 - 7.61 (m, 2 H, Ar$\underline{H}$), 7.91 (dd, *J* = 8.0, 1.0 Hz, 1 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.5 ($\underline{C}H_3CH_2CH_2S$), 23.0 ($CH_3\underline{C}H_2CH_2S$), 34.6 ($CH_3CH_2\underline{C}H_2S$), 34.8 ($S\underline{C}H_2CH$), 47.4 ($SCH_2\underline{C}H$), 52.6 ($O\underline{C}H_3$), 125.0 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 130.2 (Ar$\underline{C}$H), 132.3 (Ar$\underline{C}$H), 133.4 (Ar$\underline{C}$), 149.3 (Ar$\underline{C}$), 172.1 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{17}NNaO_4S$) requires *m/z* 306.0771, found *m/z* 306.0763.

8.4.3.24 Synthesis and characterisation of 288ae and 320

Methyl (2*R*)-2-(4-nitrophenyl)-3-(propylsulfanyl)propanoate **288ae** and dimethyl 2,4-bis(4-nitrophenyl)-2-[(propylsulfanyl)methyl]pentanedioate **320**



Ester **287t** (84 mg, 0.40 mmol, 2.0 eq) was reacted with 1-propanethiol (18 μL, 0.20 mmol, 1.0 eq) according to General Procedure **X**. The reaction mixture was purified by FCC (petroleum ether/Et_2O = 99/1 to 4/1) to elute first **288ae** as a pale yellow oil in 36% yield (16 mg) and 2% ee [determined by HPLC, Chiralcel IB, hexane/isopropanol = 98/2, 1 mL/min, λ = 220 nm, t (minor) = 10.53 min, t (major) = 11.39 min] and then **320** as a pale yellow amorphous solid 64% (62 mg) as 1.1:1 mixture of diastereomers.

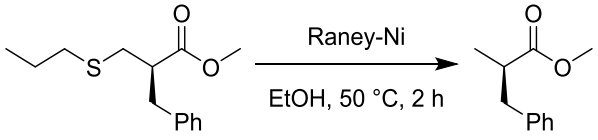
Characterisation data for **288ae**: **IR** (film) ν_{max}/cm^{-1}: 2960, 1735, 1520, 1346, 1157, 855, 733; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.95 (t, *J* = 7.5 Hz, 3 H, $SCH_2CH_2C\underline{H}_3$), 1.58 ('sxt', *J* = 7.5 Hz, 2 H, $SCH_2C\underline{H}_2CH_3$), 2.48 (td, *J* = 7.5, 2.0 Hz, 2 H, $SC\underline{H}_2CH_2CH_3$), 2.88 (dd, *J* = 13.3, 8.0 Hz, 1 H, $SC\underline{H}_AH_BCH$), 3.21 (dd, *J* = 13.5, 8.0 Hz, 1 H, $SCH_A\underline{H}_BCH$), 3.71 (s, 3 H, $OC\underline{H}_3$), 3.90 ('t', *J* = 8.0 Hz, 1 H, $SCH_AH_BC\underline{H}$), 7.47 - 7.52 (m, 2 H, Ar$\underline{H}$), 8.16 - 8.23 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.5 ($SCH_2CH_2\underline{C}H_3$), 22.9 ($SCH_2\underline{C}H_2CH_3$), 34.9 ($S\underline{C}H_2CH_2CH_3$), 35.1 ($S\underline{C}H_AH_BCH$), 52.0 ($SCH_AH_B\underline{C}H$), 52.7 ($O\underline{C}H_3$), 124.1 (Ar$\underline{C}$H), 129.1 (Ar$\underline{C}$H), 145.0 (Ar$\underline{C}$), 147.6 (Ar$\underline{C}$), 172.2 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{17}NNaO_4S$) requires *m/z* 306.0770, found *m/z* 306.0771.

Characterisation data for **320**: **IR** (film) ν_{max}/cm^{-1}: 2956, 1733, 1605, 1519, 1346, 856; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 8.20 – 8.13 (m, ArCH), 7.46 – 7.41 (m, ArCH), 3.79 – 3.71 (m, 1H, ArC<u>H</u>CH_AH_B), 3.69 (s, 3H, OC<u>H</u>$_3$), 3.65 – 3.61 (m, 1H, ArC<u>H</u>CH_AH_B), 3.57 (s, 3H, OC<u>H</u>$_3$), 3.46 (s, 3H, OC<u>H</u>$_3$), 3.45 (s, 3H, OC<u>H</u>$_3$), 3.24 – 3.16 (m,), 3.01 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.67 (dd, *J* = 14.5, 4.0 Hz, 1H), 2.62 (dd, *J* = 14.5, 4.0 Hz, 1H), 2.30 – 2.24 (m, 2H, SC<u>H$_2$</u>CH_2CH_3), 1.48 ('sxt', *J* = 7.5 Hz, SCH_2C<u>H$_2$</u>CH_3), 0.88 (t, *J* = 7.5 Hz, SCH_2CH_2C<u>H$_3$</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 173.5 (<u>C</u>=O), 173.3 (<u>C</u>=O), 172.7 (<u>C</u>=O), 172.5 (<u>C</u>=O), 147.6 (Ar<u>C</u>), 147.5 (Ar<u>C</u>), 147.4 (Ar<u>C</u>), 147.4 (Ar<u>C</u>), 147.2 (Ar<u>C</u>), 147.2 (Ar<u>C</u>), 146.5 (Ar<u>C</u>), 146.2 (Ar<u>C</u>), 129.1 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 124.1 (Ar<u>C</u>H), 124.1 (Ar<u>C</u>H), 123.6 (Ar<u>C</u>H), 123.6 (Ar<u>C</u>H), 55.5 (<u>C$_q$</u>), 55.2 (<u>C$_q$</u>), 52.9 (O<u>C</u>H_3), 52.8 (O<u>C</u>H_3), 52.7 (O<u>C</u>H_3), 52.6 (O<u>C</u>H_3), 47.7 (Ar<u>C</u>HCH_AH_B), 47.4 (Ar<u>C</u>HCH_AH_B), 39.7, 39.1, 38.8, 38.3 (ArCH<u>C</u>H_AH_B and S<u>C</u>H_2C_q), 36.0, 36.0 (S<u>C</u>$H_2CH_2CH_3$), 22.9, 22.9 (SCH_2<u>C</u>H_2CH_3), 13.4 (SCH_2CH_2<u>C</u>H_3); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{23}H_{26}N_2NaO_8S$) requires *m/z* 513.1302, found *m/z* 513.1301.

8.4.4 Determination of Absolute Configuration

8.4.4.1 Synthesis and characterisation of 321

<u>Methyl (2*R*)-2-methyl-3-phenylpropanoate **321**</u>



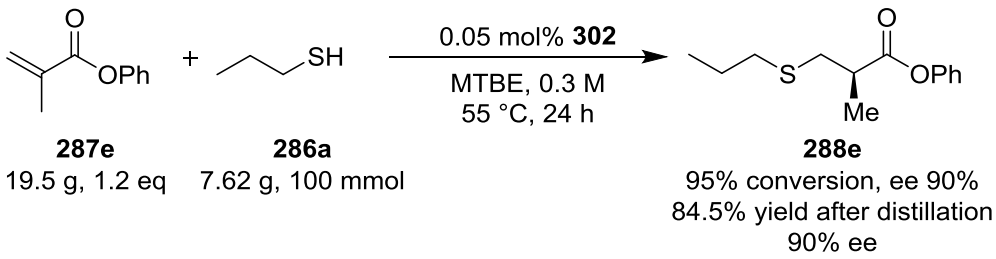
Raney®-Nickel (approximately 300 mg wet) was weighed into a round bottom flask under an argon atmosphere and the water was decanted with washings (3 x 2 mL EtOH). The activated catalyst was suspended in 2 mL EtOH and a solution of **288w** (20 mg,

0.079 mmol, 86% ee) in 0.5 mL EtOH was added and the reaction mixture placed under a hydrogen atmosphere. The reaction mixture was warmed to 50 ℃ and stirring was maintained for 2 h whereupon the reaction mixture was cooled to rt, filtered through a pad of silica washing with CH_2Cl_2 and MeOH, and the volatiles were removed *in vacuo*. The crude product was purified by FCC (petroleum ether to petroleum ether/Et_2O 19/1) to afford the title compound **321** as a colourless oil in 86% yield (12 mg) and 83% 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 ℃ ramp 1 ℃/min to 90 ℃ then 90 ℃ t (major) = 72.96 min, t (minor) = 73.82 min].

$[\alpha]_D^{21}$ = -27.2 (*c* 0.6, $CHCl_3$), [lit.[229] $[\alpha]_D$ = -35.3, (*c* 0.5, $CHCl_3$)], [lit.[230] $[\alpha]_D^{25}$ = -33.7, (*c* 1, $CHCl_3$)]. From the optical rotation, the absolute configuration was determined to be (*R*).[229,230]

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.17 (d, *J* = 7.0 Hz, 3 H, $CHC\underline{H}_3$), 2.61 - 2.83 (m, 2 H, $PhC\underline{H}_AH_BCH(CH_3)$ and $C\underline{H}(CH_3)C{=}O$), 3.04 (dd, *J* = 13.0, 6.5 Hz, 1 H, $PhCH_A\underline{H}_BCH(CH_3)$), 3.65 (s, 3 H, $OC\underline{H}_3$), 7.11 - 7.34 (m, 5 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 16.7 ($CH\underline{C}H_3$), 39.7 ($Ph\underline{C}H_AH_BCH(CH_3)$), 41.4 ($\underline{C}H(CH_3)C{=}O$), 51.6 ($O\underline{C}H_3$), 126.3 (Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 128.9 (Ar$\underline{C}$H), 139.4 (Ar$\underline{C}$), 176.5 ($\underline{C}{=}O$). Data is consistent with that given in the literature.[229]

8.4.5 Preparative Scale Synthesis of 288e



287e
19.5 g, 1.2 eq

286a
7.62 g, 100 mmol

288e
95% conversion, ee 90%
84.5% yield after distillation
90% ee

Under an argon atmosphere, azide **306** (24 mg, 0.05 mmol, 0.0005 eq) and tris(4-methoxyphenyl)phosphine (18 mg, 0.05 mmol, 0.0005 eq) were stirred in diethyl ether (0.5 mL) at room temperature for 24 h.

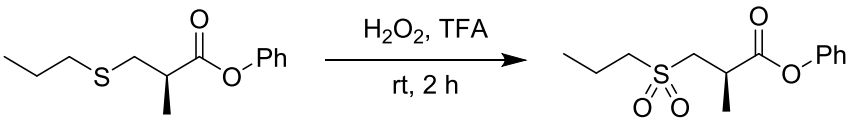
To a two-necked 500 mL R.B. was charged phenyl methacrylate **287e** (19.5 g, 120 mmol, 1.2 eq), freshly distilled MTBE (330 mL) and distilled 1-propanethiol (9.05 mL, 100 mmol, 1.00 eq) under an argon atmosphere at room temperature. The *in situ* generated catalyst was then transferred with washings (3 mL MTBE) to the flask and the reaction mixture was stirred at reflux for 24 h (an aliquot taken after 22 h showed 95% conversion by ^{1}H NMR and an ee of 90%) whereupon it was quenched by the addition of 1 M AcOH in CH_2Cl_2 (2 mL). The solvent was removed *in vacuo* and the crude product was purified by distillation [120℃, 0.7 mmHg] to afford the pure title compound **288e** as a colourless oil in 84.5% yield (20.1 g)[xlviii] and 90% ee [determined by HPLC, Chiralpak AD, hexane/isopropanol = 99/1, 1 mL/min, λ = 220 nm, t (major) = 8.68 min, t (minor) = 9.25 min]. $[\alpha]_D^{23}$ = +47.3 (*c* 0.99, $CHCl_3$); all other spectroscopic data was in accordance to that reported in Section 8.4.3.4..

[xlviii] The isolated yield of title compound **288e** is lower than the conversion due to the occurrence of mixed distillates resulting from a suspected azeotrope with phenyl methacrylate.

8.4.6 Derivatisation of 288e

8.4.6.1 Synthesis and characterisation of 322

Phenyl (2*R*)-2-methyl-3-(propane-1-sulfonyl)propanoate **322**



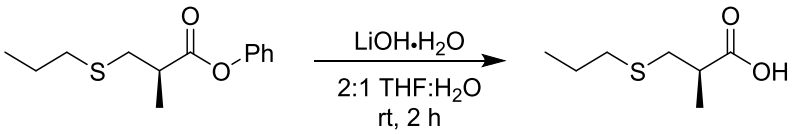
According to a modified literature procedure,[209] to a solution of **288e** (119 mg, 0.500 mmol, 90% ee) in trifluoroacetic acid (5 mL) was added 30% H_2O_2 (5 mL). The reaction mixture was stirred at room temperature for 4 hours whereupon it was diluted with water (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organics were washed (brine), dried ($MgSO_4$) and the volatiles were removed *in vacuo*. The crude product was purified by FCC (petroleum ether to petroleum ether/Et_2O 4/1) to afford the title compound **322** as a pale yellow oil in >99% yield (135 mg) and 89% ee [determined by HPLC, Chiralpak IB, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 21.91 min, t (minor) = 25.29 min].

$[\alpha]_D^{22}$ = +27.7 (*c* 0.93, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2979, 2940, 2356, 1757 (C=O), 1382, 1253 (S=O), 1131 (S=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.09 (t, *J* = 7.5 Hz, 3 H, C$\underline{H_3}$CH$_2$CH$_2$S), 1.55 (d, *J* = 7.0 Hz, 3 H, CH(C$\underline{H_3}$)C=O), 1.87 - 1.97 (m, 2 H, CH$_3$C$\underline{H_2}$CH$_2$S), 2.99 - 3.04 (m, 2 H, CH$_3$CH$_2$C$\underline{H_2}$S), 3.05 (dd, *J* = 14.0, 5.0 Hz, 1 H, SC$\underline{H_A}$H$_B$CH(CH$_3$)), 3.37 - 3.47 (m, 1 H, C$\underline{H}$(CH$_3$)C=O), 3.66 (dd, *J* = 14.0, 8.0 Hz, 1 H, SCH$_A$$\underline{H_B}$CH(CH$_3$)), 7.09 - 7.14 (m, 2 H, Ar$\underline{H}$), 7.22 - 7.27 (m, 1 H, Ar$\underline{H}$), 7.36 - 7.43 (m, 2 H, Ar$\underline{H}$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.0 ($\underline{C}$H$_3$CH$_2$CH$_2$S), 15.7 (CH$_3$$\underline{C}H_2CH_2$S), 17.8 (CH($\underline{C}H_3$)C=O), 34.2 ($\underline{C}$H(CH$_3$)C=O), 55.1 (S$\underline{C}H_2$CH(CH$_3$)), 55.8 (CH$_3CH_2$$\underline{C}H_2$S), 121.3 (Ar$\underline{C}$H), 126.1 (Ar$\underline{C}$H), 129.4 (Ar$\underline{C}$H), 150.4 (Ar$\underline{C}$), 172.7 ($\underline{C}$=O);

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{18}NaO_4S$) requires *m/z* 293.0818, found *m/z* 293.0810.

8.4.6.2 Synthesis and characterisation of 323

(2*R*)-2-Methyl-3-(propylsulfanyl)propanoic acid **323**



To a solution of **288e** (238 mg, 1.00 mmol, 1.00 eq, 90% ee) in THF (6.0 mL) at rt was added LiOH•H_2O (210 mg, 5.00 mmol, 5.00 eq) in H_2O (3.0 mL). Stirring was maintained for 2 h whereupon the reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (2 x 10 mL). The aqueous layer was acidified to pH 2 using 1 M HCl (aq) and extracted with CH_2Cl_2 (4 x 10 mL). The organics were washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo.* The crude product was purified by FCC (petroleum ether/Et_2O 9/1 to Et_2O) to yield the title compound **323** as a pale yellow oil in 82% yield (133 mgs) and 86% ee.

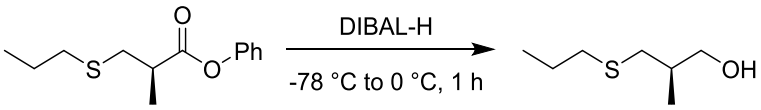
[The ee was determined by treating **323** in CH_2Cl_2/MeOH (4/1) with 1.0 eq of (trimethylsilyl)diazomethane (2.0 M in hexanes) to afford **288a** in 86% ee]

$[\alpha]_D^{22}$ = +24.3 (*c* 1.22, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2964, 2934 (O-H), 1706 (C=O), 1462, 1234, 932; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.98 (t, *J* = 7.5 Hz, 3 H, $C\underline{H_3}CH_2CH_2S$), 1.29 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H_3})$), 1.61 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H_2}CH_2S$), 2.51 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2C\underline{H_2}S$), 2.58 (dd, *J* = 13.0, 7.0 Hz, 1 H, $SC\underline{H_A}H_BCH(CH_3)$), 2.70 ('sxt', *J* = 7.0 Hz, 1 H, $SCH_AH_BC\underline{H}(CH_3)$), 2.85 (dd, *J* = 13.0, 7.0 Hz, 1 H, $SCH_A\underline{H_B}CH(CH_3)$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.6 ($\underline{C}H_3CH_2CH_2S$), 16.8 ($SCH_AH_BCH(\underline{C}H_3)$), 23.0 ($CH_3\underline{C}H_2CH_2S$), 34.9 ($CH_3CH_2\underline{C}H_2S$), 35.2 ($S\underline{C}H_AH_BCH(CH_3)$),

40.3 ($SCH_AH_B\underline{C}H(CH_3)$), 181.6 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_7H_{14}NaO_2S$) requires *m/z* 185.0607, found *m/z* 185.0608.

8.4.6.3 Synthesis and characterisation of 324

(2*R*)-2-methyl-3-(propylsulfanyl)propan-1-ol **324**

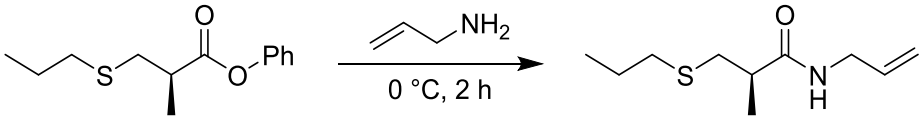


To a solution of **288e** (119 mg, 0.500 mmol, 1.00 eq, 90% ee) in THF (2.5 mL) at -78℃ was added DIBAL-H (1.10 mL, 1.10 mmol, 2.20 eq) dropwise. Upon complete addition the reaction mixture was allowed to warm to 0℃ whereupon stirring was maintained for 20 min. The reaction mixture was quenched by the addition of saturated aq NH_4Cl (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine, dried ($MgSO_4$), the volatiles *in vacuo* and purification by FCC (petroleum ether/Et_2O 9/1 to Et_2O) to afford the title compound **324** as a pale yellow oil in 64% yield (47 mg) and 90% ee. [determined by HPLC, Chiralpak IA, hexane/isopropanol = 95/5, 1 mL/min, λ = 210 nm, t (major) = 8.12 min, t (minor) = 9.15 min].

$[\alpha]_D^{22}$ = -3.1 (*c* 0.66, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 3354 (O-H), 2960 (C-H), 2930, 2872, 1457 (C-O), 1033 (C-O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 3.52 (d, *J* = 6.0 Hz, 2 H, $C\underline{H_2}OH$), 2.53 (dd, *J* = 12.5, 7.0 Hz, 1 H, $SC\underline{H_A}H_BCH(CH_3)$), 2.47 - 2.37 (m, 3 H, $SCH_A\underline{H_B}CH(CH_3)$ and $CH_3CH_2C\underline{H_2}S$), 1.98 (br s, 1 H, $O\underline{H}$), 1.91 - 1.77 (m, 1 H, $SCH_AH_BC\underline{H}(CH_3)$), 1.55 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H_2}CH_2S$), 0.97 - 0.87 (m, 6 H, $C\underline{H_3}CH_2CH_2S$ and $CH(C\underline{H_3})$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 67.4 ($\underline{C}H_2OH$), 36.3 ($S\underline{C}H_AH_BCH(CH_3)$), 35.6 ($SCH_AH_B\underline{C}H(CH_3)$), 34.8 ($CH_3CH_2\underline{C}H_2S$), 22.9 ($CH_3\underline{C}H_2CH_2S$), 16.6 ($SCH_AH_BCH(\underline{C}H_3)$), 13.4 ($\underline{C}H_3CH_2CH_2S$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_7H_{17}OS$) requires *m/z* 149.0995, found *m/z* 149.0996.

8.4.6.4 Synthesis and characterisation of 325

(2*R*)-2-Methyl-*N*-(prop-2-en-1-yl)-3-(propylsulfanyl)propanamide **325**

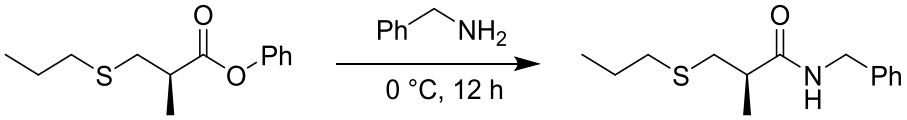


To a vial containing **288e** (119 mg, 0.500 mmol, 1.00 eq, 90% ee) at 0℃ was added allylamine (113 µL, 1.50 mmol, 3.00 eq) and the reaction mixture was stirred for 2 hours whereupon it was purified by FCC (petroleum ether to petroleum ether/Et_2O 1/1) to yield the title compound **325** as a colourless oil in 99% yield (107 mg) and 91% ee [determined by HPLC, Chiralpak AD, hexane/isopropanol = 97/3, 1 mL/min, λ = 220 nm, t (major) = 18.67 min, t (minor) = 20.16 min].

$[\alpha]_D^{22}$ = +9.9 (*c* 0.82, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 3289 (N-H), 2964, 1642 (C=O), 1548, 1248 (C-N); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.93 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.19 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)$), 1.56 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.35 - 2.49 (m, 3 H, $SCH_AH_BC\underline{H}(CH_3)$ and $CH_3CH_2C\underline{H}_2S$), 2.53 (dd, *J* = 13.0, 6.0 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 2.78 (dd, *J* = 13.0, 8.0 Hz, 1 H, $SC\underline{H}_AH_BCH(CH_3)$), 3.85 (ddd, *J* = 7.0, 4.0, 2.0 Hz, 2 H, $CHC\underline{H}_2NH$), 5.09 (dd, *J* = 10.0, 1.5 Hz, 1 H, $CH_A\underline{H}_BCHCH_2NH$), 5.18 (dd, *J* = 17.0, 1.5 Hz, 1 H, $C\underline{H}_AH_BCHCH_2NH$), 5.73 - 5.89 (m, 1 H, $CH_AH_BC\underline{H}CH_2NH$), 6.11 (br. s, 1 H, $N\underline{H}CH_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.3 ($\underline{C}H_3CH_2CH_2S$), 17.6 ($SCH_AH_BCH(\underline{C}H_3)$), 22.8 ($CH_3\underline{C}H_2CH_2S$), 34.8 ($CH_3CH_2\underline{C}H_2S$), 35.9 ($S\underline{C}H_AH_BCH(CH_3)$), 41.7 ($CH\underline{C}H_2NH$), 41.8 ($SCH_AH_B\underline{C}H(CH_3)$), 116.1 ($\underline{C}H_AH_BCHCH_2NH$), 134.1 ($CH_AH_B\underline{C}HCH_2NH$), 174.7 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{20}NOS$) requires *m/z* 202.1260, found *m/z* 202.1260.

8.4.6.5 Synthesis and characterisation of 326

(2*R*)-*N*-Benzyl-2-methyl-3-(propylsulfanyl)propanamide **326**

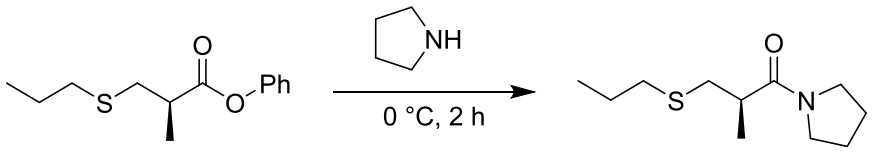


To a vial containing **288e** (119 mg, 0.500 mmol, 1.00 eq, 90% ee) at 0℃ was added benzylamine (164 µL, 1.50 mmol, 3.00 eq) and the reaction mixture was stirred for 12 hours whereupon it was purified by FCC (petroleum ether to petroleum ether/Et_2O 1/1) to yield the title compound **326** as a colourless oil in 99% yield (125 mg) and 89% ee [determined by HPLC, Chiralpak AD, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 9.24 min, t (minor) = 10.60 min].

$[\alpha]_D^{22}$ = +5.3 (*c* 1.28, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 3284 (N-H), 2963, 2930, 1645 (C=O), 1548, 1239 (C-N); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.96 (t, *J* = 7.5 Hz, 3 H, $C\underline{H}_3CH_2CH_2S$), 1.23 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)$), 1.58 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H}_2CH_2S$), 2.38 - 2.51 (m, 3 H, $SCH_AH_BC\underline{H}(CH_3)$ and $CH_3CH_2C\underline{H}_2S$), 2.56 (dd, *J* = 13.0, 6.0 Hz, 1 H, $SC\underline{H}_AH_BCH(CH_3)$), 2.82 (dd, *J* = 13.0, 8.0 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 4.37 - 4.50 (m, 2 H, $NHC\underline{H}_2$), 6.32 (br. s., 1 H, $N\underline{H}CH_2$), 7.22 - 7.37 (m, 5 H, Ar<u>H</u>); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.3 ($\underline{C}H_3CH_2CH_2S$), 17.6 ($SCH_AH_BCH(\underline{C}H_3)$), 22.8 ($CH_3\underline{C}H_2CH_2S$), 34.8 ($CH_3CH_2\underline{C}H_2S$), 35.9 ($S\underline{C}H_AH_BCH(CH_3)$), 41.9 ($SCH_AH_B\underline{C}H(CH_3)$), 43.4 ($NH\underline{C}H_2$), 127.3 (Ar<u>C</u>H), 127.6 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 138.2 (Ar<u>C</u>), 174.7 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{22}NOS$) requires *m/z* 252.1417, found *m/z* 252.1418.

8.4.6.6 Synthesis and characterisation of 327

(2*R*)-2-methyl-3-(propylsulfanyl)-1-(pyrrolidin-1-yl)propan-1-one **327**

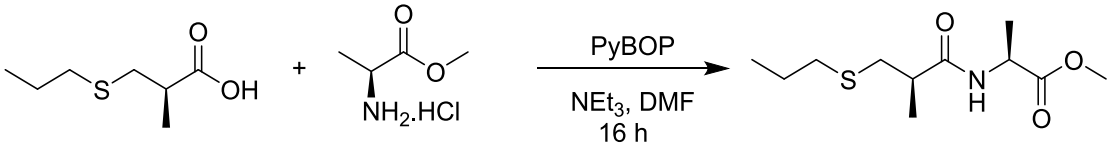


To a vial containing **288e** (238 mg, 1.00 mmol, 1.00 eq, 90% ee) at 0 ℃ was added pyrrolidine (250 µL, 3.0 mmol, 3.0 eq) and the reaction mixture was stirred for 2 hours whereupon it was purified by FCC (petroleum ether to petroleum ether/Et_2O 1/1) to yield the title compound **327** as a colourless oil in 85% yield (183 mg) and 84% ee [determined by HPLC, Chiralpak AS-H, hexane/isopropanol = 90/10, 1 mL/min, λ = 220 nm, t (major) = 7.76 min, t (minor) = 9.26 min].

$[\alpha]_D^{21}$ = +10.9 (*c* 1.03, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2964, 2872, 2361, 1638, 1432; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.95 (t, *J* = 7.5 Hz, 3 H, $SCH_2CH_2C\underline{H}_3$), 1.17 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)C{=}O$), 1.58 (sxt, *J* = 7.5 Hz, 2 H, $SCH_2C\underline{H}_2CH_3$), 1.84 (quin, *J* = 6.5 Hz, 2 H, $C(=O)NCH_2CH_2C\underline{H}_2CH_2$), 1.89 - 2.03 (m, 2 H, $C(=O)NCH_2C\underline{H}_2CH_2CH_2$), 2.40 - 2.49 (m, 2 H, $SC\underline{H}_2CH_2CH_3$), 2.52 (dd, *J* = 12.5, 6.5 Hz, 1 H, $SC\underline{H}_AH_BCH(CH_3)C{=}O$), 2.73 (sxt, *J* = 7.0 Hz, 1 H, $SCH_AH_BC\underline{H}(CH_3)C{=}O$), 2.86 (dd, *J* = 12.5, 8.0 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)C{=}O$), 3.38 - 3.51 (m, 3 H, $C(=O)NC\underline{H}_AH_BCH_2CH_2C\underline{H}_2$), 3.51 - 3.62 (m, 1 H, $C(=O)NCH_A\underline{H}_BCH_2CH_2CH_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.5 ($SCH_2CH_2\underline{C}H_3$), 17.5 ($SCH_AH_BCH(\underline{C}H_3)C{=}O$), 23.1 ($SCH_2\underline{C}H_2CH_3$), 24.4 ($C(=O)NCH_AH_BCH_2\underline{C}H_2CH_2$), 26.2 ($C(=O)NCH_AH_B\underline{C}H_2CH_2CH_2$), 35.2 ($S\underline{C}H_2CH_2CH_3$), 36.2 ($S\underline{C}H_AH_BCH(CH_3)C{=}O$), 39.1 ($SCH_AH_BC\underline{H}(CH_3)C{=}O$), 45.9 ($C(=O)NCH_AH_BCH_2CH_2\underline{C}H_2$), 46.7 $C(=O)N\underline{C}H_AH_BCH_2CH_2CH_2$), 173.8 ($\underline{C}{=}O$); **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}NOS$) requires *m/z* 216.1417, found *m/z* 216.1421.

8.4.6.7 Synthesis and characterisation of 328

Methyl (2*S*)-2-[(2*R*)-2-[(propylsulfanyl)methyl]propanamido]propanoate **328**



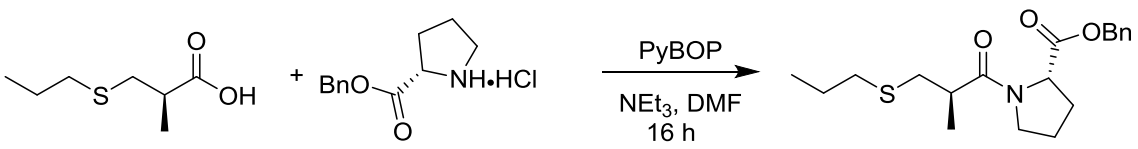
To a solution of acid **323** (32.5 mg, 0.200 mmol, 1.00 eq, 86% ee) and PyBOP (104 mg, 0.200 mmol, 1.00 eq) in DMF (1.5 mL) was added L-alanine methyl ester hydrochloride (28.0 mg, 0.200 mmol, 1.00 eq). Stirring was maintained for 5 minutes and then triethylamine (84 µL, 0.60 mmol, 3.0 eq) was added dropwise and the reaction mixture stirred for 16 h. The reaction was quenched by the addition of brine (4 mL) and extracted with EtOAc (2 x 10 mL). The combined organics were washed with 10% aq Na_2CO_3 (2 x 5 mL), washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. The crude product was purified by FCC (petroleum ether/EtOAc 9/1 to petroleum ether/EtOAc 1/1) to yield the title compound **328** as a pale yellow oil in 76% yield (37 mg) and 12.4:1 dr .

$[\alpha]_D^{21}$ = +10.7 (*c* 1.03, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 3300 (NH), 2964 (C-H), 1746 (C(=O)O), 1650 (C(=O)N), 1539 (NH), 1455, 1211; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.96 (t, *J* = 7.5 Hz, 3 H, $C\underline{H_3}CH_2CH_2S$), 1.23 (d, *J* = 7.0 Hz, 3 H, $SCH_AH_BCH(C\underline{H_3})$), 1.40 (d, *J* = 7.0 Hz, 3 H, $NHCH(C\underline{H_3})$), 1.59 ('sxt', *J* = 7.5 Hz, 2 H, $CH_3C\underline{H_2}CH_2S$), 2.41 - 2.46 (m, 1 H, $SCH_AH_BC\underline{H}(CH_3)$), 2.49 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2C\underline{H_2}S$), 2.55 (dd, *J* = 13.0, 6.5 Hz, 1 H, $SC\underline{H_A}H_BCH(CH_3)$), 2.74 (dd, *J* = 13.5, 6.5 Hz, 1 H, $SC\underline{H_A}H_BCH(CH_3)$, minor), 2.81 (dd, *J* = 13.0, 7.5 Hz, 1 H, $SC\underline{H_A}H_BCH(CH_3)$, major), 3.75 (s, 3 H, $OC\underline{H_3}$), 4.59 ('quin', *J* = 7.0 Hz, 1 H, $NHC\underline{H}(CH_3)$), 6.24 (d, *J* = 7.0 Hz, 1 H, N<u>H</u>, minor), 6.30 (d, *J* = 7.0 Hz, 1 H, N<u>H</u>, major);**^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 13.4 ($\underline{C}H_3CH_2CH_2S$), 17.4 ($SCH_AH_BCH(\underline{C}H_3)$), 18.4 ($NHCH(\underline{C}H_3)$), 22.9 ($CH_3\underline{C}H_2CH_2S$), 34.9 ($CH_3CH_2\underline{C}H_2S$), 35.8 ($S\underline{C}H_AH_BCH(CH_3)$), 41.6 ($SCH_AH_B\underline{C}H(CH_3)$), 47.9 ($NH\underline{C}H(CH_3)$), 52.4 ($O\underline{C}H_3$),

173.5 (C=O), 174.3 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{21}NNaO_3S$) requires *m/z* 270.1134, found *m/z* 270.1134.

8.4.6.8 Synthesis and characterisation of 329

Benzyl (2*S*)-1-[(2*R*)-2-methyl-3-(propylsulfanyl)propanoyl]pyrrolidine-2-carboxylate **329**



To a solution of acid **323** (32.5 mg, 0.200 mmol, 1.00 eq, 86% ee) and PyBOP (104 mg, 0.200 mmol, 1.00 eq) in DMF (1.5 mL) was added L-proline benzyl ester hydrochloride (48.3 mg, 0.200 mmol, 1.00 eq). Stirring was maintained for 5 minutes and then triethylamine (84 µL, 0.60 mmol, 3.0 eq) was added dropwise and the reaction mixture stirred for 16 h. The reaction was quenched by the addition of brine (4 mL) and extracted with EtOAc (2 x 10 mL). The combined organics were washed with 10% aq Na_2CO_3 (2 x 5 mL), washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. The crude product was purified by FCC (petroleum ether/EtOAc 9/1 to petroleum ether/EtOAc 1/1) to yield the title compound **329** as a pale yellow oil in 90% yield (63 mg) and 13.5:1 dr.

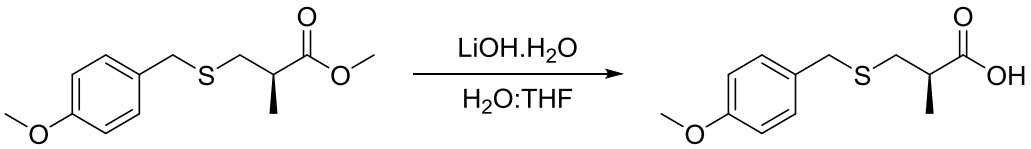
$[\alpha]_D^{21}$ = -42.3 (*c* 1.07, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2962, 2873, 1744, 1646, 1498, 1456, 1168; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm, major diastereomer exists as a 2:1 mixture of rotamers): 0.96 (t, *J* = 7.5 Hz, 3 H, $SCH_2CH_2C\underline{H}_3$), 1.21 (d, *J* = 7.0 Hz, 3 H, $SCH_AH_BCH(C\underline{H}_3)$), 1.50 - 1.63 (m, 2 H, $SCH_2C\underline{H}_2CH_3$), 1.84 - 2.32 (m, 4 H, $NCHC\underline{H}_2C\underline{H}_2$), 2.37 - 2.55 (m, 3 H, $SC\underline{H}_2CH_2CH_3$ and $SC\underline{H}_AH_BCH(CH_3)$), 2.70 - 2.80 (m, 1 H, $SCH_AH_BC\underline{H}(CH_3)$), 2.86 (dd, *J* = 13.0, 5.5 Hz, 1 H, $SCH_A\underline{H}_BCH(CH_3)$), 3.51 - 3.67 (m, 1 H, $NC\underline{H}_AH_BCH_2$), 3.71 - 3.76 (m, 1 H, $NCH_A\underline{H}_BCH_2$), 4.53 (dd, *J* = 9.0, 4.0 Hz, $NC\underline{H}CH_2CH_2$, major rotamer), 4.72 (dd, *J* = 8.5, 2.5 Hz, $NC\underline{H}CH_2CH_2$, minor rotamer), 4.58 (dd, *J* = 9.0, 4.0 Hz, $NC\underline{H}CH_2CH_2$, minor diastereomer), 5.12 (d, *J* = 12.0 Hz,

OCH_AH_BAr), 5.19 (d, *J* = 12.0 Hz, OCH_AH_BAr), 7.28 - 7.39 (m, 5 H, ArH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm, data given for major rotamer): 13.6 ($SCH_2CH_2CH_3$), 16.8 ($SCH_AH_BCH(CH_3)$), 23.1 ($SCH_2CH_2CH_3$), 24.9 ($NCHCH_2CH_2$), 29.2 ($NCHCH_2CH_2$), 35.1 ($SCH_2CH_2CH_3$), 35.8 ($SCH_AH_BCH(CH_3)$), 39.0 ($SCH_AH_BCH(CH_3)$), 47.1 (NCH_2CH_2), 59.0 ($NCHCH_2$), 66.8 (OCH_AH_BAr), 128.2 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 135.9 (ArC), 172.1 (C=O), 174.2 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{27}NNaO_3S$) requires *m/z* 372.1604, found *m/z* 372.1601.

8.4.7 Towards the Synthesis of Captopril

8.4.7.1 Synthesis and characterisation of 330

(2*R*)-3-[(4-methoxybenzyl)sulfanyl]-2-methylpropanoic acid **330**



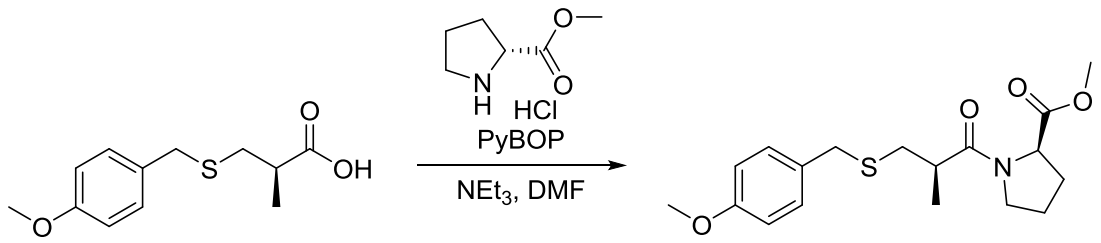
To a solution of **288l** (38 mg, 0.15 mmol, 1.0 eq, 89% ee) in THF (1.0 mL) at rt was added $LiOH•H_2O$ (19 mg, 0.45 mmol, 3.0 eq) in H_2O (1.0 mL). Stirring was maintained for 16 h whereupon the reaction mixture was diluted with H_2O (2 mL) and extracted with Et_2O (2 x 5 mL). The aqueous layer was acidified to pH 2 using 1 M HCl (aq) and extracted with CH_2Cl_2 (3 x 5 mL). The organics were washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo* to afford the title compound **330** as a pale yellow solid in 82% yield (32 mgs).

$[\alpha]_D^{21}$ = +19.9 (*c* 0.20, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2934, 1706, 1512, 1248, 1176; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 1.24 (d, *J* = 7.0 Hz, 3 H, $CH(CH_3)$), 2.46 (dd, *J* = 13.0, 7.0 Hz, 1 H, SCH_AH_BCH), 2.65 (sxt, *J* = 7.0 Hz, 1 H, $SCH_AH_BCH(CH_3)$), 2.75 (dd, *J* = 13.0, 7.0 Hz, 1 H, SCH_AH_BCH), 3.69 (s, 2 H, CH_2S), 3.80 (s, 3 H, OCH_3), 6.81 - 6.89

(m, 2 H, ArH), 7.19 - 7.25 (m, 2 H, ArH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 16.8 ($SCH_AH_BCH(\underline{C}H_3)$), 34.1 ($S\underline{C}H_AH_BCH$), 36.1 ($Ar\underline{C}H_2S$), 39.9 ($SCH_AH_B\underline{C}H(CH_3)$), 55.4 ($O\underline{C}H_3$), 114.1 (Ar<u>C</u>H), 130.0 (Ar<u>C</u>), 130.1 (Ar<u>C</u>H), 158.8 ($Ar\underline{C}OCH_3$), 181.5 (<u>C</u>=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{16}NaO_3S$) requires *m/z* 263.0712, found *m/z* 263.0714.

8.4.7.2 Synthesis and characterisation of 331

<u>Methyl 1-{(2*R*)-3-[(4-methoxybenzyl)sulfanyl]-2-methylpropanoyl}-D-prolinate **331**</u>



To a solution of acid **330** (24 mg, 0.10 mmol, 1.0 eq) and PyBOP (52 mg, 0.10 mmol, 1.0 eq) in DMF (0.7 mL) was added D-proline methyl ester hydrochloride (17 mg, 0.10 mmol, 1.0 eq). Stirring was maintained for 5 minutes and then triethylamine (42 µL, 0.30 mmol, 3.0 eq) was added dropwise and the reaction mixture stirred for 16 h. The reaction was quenched by the addition of brine (2 mL) and extracted with EtOAc (2 x 5 mL). The combined organics were washed with 10% aq Na_2CO_3 (2 x 3 mL), washed with brine, dried ($MgSO_4$) and the volatiles removed *in vacuo*. The crude product was purified by FCC (petroleum ether/EtOAc 4/1 to EtOAc 1/1) to yield the title compound **331** as a colourless oil in 66% yield (23 mg) and 19:1 dr.

$[\alpha]_D^{21}$ = +48.7 (*c* 0.46, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2954, 1745, 1643, 1512, 1431, 1247, 1175, 1033, 834; **^{1}H NMR** ($CDCl_3$, 500 MHz, compound exists as a mixture of diastereomers (19:1) and rotamers (8.9:1 for the major diastereomer) δ (ppm): 1.16 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H}_3)$), 1.89 - 2.00 (m, 2 H, $NCHC\underline{H}_AH_BC\underline{H}_AH_B$), 2.00 - 2.08 (m, 1 H,

NCHCH$_A$H$_B$CH$_A$H$_B$), 2.14 - 2.21 (m, 1 H, NCHCH$_A$H$_B$), 2.43 (dd, *J* =13.0, 6.0 Hz, 1 H, SCH$_A$H$_B$CH), 2.61 - 2.70 (m, 1 H, SCH$_A$H$_B$CH(CH$_3$)), 2.82 (dd, *J* = 13.0, 8.0 Hz, 1 H, SCH$_A$H$_B$CH), 3.44 - 3.50 (m, 1 H, NCH$_A$H$_B$CH$_2$), 3.51 - 3.58 (m, 1 H, NCH$_A$H$_B$CH$_A$H$_B$), 3.66 (s, 2 H, CH$_2$S), 3.70 (s, 3 H, C(O)OCH$_3$), 3.78 (s, 3 H, ArCOCH$_3$), 4.35 (dd, *J* = 8.5, 2.5 Hz, 1 H, NCHCH$_2$CH$_2$, minor rotamer), 4.39 (dd, *J* = 8.5, 4.0 Hz, 1 H, NCHCH$_2$CH$_2$, minor diastereomer), 4.50 (dd, *J* = 8.5, 4.0 Hz, 1 H, NCHCH$_2$CH$_2$), 6.80 - 6.88 (m, 2 H, ArH), 7.17 - 7.24 (m, 2 H, ArH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ (ppm): 17.3 (CH(CH$_3$)), 24.9 (NCHCH$_2$CH$_2$), 29.2 (NCHCH$_2$), 35.1 (SCH$_A$H$_B$CH(CH$_3$)), 36.8 (ArCH$_2$S), 38.8 (SCH$_A$H$_B$CH(CH$_3$)), 47.0 (NCH$_2$CH$_2$), 52.3 C(O)OCH$_3$), 55.4 (ArCOCH$_3$), 58.7 (NCHCH$_2$CH$_2$), 114.0 (ArCH), 130.0 (ArCH), 130.7 (ArC), 158.8 (ArCOCH$_3$), 172.9 (C=O), 174.1 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{25}NaNO_4S$) requires *m/z* 374.1397, found *m/z* 374.1397.

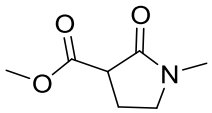
8.5 β-Amido Ester Conjugate Addition Reactions to Nitro-olefins

8.5.1 Synthesis and Characterisation of β-Amido Esters

The starting materials **344**, **347**, **349**, **351** and **353** were kindly provided by Dr Pavol Jakubec and were synthesised according to literature procedures.

8.5.1.1 Synthesis and characterisation of 80

(±)-1-Methyl-2-oxo-pyrrolidine-3-carboxylic acid methyl ester **80**



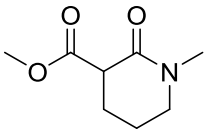
According to a literature procedure,[109] 2.5 M ^{n}BuLi in hexanes (25.0 mL, 63.6 mmol, 2.10 eq) was added dropwise to a solution of diisopropylamine (8.5 mL, 60.5 mmol, 2.0 eq) in THF (30 mL) at -78 °C and the mixture was stirred at -78 °C for 30 min. *N*-methylpyrrolidinone (2.90 mL, 30.3 mmol, 1.0 eq) was added and the mixture was stirred at -78 °C. After 1 h dimethylcarbonate (2.55 mL,

30.3 mmol, 1.0 eq) was added dropwise with vigorous stirring and the resulting suspension was stirred 4 h at rt. The suspension was poured into a saturated solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and the volatiles removed *in vacuo*. Purification by flash column chromatography [EtOAc] afforded the title compound **80** as a yellow oil in 60% yield (2.88 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.23 - 2.34 (m, 1 H, $C\underline{H_A}H_BCH$), 2.38 - 2.50 (m, 1 H, $CH_A\underline{H_B}CH$), 2.90 (s, 3 H, $NC\underline{H_3}$), 3.38 (td, *J* = 9.0, 5.5 Hz, 1 H, $C\underline{H_A}H_BN$), 3.46 (dd, *J* = 9.5, 6.5 Hz, 1 H, $C\underline{H}CH_2$), 3.53 (td, *J* = 9.0, 5.5 Hz, 1 H, $CH_A\underline{H_B}N$), 3.80 (s, 3 H, $OC\underline{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 22.3 ($\underline{C}H_2CH$), 30.2 ($\underline{C}H_3N$), 48.0 ($\underline{C}H_2N$), 48.2 ($CH_2\underline{C}H$), 52.8 ($O\underline{C}H_3$), 169.8 ($\underline{C}$=O), 170.9 ($\underline{C}$=O). Data is consistent with that given in the literature.[109]

8.5.1.2 Synthesis and characterisation of 342

(±)-Methyl 1-methyl-2-oxopiperidine-3-carboxylate **342**



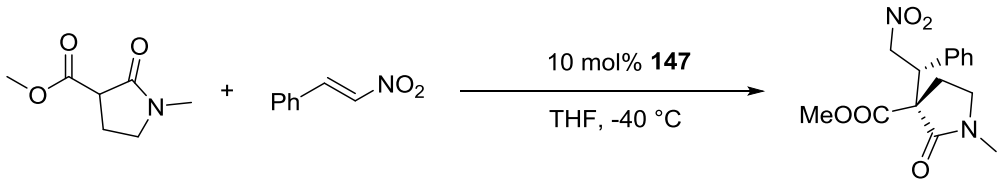
2.5 M ^{n}BuLi in hexanes (14.9 mL, 37.2 mmol, 2.10 eq) was added dropwise to a solution of diisopropylamine (5.0 mL, 35.4 mmol, 2.0 eq) in THF (20 mL) at -78 °C and the mixture was stirred at -78 °C for 30 min. *N*-methylpiperidin-2-onedin-2-one (2.00 g, 17.7 mmol, 1.0 eq) was added and the mixture was stirred at -78 °C. After 1 h dimethylcarbonate (1.49 mL, 17.7 mmol, 1.0 eq) was added dropwise with vigorous stirring and the resulting suspension was stirred 4 h at rt. The suspension was poured into a saturated solution of NH_4Cl (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$ and the volatiles removed *in vacuo*. Purification by flash column chromatography [EtOAc] afforded the title compound **342** as a pale yellow solid in 42% yield (1.28 g).

MP 48 - 50 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.71 - 1.81 (m, 1H, C$\underline{H_A}H_BCH_2N$), 1.89 - 2.14 (m, 3H, CHC$\underline{H_2}$, $CH_A\underline{H_B}CH_2N$), 2.93 (s, 3H, NC$\underline{H_3}$), 3.22 - 3.28 (m, 1H, C$\underline{H_A}H_BN$), 3.31 - 3.39 (m, 2H, C$\underline{H}CH_2$ and $CH_A\underline{H_B}N$), 3.71 (s, 3H, OC$\underline{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 21.0 ($\underline{C}H_AH_BCH_2N$), 25.3 (CH$\underline{C}H_2$), 35.0 (N$\underline{C}H_3$), 49.0 ($\underline{C}HCH_2$), 49.8 (N$\underline{C}H_2CH_2$), 54.4 (O$\underline{C}H_3$), 165.8 ($\underline{C}$=O), 171.6 ($\underline{C}$=O). Data is consistent with that given in the literature.[338]

8.5.2 Synthesis and Characterisation of Cyclic β-amido Ester Addition Products

8.5.2.1 Synthesis and characterisation of 81

Methyl (3*S*)-1-methyl-3-[(1*S*)-2-nitro-1-phenylethyl]-2-oxopyrrolidine-3-carboxylate **81**



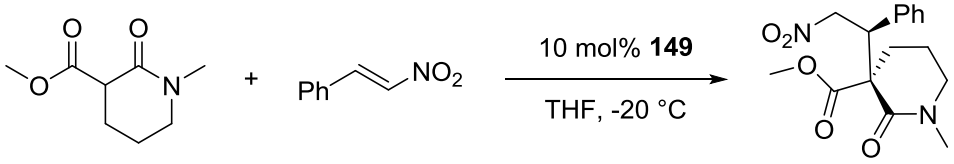
To a solution of pro-nucleophile **80** (76 mg, 0.48 mmol, 1.0 eq) and trans-nitrostyrene (83 mg, 0.576 mmol, 1.2 eq) in THF (0.72 mL) at -40 °C was added catalyst **147** (35 mg, 0.048 mmol, 0.10 eq). Stirring was maintained for 12 hours whereupon the reaction mixture was quenched by the addition of a 1 M acetic acid solution in CH_2Cl_2 (0.10 mL). The volatiles were removed *in vacuo* and purification by flash column chromatography [Et_2O] yielded the title compound **81** as an 8.3: 1 mixture of diastereomers (140 mg, 95% yield). The ee was determined by HPLC analysis (Chiralpak AS-H, hexane/*iso*-propanol 90:10, λ 220 nm, 1.0 mL/min): major: t (major) = 19.50 min., t (minor) = 27.04 min (ee 91%), minor: t (major) = 25.51 min., t (minor) = 33.80 min (ee 52%).

$[\alpha]_D^{24}$ = - 43.6 (c = 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.92 – 2.06 (m, 1H, major & minor), 2.15 (td, *J* = 8.8, 5.7 Hz, 1H, major & minor), 2.22 – 2.32 (m, 1H, major), 2.35 – 2.43 (m, 1H, minor), 2.70 (s, 3H, minor), 2.72 (s, 3H, major), 2.87 – 2.92 (m, 1H,

minor), 3.06 (td, *J* = 9.0, 4.4 Hz, 1H, major), 3.23 – 3.29 (m, 1H, minor), 3.75 (s, 3H, minor), 3.76 (s, 3H, major), 4.11 (dd, *J* = 11.1, 3.5 Hz, 1H, minor), 4.18 (dd, *J* = 11.1, 3.3 Hz, 1H, major), 4.99 (dd, *J* = 13.6, 3.3 Hz, 1H, major), 5.08 (dd, *J* = 13.6, 11.1 Hz, 1H, minor), 5.25 (dd, *J* = 13.6, 11.1 Hz, 1H, major), 5.46 (dd, *J* = 13.6, 3.5 Hz, 1H, minor), 7.17 – 7.34 (m, 5H, major & minor); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 26.4 (minor), 28.2 (major), 29.9 (major), 30.0 (minor), 46.3 (minor), 46.5 (major), 47.0 (minor), 47.2 (major), 53.0 (minor), 53.0 (major), 57.6 (major), 58.0 (minor), 76.3 (minor), 76.9 (major), 128.2 (minor), 128.4 (major), 128.6 (minor), 128.6 (major), 128.8 (minor), 128.9 (major), 135.0 (major), 135.4 (minor), 169.8 (minor), 170.3 (minor), 170.4 (major), 171.7 (major); **MP** 94 - 97 °C [lit. 106-107 °C, racemate of major diastereomer][109]. Data of the major diastereomer consistent with that given in the literature.[109]

8.5.2.2 Synthesis and characterisation of 343

Methyl (3*S*)-1-methyl-3-[(1*S*)-2-nitro-1-phenylethyl]-2-oxopiperidine-3-carboxylate **343**



To a solution of **342** (41 mg, 0.24 mmol, 1.2 eq) and nitrostyrene (30 mg, 0.20 mmol, 1.0 eq) in THF (0.66 mL) at -20 °C was added **149** (17 mg, 0.020 mmol, 0.10 eq) and the reaction mixture was stirred for 22 h whereupon it was quenched by the addition of 1 M AcOH in CH_2Cl_2 (0.1 mL) and the volatiles were removed *in vacuo*. Purification by flash column chromatography [Et_2O] afforded the title compound **343** as a colourless solid in 78% yield and as a 4.0:1 mixture of diastereomers (50 mg). The ee was determined by HPLC analysis (Chiralpak AD, hexane/*iso*-propanol 90:10, λ 220 nm, 1.0 mL/min): major:

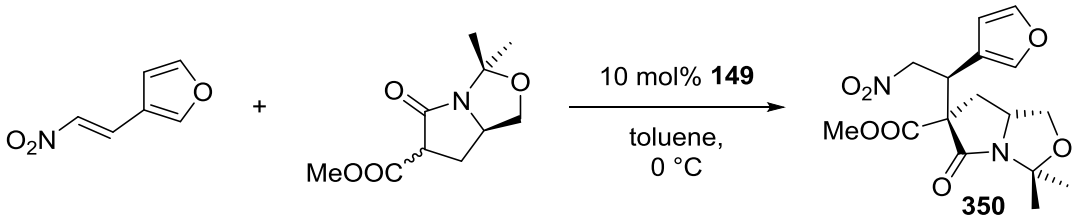
t (minor) = 21.50 min., t (major) = 40.99 min (ee 91%), minor: t (major) = 18.74 min., t (minor) = 23.32 min (ee 44%).

MP 115 - 117 °C; **$[\alpha]_D^{23}$** = + 71.2 (c = 1.1, $CHCl_3$); **IR** (film) ν_{max}/cm^{-1}: 2952, 1731, 1637, 1548, 1496, 1454, 1434, 1433, 1402, 1379, 1331, 1291, 1242, 1197, 1182, 1148; **^{1}H NMR** (500 MHz, C_6D_6) δ ppm 0.70 - 0.77 (m, 1H, $CH_AH_BC\underline{H}_AH_BCH_AH_BN$, major), 1.11 - 1.19 (m, 1H, $CH_AH_BC\underline{H}_AH_BCH_AH_BN$, minor), 1.27 - 1.36 (m, 1H, $CH_AH_BCH_A\underline{H}_BCH_AH_BN$, major and minor), 1.37 - 1.43 (m, 1H, $C\underline{H}_AH_BCH_AH_BCH_AH_BN$, major and minor), 1.71 - 1.76 (m, 1H, $CH_A\underline{H}_BCH_AH_BCH_AH_BN$, major and minor), 2.01 ('td', *J* = 11.5 Hz, 4.5 Hz, 1H, $C\underline{H}_AH_BN$, major), 2.19 - 2.23 (m, 1H, $C\underline{H}_AH_BN$, minor), 2.24 - 2.28 (m, 1H, $CH_A\underline{H}_BN$, major), 2.31 - 2.36 (m, 1H, $CH_A\underline{H}_BN$, minor), 2.45 (s, 3H, $NC\underline{H}_3$, minor), 2.53 (s, 3H, $NC\underline{H}_3$, major), 3.22 (s, 3H, $OC\underline{H}_3$, minor), 3.28 (s, 3H, $OC\underline{H}_3$, major), 4.21 (dd, *J* = 10.6 Hz, 3.0 Hz, 1H, $C\underline{H}CH_AH_BNO_2$, major), 4.48 (dd, *J* = 10.6 Hz, 4.0 Hz, 1H, $C\underline{H}CH_AH_BNO_2$, minor), 4.97 (dd, *J* = 13.5 Hz, 10.5 Hz, 1H, $CHC\underline{H}_AH_BNO_2$, minor), 5.08 (dd, *J* = 13.5 Hz, 3.0 Hz, 1H, $CHC\underline{H}_AH_BNO_2$, major), 5.42 (dd, *J* = 13.5 Hz, 4.0 Hz, 1H, $CHCH_A\underline{H}_BNO_2$, minor), 5.70 (dd, *J* = 13.5 Hz, 10.5 Hz, 1H, $CHCH_A\underline{H}_BNO_2$, major), 6.95 – 7.05 (m, 3H, Ar$\underline{H}$, major and minor), 7.21 – 7.24 (m, 2H, Ar$\underline{H}$, major), 7.37 – 7.41 (m, 2H, Ar$\underline{H}$, minor), **^{13}C NMR** (125 MHz, C_6D_6) δ ppm 20.0 ($C_qCH_2\underline{C}H_2CH_2N$, minor), 20.1 ($C_qCH_2\underline{C}H_2CH_2N$, major), 29.2 ($C_q\underline{C}H_2CH_2CH_2N$, minor), 32.3 ($C_q\underline{C}H_2CH_2CH_2N$, major), 35.2 ($N\underline{C}H_3$, major), 35.5 ($N\underline{C}H_3$, minor), 49.2 ($\underline{C}HCH_2NO_2$, minor), 49.2 ($C_qCH_2CH_2\underline{C}H_2N$, minor), 49.2 ($C_qCH_2CH_2\underline{C}H_2N$, major), 51.2 ($\underline{C}HCH_2NO_2$, major), 52.5 ($O\underline{C}H_3$, minor), 52.7 ($O\underline{C}H_3$, major), 57.2 ($\underline{C}_qCH_2CH_2CH_2N$, minor), 58.4, ($\underline{C}_qCH_2CH_2CH_2N$, major), 78.4 ($CH\underline{C}H_2NO_2$, minor), 80.5 ($CH\underline{C}H_2NO_2$, major), 128.5 (Ar$\underline{C}$H, minor), 128.7 (Ar$\underline{C}$H, major), 128.9 (Ar$\underline{C}$H, minor), 129.3 (Ar$\underline{C}$H, major), 130.6 (Ar$\underline{C}$H, major), 130.7 (Ar$\underline{C}$H, minor), 137.1 (Ar$\underline{C}$, minor), 137.5 (Ar$\underline{C}$, major) 167.0 ($\underline{C}$=O, major), 167.2 ($\underline{C}$=O, minor), 172.2 ($\underline{C}$=O, minor), 173.3 ($\underline{C}$=O, major); **HRMS**

(ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{21}N_2O_5$) requires *m/z* 321.1445, found *m/z* 321.1437.

8.5.2.3 Synthesis and characterisation of 350

Methyl (7a*S*)-6-[(1*S*)-1-(furan-3-yl)-2-nitroethyl]-3,3-dimethyl-5-oxotetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazole-6-carboxylate **350**



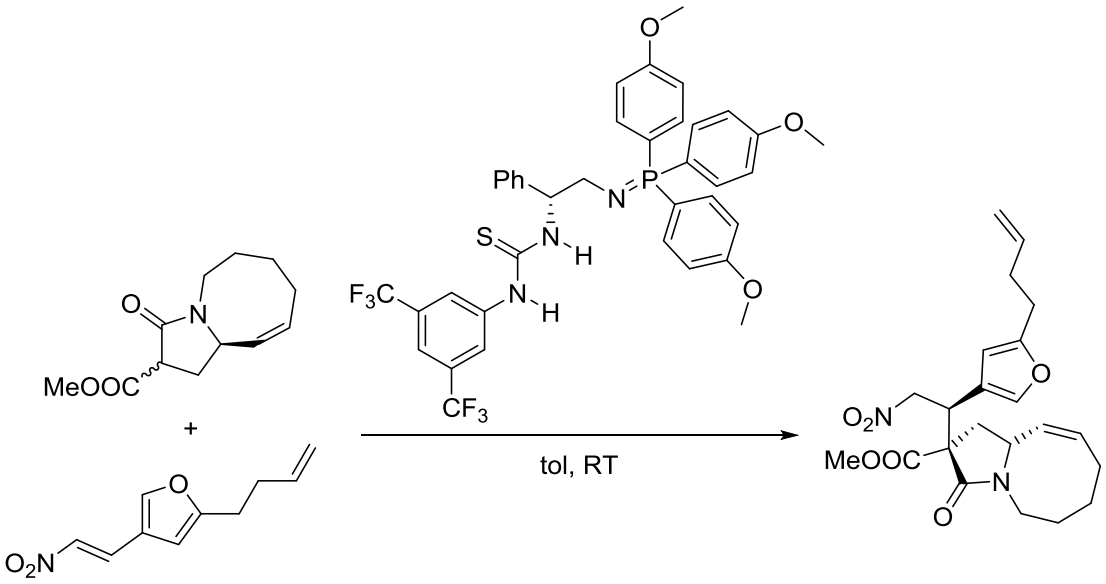
To a solution of nitro-olefin **349** (28 mg, 0.20 mmol, 1.0 eq) and pro-nucleophile **344** (85 mg, 0.40 mmol, 2.0 eq) in toluene (0.67 mL) at 0 °C was added catalyst **149** (1.7 mg, 0.0020 mmol, 0.01 eq). The reaction mixture was stirred at 0 °C for 80 min whereupon it was quenched by the addition of 1 M AcOH in CH_2Cl_2 (0.1 mL) and the volatiles removed *in vacuo*. The crude diastereomeric ratio was determined to be 98:2:0:0 by ^{1}H NMR. Purification by flash column chromatography [Petroleum ether then petroleum ether: EtOAc: CH_2Cl_2 5:5:1] followed by trituration in Et_2O afforded the title compound **350** as a colourless solid in 68% yield (48 mg) and as a single diastereomer.

$[\alpha]_D^{24}$ = +0.78 (c = 0.9, $CHCl_3$) [lit $[\alpha]_D^{26}$ = +2.1 (c 0.75, $CHCl_3$)][240]; **MP** 153- 155 °C [lit. 157 °C][240]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.42 (s, 3 H, C(C$\underline{H}_3$)(CH_3)), 1.67 (s, 3 H, C(CH_3)(C$\underline{H}_3$)), 2.16 (dd, *J* = 13.5, 7.5 Hz, 1 H, $C_qC\underline{H}_AH_BCHN$), 2.20 (dd, *J* = 13.5, 7.0 Hz, 1 H, $C_qCH_AH_BCHN$), 3.24 - 3.34 (m, 1 H, $C_qCH_AH_BC\underline{H}N$), 3.35 - 3.44 (m, 1 H, $OC\underline{H}_AH_BCHN$), 3.82 (s, 3 H, $OC\underline{H}_3$), 3.90 (dd, *J* = 7.5, 5.5 Hz, 1 H, $OCH_A\underline{H}_BCHN$), 4.14 (dd, *J* = 11.0, 4.0 Hz, 1 H, $C\underline{H}CH_AH_BNO_2$), 4.92 (dd, *J* = 13.5, 11.0 Hz, 1 H, $CHC\underline{H}_AH_BNO_2$), 4.99 (dd, *J* = 13.5, 4.0 Hz, 1 H, $CHCH_A\underline{H}_BNO_2$), 6.41 (s, 1 H, Ar$\underline{H}$), 7.39 - 7.43 (m, 1 H, Ar$\underline{H}$), 7.44 (s, 1 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 23.4

($C(\underline{C}H_3)(CH_3)$), 26.4 ($C(CH_3)(\underline{C}H_3)$), 33.4 ($C_q\underline{C}H_AH_BCHN$), 38.7 ($\underline{C}HCH_AH_BNO_2$), 53.6 ($O\underline{C}H_3$), 58.7 ($C_qCH_AH_B\underline{C}HN$), 63.6 ($\underline{C}_qCH_AH_BN$), 70.0 ($O\underline{C}H_AH_BCHN$), 76.9 ($CH\underline{C}H_AH_BNO_2$), 92.1 ($\underline{C}(CH_3)(CH_3)$), 109.6 (Ar$\underline{C}$H), 119.3 (Ar$\underline{C}$), 142.1 (Ar$\underline{C}$H), 144.1 (Ar$\underline{C}$H), 167.4 ($\underline{C}$=O), 171.8 ($\underline{C}$=O). Data is consistent with that given in the literature.[240]

8.5.2.4 Synthesis and characterisation of 352

Methyl (2*S*,9*Z*,10a*R*)-2-{(1*S*)-1-[5-(but-3-en-1-yl)-3-furyl]-2-nitroethyl}-3-oxo-1,2,3,5,6,7,8,10a-octahydropyrrolo[1,2-*a*]azocine-2-carboxylate **352**



To a solution of pro-nucleophile **351** (30 mg, 0.14 mmol, 1.0 eq) in toluene (0.40 mL), at room temperature was added nitro olefin **347** (29 mg, 0.15 mmol, 1.1 eq), then catalyst **148** (10 mg, 0.014 mmol, 0.10 eq). The reaction mixture was stirred at RT for 2 h with the exclusion of light. The reaction mixture was passed through a pad of silica [Et_2O] and the volatiles removed *in vacuo*. Purification by flash column chromatography [petrol: Et_2O 2:1 then 1: 1] afforded the title compound **352** as a pale yellow oil with a dr of 4.5: 1 (33 mg, 59% yield).

$[\alpha]_D^{24}$ = - 16.2 (c = 1.4, $CHCl_3$), lit $[\alpha]_D^{25}$ = -15.2 (c = 1.57, $CHCl_3$)[160]. Major diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.45 - 1.63 (m, 3H), 1.86 - 2.00 (m, 2H),

2.13 (dd, *J* = 13.5., 6.4 Hz, 1H), 2.29 - 2.41 (m, 4H), 2.65 (t, *J* = 7.6 Hz, 2H), 3.30 - 3.36 (m, 1H), 3.43 - 3.48 (m, 1H), 3.55 ('q', *J* = 7.0 Hz, 1H), 3.78 (s, 3H), 4.04 (dd, *J* = 11.0, 3.2 Hz, 1H), 4.88 (dd, *J* = 13.1, 3.3 Hz, 1H), 4.96 - 5.10 (m, 3H), 5.27 (dd, *J* = 10.9, 6.6 Hz, 1H), 5.72 - 5.84 (m, 2H), 5.93 (s, 1H), 7.26 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 25.3, 25.5, 27.2, 27.5, 31.8, 37.3, 39.4, 41.9, 53.1, 54.3, 57.6, 77.1, 102.2, 115.5, 119.7, 129.0, 133.4, 137.0, 157.0, 170.0, 172.3. Data is consistent with that given in the literature.[160]

8.6 Miscellaneous Organocatalytic Addition Reactions

8.6.1 General Procedures

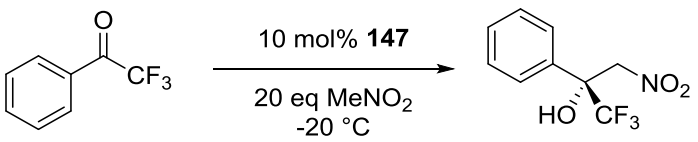
General Procedure XI **for the Addition of $MeNO_2$ to β-Substituted α,β-Unsaturated Esters**

To a solution of the β-substituted α,β-unsaturated ester **55** (0.20 mmol) in nitromethane (0.11 mL, 2.0 mmol, 10 eq) in a sealed vial was added catalyst **149** (17 mg, 0.020 mmol, 0.10 eq) and the reaction mixture was stirred at rt for 96 h. Purification by flash column chromatography [Petroleum ether to petroleum ether: Et_2O 4:1] afforded the desired γ-nitroester **378**.

8.6.2 Synthesis and Characterisation of Miscellaneous Addition Reactions

8.6.2.1 Synthesis and characterisation of 358

(*R*)-1,1,1-Trifluoro-3-nitro-2-phenyl-propan-2-ol **358**

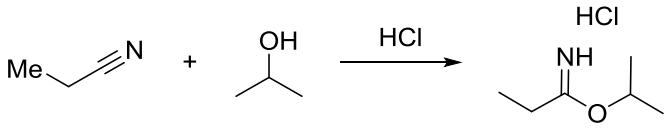


To catalyst **147** (15 mg, 0.020 mmol, 0.10 eq) in nitromethane (0.22 mL, 4.0 mmol, 20 eq) at -20 °C was added 2,2,2-trifluoroacetophenone (28 µL, 0.20 mmol, 1.0 eq). Stirring was maintained for 8 h whereupon it was quenched by the addition of 0.1 mL 1 M AcOH in CH_2Cl_2 and the volatiles removed *in vacuo.* Purification by flash column chromatography (Petroleum ether to petroleum ether/Et_2O 9/1) afford the title compound **358** as a colourless oil in 94% yield (44 mg) and 66% ee [determined by HPLC, Chiralcel AS-H, hexane/isopropanol = 90/10, 1.0 mL/min, λ = 220 nm, t (major) = 10.55 min, t (minor) = 11.34 min].

$[\alpha]_D^{24}$ = - 38.6 (c = 0.28, $CHCl_3$), [lit. -67, c = 1.54, MeOH][249]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 4.63 (s, 1 H, O<u>H</u>), 5.01 (d, *J* = 13.7 Hz, 1 H, C<u>H</u>$_A$H$_B$NO$_2$), 5.10 (d, *J* = 13.7 Hz, 1 H, CH$_A$<u>H</u>$_B$NO$_2$), 7.41 - 7.50 (m, 3 H, Ar<u>H</u>), 7.56 - 7.64 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 76.4 (q, J_{FC} = 29.4 Hz, <u>C</u>CF$_3$), 77.6 (<u>C</u>H$_A$H$_B$NO$_2$), 123.5 (q, J_{FC} = 286.0 Hz, C<u>C</u>F$_3$), 126.3 (Ar<u>C</u>H), 129.1 (Ar<u>C</u>H), 130.2 (Ar<u>C</u>H), 133.1 (Ar<u>C</u>); **^{19}F NMR** (376 MHz, $CDCl_3$) δ ppm -78.7. Data is consistent with that given in the literature.[248]

8.6.2.2 Synthesis and characterisation of 362

<u>Isopropyl propionimidate hydrochloride **362**</u>



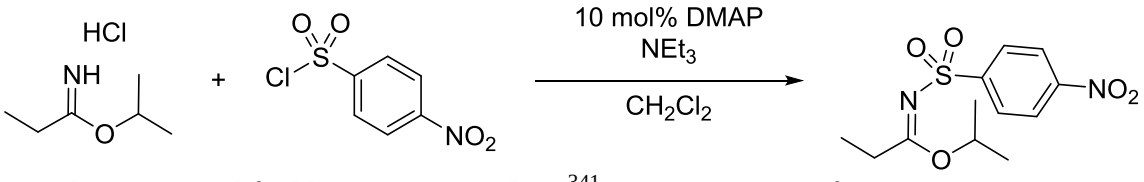
According to a literature procedure,[339] hydrogen chloride gas [generated by the dropwise addition of conc. HCl (12.5 mL) to anhydrous $CaCl_2$ (15 g)][340] was bubbled into a solution of propionitrile (6.5 mL, 91 mmol, 1.07 eq) and isopropanol (6.5 mL, 85 mmol, 1.0 eq) at room temperature for 10 min. The reaction mixture was stirred at rt for 2 h and then the volatiles were removed under a stream of nitrogen. The resultant precipitate was washed

with Et_2O to afford the title compound **362** as an amorphous colourless solid in 33% yield (4.20 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.22 (t, *J* = 7.5 Hz, 3 H, C<u>H</u>$_3$CH$_2$), 1.40 (d, *J* = 6.0 Hz, 6 H, CH(C<u>H</u>$_3$)$_2$), 2.68 (q, *J* = 7.5 Hz, 2 H, CH$_3$C<u>H</u>$_2$), 5.45 (spt, *J* = 6.0 Hz, 1 H, C<u>H</u>(CH$_3$)$_2$), 11.30 (br. s., 1 H, N<u>H</u>), 12.07 (br. s., 1 H, N<u>H</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 9.8 (<u>C</u>H$_3$CH$_2$), 21.2 (CH(<u>C</u>H$_3$)$_2$), 27.1 (CH$_3$<u>C</u>H$_2$), 78.9 (<u>C</u>H(CH$_3$)$_2$), 178.6 (<u>C</u>(=N)O).

8.6.2.3 Synthesis and characterisation of 363

<u>Propan-2-yl-*N*-[(4-nitrophenyl)sulfonyl]propanimidoate **363**</u>

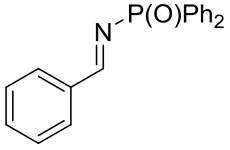


According to a modified literature procedure,[341] to a suspension of **362** (1.00 g, 6.62 mmol, 1.0 eq) in CH_2Cl_2 (17 mL) was added sequentially triethylamine (2.77 mL, 19.9 mmol, 3.0 eq), 4-nitrobenzenesulfonyl chloride (1.47 g, 6.62 mmol, 1.0 eq) and DMAP (81 mg, 0.66 mmol, 0.10 eq) at room temperature. The reaction mixture was stirred at rt for 14 h and the volatiles concentrated *in vacuo*. Purification by flash column chromatography [Petroleum ether: EtOAc 9:1] afforded the title compound **363** in 72% yield (1.43 g).

MP 71 - 72 °C [lit. 70 - 71 °C][341]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.20 - 1.28 (m, 9 H, C<u>H</u>$_3$CH$_2$ and CH(C<u>H</u>$_3$)$_2$), 2.91 (q, *J* = 7.5 Hz, 2 H, CH$_3$C<u>H</u>$_2$), 4.99 (spt, *J* = 6.5 Hz, 1 H, C<u>H</u>(CH$_3$)$_2$), 8.07 - 8.15 (m, 2 H, Ar<u>H</u>), 8.31 - 8.38 (m, 2 H, Ar<u>H</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 10.1 (<u>C</u>H$_3$CH$_2$), 21.0 (CH(<u>C</u>H$_3$)$_2$), 28.4 (CH$_3$<u>C</u>H$_2$), 72.8 (<u>C</u>H(CH$_3$)$_2$), 124.0 (Ar<u>C</u>H), 127.7 (Ar<u>C</u>H), 147.6 (Ar<u>C</u>), 149.7 (Ar<u>C</u>), 177.5 (<u>C</u>(=N)O). Data is consistent with that given in the literature.[341]

8.6.2.4 Synthesis and characterisation of 172

P,*P*-Diphenyl-*N*-[(*E*)-phenylmethylidene]phosphinic amide **172**

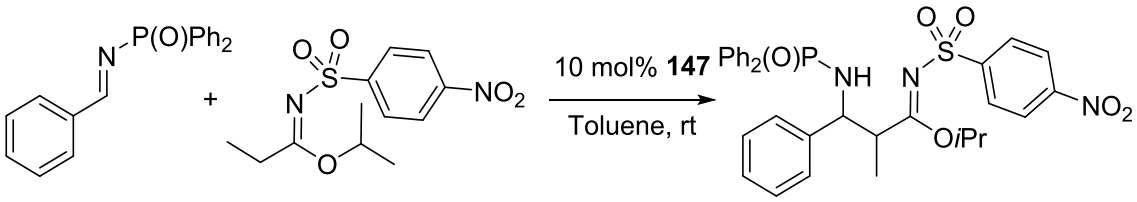


A solution of benzaldehyde (4.8 mL, 47 mmol, 1.0 eq), hydroxylamine hydrochloride (4.8 g, 71 mmol, 1.5 eq) and sodium acetate (5.8 g, 71 mmol, 1.5 eq) in 1:1 water: EtOH (38 mL) was refluxed for 14 h. The reaction mixture was cooled and volatiles removed *in vacuo* and the reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organics were washed with brine (30 mL), dried ($MgSO_4$). The crude product was purified by distillation [8 mBar, 115 °C] (lit.[342] bp 10 Torr, 120 - 125 °C) to afford the oxime as a colourless solid in 78% yield (4.5 g). The aldimine was synthesised according to General Procedure **III**, on a 16.5 mmol scale of the oxime to afford the title compound **172** as a colourless solid after purification by flash column chromatography (3.00 g, 60% yield).

MP 130 - 132 °C [136 - 137 °C][343]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.41 - 7.56 (m, 8 H, ArH), 7.56 - 7.63 (m, 1 H, ArH), 7.91 - 8.00 (m, 4 H, ArH), 8.00 - 8.06 (m, 2 H, ArH), 9.34 (d, J_{PH} = 32.0 Hz, 1 H, C(=N)H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 128.5 (d, J_{PC} = 12.7 Hz), 129.0, 130.2, 131.6 (d, J_{PC} = 8.7 Hz), 131.8 (d, J_{PC} = 2.4 Hz), 133.0 (d, J_{PC} = 127.2 Hz), 133.7, 135.9 (d, J_{PC} = 25.4 Hz), 173.8 (d, J_{PC} = 7.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ ppm 24.9. Data is consistent with that given in the literature.[317,344]

8.6.2.5 Synthesis and characterisation of 364

Propan-2-yl (1*Z*)-3-[(diphenylphosphoryl)amino]-2-methyl-*N*-[(4-nitrophenyl)sulfonyl]-3-phenylpropanimidoate **364**



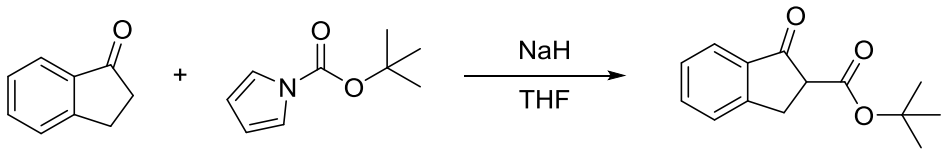
To a solution of *N*-DPP aldimine **172** (73 mg, 0.24 mmol, 1.2 eq) and pro-nucleophile **363** (60 mg, 0.20 mmol, 1.0 eq) in toluene (1.0 mL) was added catalyst **147** (15 mg, 0.020 mmol, 0.10 eq) and the reaction mixture was allowed to stir at rt for 36 h whereupon the reaction mixture was quenched by the addition of 1 M AcOH in CH_2Cl_2 (0.1 mL) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to petroleum ether: EtOAc 1:1] afforded the title compound **364** as a pale yellow oil in 87% yield (105 mg) and 1% ee. The ee was determined by HPLC analysis (Chiralpak IA, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 12.05 min, t (major) = 24.44 min (1%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.98 (d, *J* = 6.5 Hz, 3 H, $CH_3CHCHNH$), 1.30 (d, *J* = 6.0 Hz, 3 H, $OCH(CH_3)_2$), 1.48 (d, *J* = 6.0 Hz, 3 H, $OCH(CH_3)_2$), 4.00 (dq, *J* =10.5, 6.5 Hz, 1 H, $CH_3CHCHNH$), 4.29 ('q', *J* = 10.5 Hz, 1 H, $CH_3CHCHNH$), 4.86 ('t', *J* = 11.0 Hz, 1 H, CHNH), 5.11 (spt, *J* = 6.0 Hz, 1 H, $OCH(CH_3)_2$), 7.10 - 7.28 (m, 7 H, ArH), 7.28 - 7.39 (m, 3 H, ArH), 7.39 - 7.54 (m, 3 H, ArH), 7.63 - 7.79 (m, 2 H, ArH), 7.89 - 7.98 (m, 2 H, ArH), 8.21 - 8.35 (m, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 15.4 ($CH_3CHCHNH$), 21.1 ($OCH(CH_3)_2$), 21.5 ($OCH(CH_3)_2$), 48.1 ($CH_3CHCHNH$), 58.7 ($CH_3CHCHNH$), 74.7 ($OCH(CH_3)_2$), 124.2 (ArCH), 127.2 (ArCH), 127.9 (ArCH), 128.0 (d, J_{PC} = 13.2 Hz, ArCH), 128.5 (d, J_{PC} = 12.5 Hz, ArCH), 128.7 (ArCH), 131.8 (d, J_{PC} = 128.4 Hz, ArC), 131.3 (ArCH), 131.4 (ArCH), 131.4 (d, J_{PC} = 2.9 Hz, ArC), 132.6 (d, J_{PC}

= 10.3 Hz), 133.6 (d, J_{PC} = 127.7 Hz, Ar<u>C</u>), 141.5 (d, J_{PC} = 2.2 Hz, Ar<u>C</u>), 147.4 (Ar<u>C</u>), 149.9 (Ar<u>C</u>), 178.1 ((<u>C</u>=N)O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{31}H_{32}N_3O_6PS$) requires *m/z* 606.1822, found *m/z* 606.1820.

8.6.2.6 Synthesis and characterisation of 82

<u>*tert*-Butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **82**</u>

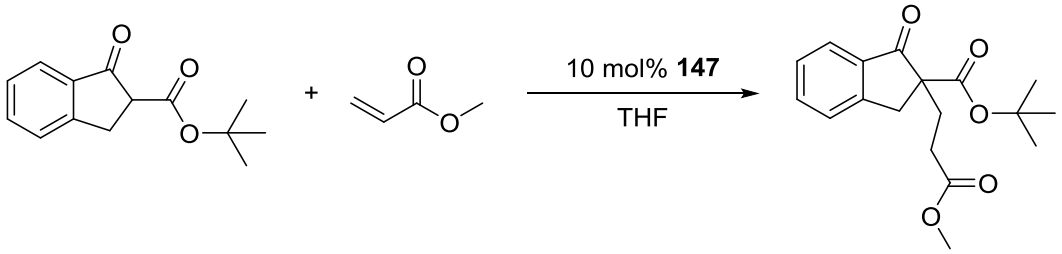


According to a literature procedure,[345] 1-indanone (660 mg, 5.0 mmol, 1.0 eq) was added to a suspension of NaH (60% in mineral oil, 400 mg, 10 mmol, 2.0 eq) in THF (20 mL). The reaction mixture was warmed to reflux and *N*-Boc pyrrole (1.7 mL, 10 mmol, 2.0 eq) was added dropwise and reflux maintained for 5 h. The reaction mixture was cooled to 0 °C, acidified with 1 M HCl and extracted with EtOAc (2 x 25 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$) and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to petroleum ether: Et_2O 4:1] afforded the title compound **82** as a purple oil in 73% yield (850 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.49 (s, 9 H, OC(C<u>H</u>$_3$)$_3$), 3.33 (dd, *J* = 17.5, 8.0 Hz, 1 H, C<u>H</u>$_A$H$_B$CH), 3.50 (dd, *J* = 17.5, 4.0 Hz, 1 H, CH$_A$<u>H</u>$_B$CH), 3.62 (dd, *J* = 8.0, 4.0 Hz, 1 H, CH$_A$H$_B$C<u>H</u>), 7.35 - 7.41 (m, 1 H, Ar<u>H</u>), 7.49 (d, *J* = 8.0 Hz, 1 H, Ar<u>H</u>), 7.58 - 7.64 (m, 1 H, Ar<u>H</u>), 7.76 (d, *J* = 8.0 Hz, 1 H, Ar<u>H</u>); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 28.1 (OC(<u>C</u>H$_3$)$_3$), 30.4 (CH<u>C</u>H$_2$), 54.5 (<u>C</u>HCH$_2$), 82.2 (O<u>C</u>(CH$_3$)$_3$), 124.7 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 127.8 (Ar<u>C</u>H), 135.4 (Ar<u>C</u>H), 135.6 (Ar<u>C</u>), 153.8 (Ar<u>C</u>), 168.5 (<u>C</u>(=O)O), 200.2 (<u>C</u>=O). Data is consistent with that given in the literature.[345]

8.6.2.7 Synthesis and characterisation of 365

tert-Butyl 2-(3-methoxy-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **365**

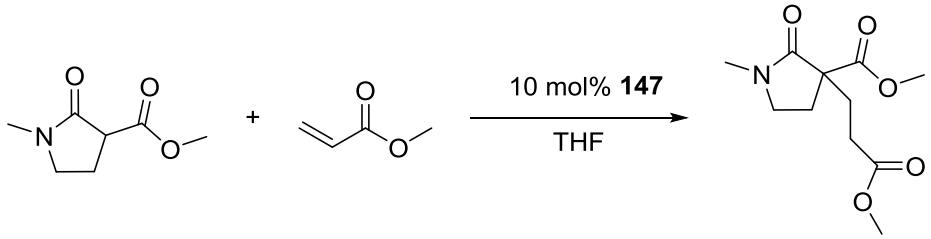


To a solution of **82** (50 mg, 0.20 mmol, 1.0 eq) and methyl acrylate (54 μL, 0.60 mmol, 3.0 eq) in THF (0.40 mL) was added catalyst **147** (15 mg, 0.020 mmol, 0.10 eq) at room temperature. The reaction mixture was stirred at rt for 48 h and the volatiles removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to petroleum ether: Et_2O 4:1] afforded the title compound **365** as a pale yellow oil in 68% yield (43 mg). The ee was determined by HPLC analysis (Chiralpak AD, hexane/*iso*-propanol 80:20, λ 220 nm, 1.0 mL/min): t (minor) = 8.09 min, t (major) = 8.90 min (18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.32 (s, 9 H, $OC(C\underline{H}_3)_3$), 2.09 - 2.17 (m, 1 H, $C_qC\underline{H}_AH_BCH_AH_BC{=}O$), 2.21 - 2.33 (m, 2 H, $C_qCH_AH_BC\underline{H}_A\underline{H}_BC{=}O$), 2.34 - 2.42 (m, 1 H, $C_qCH_A\underline{H}_BCH_AH_BC{=}O$), 2.95 (d, *J* = 17.0 Hz, 1 H, $C_qC\underline{H}_AH_BC_{Ar}$), 3.56 (d, *J* = 17.0 Hz, 1 H, $C_qCH_A\underline{H}_BC_{Ar}$), 3.57 (s, 3 H, $OC\underline{H}_3$), 7.29 - 7.36 (m, 1 H, Ar$C\underline{H}$), 7.40 (d, *J* = 8.0 Hz, 1 H, Ar$C\underline{H}$), 7.51 - 7.58 (m, 1 H, Ar$C\underline{H}$), 7.69 (d, *J* = 8.0 Hz, 1 H, Ar$C\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 27.9 ($OC(\underline{C}H_3)_3$), 29.7, 29.8 ($C_q\underline{C}H_2\underline{C}H_2C{=}O$), 37.4 ($C_q\underline{C}H_2C_{Ar}$), 51.8 ($O\underline{C}H_3$), 60.3 ($\underline{C}_q$), 82.2 ($O\underline{C}(CH_3)_3$), 124.8 (Ar$\underline{C}$H), 126.4 (Ar$\underline{C}$H), 127.9 (Ar$\underline{C}$H), 135.3 (Ar$\underline{C}$), 135.4 (Ar$\underline{C}$H), 152.8 (Ar$\underline{C}$), 169.9 (Ar$\underline{C}$), 173.4 ($\underline{C}(=O)O$), 202.5 ($\underline{C}{=}O$). Data is consistent with that given in the literature.[256]

8.6.2.8 Synthesis and characterisation of 366

Methyl 3-(3-methoxy-3-oxopropyl)-1-methyl-2-oxopyrrolidine-3-carboxylate **366**

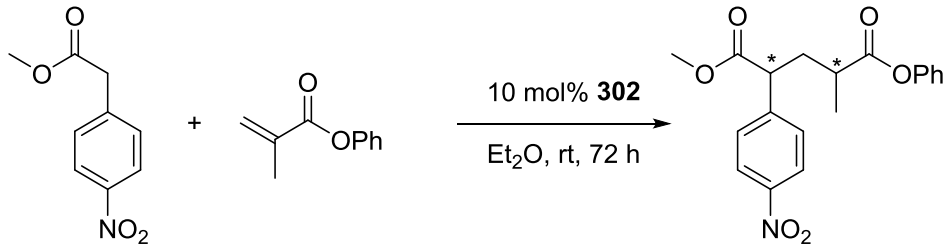


To a solution of **80** (47 mg, 0.30 mmol, 1.5 eq) and methyl acrylate (18 μL, 0.20 mmol, 1.0 eq) in THF (0.40 mL) was added catalyst **147** (15 mg, 0.020 mmol, 0.10 eq) at room temperature. The reaction mixture was stirred for 72 h whereupon the volatiles were removed *in vacuo*. Purification by flash column chromatography [Petroleum ether to Et_2O] afforded the title compound as a colourless oil in 14% yield (7 mg). The ee was determined by HPLC analysis (Chiralpak AD-H, hexane/*iso*-propanol 95:5, λ 220 nm, 1.0 mL/min): t (major) = 31.20 min, t (minor) = 33.71 min (16%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.94 (ddd, *J* = 13.0, 9.0, 7.0 Hz, 1 H, $NCH_AH_BC\underline{H_A}H_B$), 2.05 - 2.15 (m, 1 H, $C_qC\underline{H_A}H_BCH_AH_BC{=}O$), 2.27 - 2.40 (m, 2 H, $C_qCH_AH_BC\underline{H_A}\underline{H_B}C{=}O$), 2.44 - 2.54 (m, 2 H, $NCH_AH_BCH_A\underline{H_B}$ and $C_qCH_A\underline{H_B}CH_AH_BC{=}O$), 2.87 (s, 3 H, $NC\underline{H_3}$), 3.30 (td, *J* = 9.0, 4.0 Hz, 1 H, $NC\underline{H_A}H_BCH_AH_B$), 3.41 - 3.50 (m, 1 H, $NCH_A\underline{H_B}CH_AH_B$), 3.66 (s, 3 H, $OC\underline{H_3}$), 3.73 (s, 3 H, $OC\underline{H_3}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 28.8 ($NCH_AH_B\underline{C}H_AH_B$), 29.3 ($C_q\underline{C}H_2CH_2C{=}O$), 29.7 ($C_qCH_2\underline{C}H_2C{=}O$), 30.3 ($N\underline{C}H_3$), 46.9 ($N\underline{C}H_AH_BCH_AH_B$), 51.9 ($O\underline{C}H_3$), 52.9 ($O\underline{C}H_3$), 54.9 ($\underline{C_q}$), 171.6 ($\underline{C}{=}O$), 172.0 ($\underline{C}{=}O$), 173.5 ($\underline{C}{=}O$); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{17}NNaO_5$) requires *m/z* 266.0999, found *m/z* 266.0998.

8.6.2.9 Synthesis and characterisation of 367

5-Methyl 1-phenyl 2-methyl-4-(4-nitrophenyl)pentanedioate **367**



Azide **306** (9.6 mg, 0.020 mmol, 0.10 eq) and tris(4-methoxyphenyl)phosphine (7.0 mg, 0.020 mmol, 0.10 eq) were stirred in diethyl ether (0.2 mL) in a sealed vial at room temperature for 24 h. To the *in situ* generated catalyst was added a solution of methyl 2-(4-nitrophenyl)acetate **319** (78 mg, 0.40 mmol, 2.0 eq) and phenyl methacrylate (31 μL, 0.20 mmol, 1.0 eq) in Et_2O (0.47 mL) at rt. The reaction mixture was stirred for 72 h whereupon it was quenched by the addition of 1 M AcOH in CH_2Cl_2 (0.1 mL) and the volatiles removed *in vacuo*. The crude conversion was determined to be 67% by ^{1}H NMR. Purification by flash column chromatography [Petroleum ether to Et_2O] afforded the title compound **367** in 1.15:1 dr and excess **319** as a pale yellow amorphous solid (88 mg). The ee was determined by HPLC analysis (Chiralpak AD, hexane/*iso*-propanol 95:5, λ 220 nm, 1.0 mL/min): major t (minor) = 19.30 min, t (major) = 28.62 min (25%), minor t (major) = 20.82 min, t (major) = 23.56 min (26%).

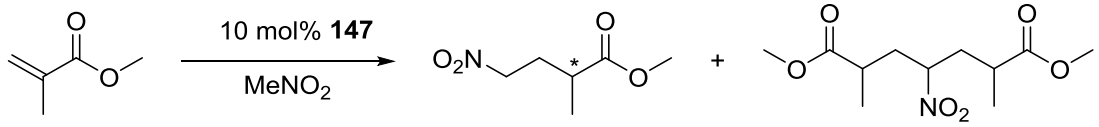
^{1}H NMR (400 MHz, $CDCl_3$)[xlix] δ ppm 1.33 (d, *J* = 7.0 Hz, 3H, CH(C$\underline{H}_3$)), 1.36 (d, *J* = 7.0 Hz, 3H, CH(C$\underline{H}_3$)), 2.05 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1H, one of C$\underline{H}_A$H$_B$CH(CH$_3$)), 2.22 - 2.37 (m, 2H, two of C$\underline{H}_A\underline{H}_B$CH(CH$_3$)), 2.46 - 2.55 (m, 1H, C$\underline{H}$(CH$_3$)), 2.59 - 2.64 (m, 1H, one of CH$_A\underline{H}_B$CH(CH$_3$)), 2.66 - 2.73 (m, 1H, C$\underline{H}$(CH$_3$)), 3.67 (s, 3H, OC$\underline{H}_3$), 3.71 (s, 3H, OC$\underline{H}_3$), 3.91 (dd, *J* = 6.5, 9.0 Hz, 1H, ArC$\underline{H}$CH$_A$H$_B$), 3.93 (dd, *J* = 6.5, 9.0 Hz, 1H, ArC$\underline{H}$CH$_A$H$_B$), 7.04 - 7.08 (m, 4H, Ar$\underline{H}$), 7.20 - 7.26 (m, 2H, Ar$\underline{H}$), 7.35 - 7.40 (m, 4H,

[xlix] NMR data is given for the racemic compound synthesised using 10 mol% BEMP as catalyst in 1.1:1dr.

ArH), 7.49 - 7.53 (m, 4H, ArH), 8.16 - 8.22 (m, 4H, ArH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 17.4 (CH(CH$_3$)), 17.5 (CH(CH$_3$)), 36.6 (CHCH$_2$CH(CH$_3$)), 36.9 (CHCH$_2$CH(CH$_3$)), 37.1 (CH(CH$_3$)), 37.6 (CH(CH$_3$)), 48.9 (ArCHCH$_2$), 49.0 (ArCHCH$_2$), 52.4 (OCH$_3$), 52.4 (OCH$_3$), 121.2 (ArCH), 121.2 (ArCH), 123.9 (ArCH), 123.9 (ArCH), 125.8 (ArCH), 125.8 (ArCH), 128.8 (ArCH), 129.0 (ArCH), 129.3 (ArCH), 129.4 (ArCH), 145.4 (ArC), 145.6 (ArC), 147.2 (ArC), 147.3 (ArC), 150.4 (ArC), 150.4 (ArC), 172.6 (C=O), 172.6 (C=O), 173.8 (C=O), 174.0 (C=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{19}NNaO_6$) requires *m/z* 380.1101, found *m/z* 380.1104.

8.6.2.10 Synthesis and characterisation of 376 and 377

Methyl 2-methyl-4-nitrobutanoate **376** and dimethyl 2,6-dimethyl-4-nitroheptanedioate **377**



To a solution of methyl methacrylate (0.021 mL, 0.20 mmol, 1.0 eq) in nitromethane (0.11 mL, 2.0 mmol, 10 eq) was added catalyst **147** at room temperature and stirring maintained for 6 h. Purification by flash column chromatography [Petroleum ether to petroleum ether/Et_2O 3/2] eluted **376** as a colourless oil in 38% yield (12 mgs) and 33% ee [determined by HPLC, chiralpak AS, hexane/isopropanol = 90/10, 1 mL/min, λ = 230.8 nm, t (major) = 10.40 min, t (minor) = 15.56 min] then **377** as a colourless oil in 15% yield (8 mgs) as 1:1 mixture of diastereomers.

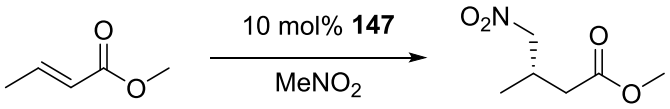
Characterisation data for **376**: **$[\alpha]_D^{24}$** = +6.8 (c = 0.56, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.24 (d, *J* = 7.0 Hz, 3 H, CH(CH$_3$)C=O), 2.15 (dtd, *J* = 14.5, 7.5, 5.5 Hz, 1 H, CH$_A$H$_B$CH(CH$_3$)), 2.25 - 2.40 (m, 1 H, CH$_A$H$_B$CH(CH$_3$)), 2.59 (dqd, *J* = 9.0, 7.0, 5.5 Hz, 1 H, CH(CH$_3$)C=O), 3.70 (s, 3 H, OCH$_3$), 4.43 (dt, *J* =13.5, 7.0 Hz, 1 H, CH$_A$H$_B$NO$_2$),

4.47 (dt, *J* = 13.5, 7.0 Hz, 1 H, $CH_A\underline{H_B}NO_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 17.2 ($CH(\underline{C}H_3)$), 30.5 ($\underline{C}H(CH_3)$), 36.4 ($\underline{C}H_2CH(CH_3)$), 52.0 ($O\underline{C}H_3$), 73.4 ($O_2N\underline{C}H_2CH_2$), 175.3 ($\underline{C}$=O). Data is consistent with that given in the literature.[268]

Characterisation data for **377**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.21 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H_3})$), 1.24 (d, *J* = 7.0 Hz, 3 H, $CH(C\underline{H_3})$), 1.75 - 1.89 (m, 1 H, $C\underline{H_A}H_B$), 1.96 - 2.15 (m, 2 H, $C\underline{H_A}\underline{H_B}$), 2.38 - 2.52 (m, 3 H, $C\underline{H}(CH_3)$, $C\underline{H}(CH_3)$ and of $CH_A\underline{H_B}$), 3.69 (s, 3 H, $OC\underline{H_3}$), 3.71 (s, 3 H, $OC\underline{H_3}$), 4.59 - 4.70 (m, 1 H, $C\underline{H}NO_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 17.8, 18.1 ($CH(\underline{C}H_3)$), 36.2, 37.3, 37.4 ($CH\underline{C}H_2CH(CH_3)$), 52.0, 52.0 ($O\underline{C}H_3$), 84.7 ($\underline{C}HNO_2$), 176.7 ($\underline{C}$=O). Data is consistent with that given in the literature.[268]

8.6.2.11 Synthesis and characterisation of 378a

(*S*)-Methyl 3-methyl-4-nitrobutanoate **378a**



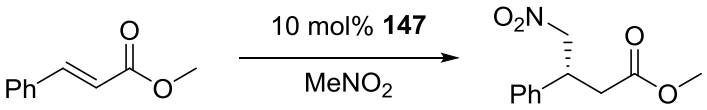
To a solution of methyl crotonate (0.021 mL, 0.20 mmol, 1.0 eq) in nitromethane (0.11 mL, 2.0 mmol, 10 eq) at room temperature was added catalyst **147** (15 mg, 0.020 mmol, 0.10 eq). Stirring was maintained for 96 h and the crude reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography [Petrol: Et_2O 9:1] to afford the title compound **378a** as a colourless oil in 69% yield (22 mg). The ee was determined by HPLC analysis (Chiralpak AS-H, hexane/*iso*-propanol 95:5, λ 220 nm, 1.0 mL/min): t (minor) = 17.76 min, t (major) = 20.74 min (60%).

$[\alpha]_D^{24}$ = + 11.3 (c = 0.30, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.09 (d, *J* = 7.0 Hz, 3 H, $C\underline{H_3}CH$), 2.36 (dd, *J* = 16.0, 6.5 Hz, 2 H, $CHC\underline{H_A}H_BC(=O)$), 2.45 (dd, *J* = 16.0, 7.0 Hz, 2 H, $CHCH_A\underline{H_B}C(=O)$), 2.70 - 2.86 (m, 1 H, $CH_3C\underline{H}CH_AH_B$), 3.69 (s, 3 H, $OC\underline{H_3}$), 4.34 (dd, *J* = 12.0, 7.0 Hz, 1 H, $C\underline{H_A}H_BNO_2$), 4.47 (dd, *J* = 12.0, 6.5 Hz, 1 H, $CH_A\underline{H_B}NO_2$);

^{13}C NMR (50 MHz, $CDCl_3$) δ ppm 17.3 ($\underline{C}H_3CH$), 29.4 ($CH_3\underline{C}HCH_AH_BC(=O)$), 37.6 ($CH_3CH\underline{C}H_AH_BC(=O)$), 51.8 ($O\underline{C}H_3$), 80.1 ($\underline{C}H_AH_BNO_2$), 171.7 ($\underline{C}$=O). Data is consistent with that given in the literature.[268]

8.6.2.12 Synthesis and characterisation of 378b

(*R*)-Methyl 4-nitro-3-phenylbutanoate **378b**

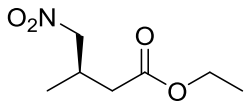


To a solution of methyl cinnamate (32 mg, 0.0.20 mmol, 1.0 eq) in nitromethane (0.110 mL, 2.0 mmol, 10 eq) at room temperature was added catalyst **147** (15 mg, 0.020 mmol, 0.10 eq). Stirring was maintained for 96 h and the crude reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography [Petrol: Et_2O 9:1] to afford the title compound **378b** as a colourless oil in 42% yield (18 mg). The ee was determined by HPLC analysis (Chiralpak AS-H, hexane/*iso*-propanol 95:5, λ 220 nm, 1.0 mL/min): t (minor) = 28.91 min, t (major) = 34.46 min (63%).

$[\alpha]_D^{24}$ = + 27.6 (c = 0.24, $CHCl_3$) [lit. -13.3, c = 0.21, $CHCl_3$ for (*S*)-**378b**][213]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 2.80 (d, *J* = 7.5 Hz, 2 H, $CHC\underline{H}_2$), 3.65 (s, 3 H, $OC\underline{H}_3$), 4.01 ('quin', *J* = 7.5 Hz, 1 H, $C\underline{H}CH_2$), 4.66 (dd, *J* = 12.5, 7.5 Hz, 1 H, $C\underline{H}_AH_BNO_2$), 4.76 (dd, *J* = 12.5, 7.5 Hz, 1 H, $CH_A\underline{H}_BNO_2$), 7.20 - 7.43 (m, 5 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 37.6 ($CH\underline{C}H_2$), 40.3 ($\underline{C}HCH_2$), 52.1 ($O\underline{C}H_3$), 79.5 ($\underline{C}H_AH_BNO_2$), 127.4 (Ar$\underline{C}$H), 128.2 (Ar$\underline{C}$H), 129.2 (Ar$\underline{C}$H), 138.4 (Ar$\underline{C}$), 171.2 ($\underline{C}$=O). Data is consistent with that given in the literature.[346]

8.6.2.13 Synthesis and characterisation of 378c

Ethyl (3*R*)-3-methyl-4-nitrobutanoate **378c**

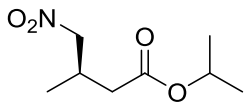


Synthesised according to General Procedure **XI** from ethyl crotonate (25 μL, 0.20 mmol, 1.0 eq) to afford the title compound **378c** as a colourless oil in 69% yield (24 mg) and 73% ee [determined by HPLC, Chiralpak AS-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 11.79 min, t (minor) = 14.13 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.10 (d, *J* = 7.0 Hz, 3 H, $C\underline{H_3}CH$), 1.26 (t, *J* = 7.0 Hz, 3 H, $OCH_2C\underline{H_3}$), 2.34 (dd, *J* = 16.0, 7.0 Hz, 1 H, $CHC\underline{H_A}H_BC(=O)$), 2.43 (dd, *J* = 16.0, 6.5 Hz, 1 H, $CHCH_A\underline{H_B}C(=O)$), 2.78 ('octet', *J* = 7.0 Hz, 1 H, $CH_3C\underline{H}CH_AH_B$), 4.15 (q, *J* = 7.0 Hz, 2 H, $OC\underline{H_2}CH_3$), 4.33 (dd, *J* = 12.0, 7.0 Hz, 1 H, $C\underline{H_A}H_BNO_2$), 4.47 (dd, *J* = 12.0, 6.5 Hz, 1 H, $CH_A\underline{H_B}NO_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 14.3 ($OCH_2\underline{C}H_3$), 17.4 ($\underline{C}H_3CH$), 29.6 ($CH_3\underline{C}HCH_AH_BC(=O)$), 38.1 ($CH_3CH\underline{C}H_AH_BC(=O)$), 60.9 ($O\underline{C}H_2CH_3$), 80.4 ($\underline{C}H_AH_BNO_2$), 171.3 ($\underline{C}$=O). Data is consistent with that given in the literature.[347]

8.6.2.14 Synthesis and characterisation of 378d

Propan-2-yl (3*R*)-3-methyl-4-nitrobutanoate **378d**



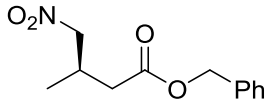
Synthesised according to General Procedure **XI** from isopropyl crotonate (25.6 mg, 0.20 mmol, 1.0 eq) to afford the title compound **378d** as a colourless oil in 45% yield (17 mg) and 56% ee [determined by HPLC, Chiralpak AS-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 8.79 min, t (minor) = 9.61 min].

IR ν_{max}/cm^{-1} 3272, 2982, 1725, 1550, 1375, 1180, 1106; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.09 (d, *J* = 7.0 Hz, 3 H, $C\underline{H_3}CH$), 1.23 (d, *J* = 6.5 Hz, 6 H, $OCH(C\underline{H_3})_2$), 2.30 (dd, *J* = 16.0, 7.0 Hz, 1 H, $CHC\underline{H_A}H_BC(=O)$), 2.39 (dd, *J* = 16.0, 6.5 Hz, 1 H, $CHCH_A\underline{H_B}C(=O)$),

2.77 (‘octet’, *J* = 7.0 Hz, 1 H, $CH_3C\underline{H}CH_AH_B$), 4.32 (dd, *J* = 12.0, 7.0 Hz, 1 H, $C\underline{H_A}H_BNO_2$), 4.46 (dd, *J* = 12.0, 6.5 Hz, 1 H, $CH_A\underline{H_B}NO_2$), 5.02 (spt, *J* = 6.5 Hz, 1 H, $OC\underline{H}(CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 17.4 ($\underline{C}H_3CH$), 21.9, 21.9 ($OCH(\underline{C}H_3)_2$), 29.7 ($CH_3\underline{C}HCH_AH_BC(=O)$), 38.4 ($CH_3CH\underline{C}H_AH_BC(=O)$), 68.4 ($O\underline{C}H(CH_3)_2$), 80.4 ($\underline{C}H_AH_BNO_2$), 170.8 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_8H_{15}NNaO_4$) requires *m/z* 212.0893, found *m/z* 212.0893.

8.6.2.15 Synthesis and characterisation of 378e

Benzyl (3*R*)-3-methyl-4-nitrobutanoate **378e**



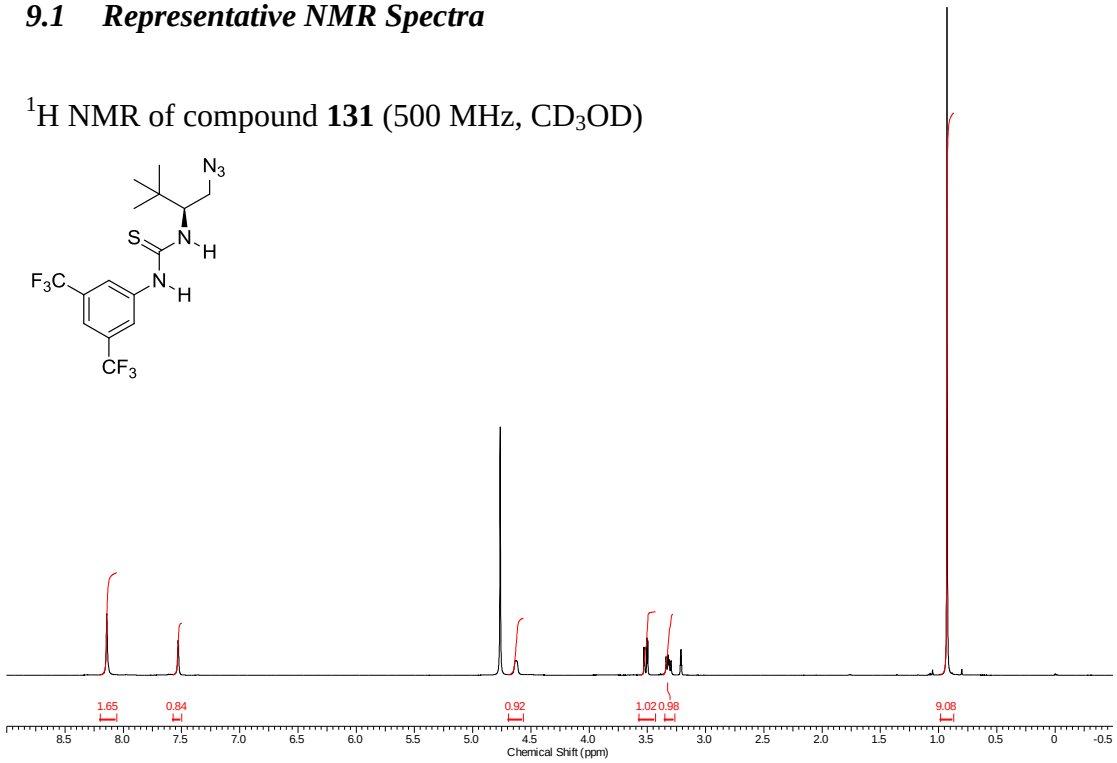
Synthesised according to General Procedure **XI** from benzyl crotonate (35 mg, 0.20 mmol, 1.0 eq) to afford the title compound **378e** as a colourless oil in 89% yield (42 mg) and 69% ee [determined by HPLC, Chiralpak IA, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 17.17 min, t (major) = 18.20 min].

$[\alpha]_D^{24}$ = + 11.4 (c = 0.7, $CHCl_3$); **IR** ν_{max}/cm^{-1} 2970, 1733, 1550, 1456, 1219, 1171, 773, 698; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 1.10 (d, *J* = 7.0 Hz, 3 H, $C\underline{H_3}CH$), 2.41 (dd, *J* = 16.0, 7.0 Hz, 1 H, $CHC\underline{H_A}H_BC(=O)$), 2.50 (dd, *J* = 16.0, 6.5 Hz, 1 H, $CHCH_A\underline{H_B}C(=O)$), 2.80 (‘octet’, *J* = 7.0 Hz, 1 H, $CH_3C\underline{H}CH_AH_B$), 4.33 (dd, *J* = 12.0, 7.0 Hz, 1 H, $C\underline{H_A}H_BNO_2$), 4.46 (dd, *J* = 12.0, 6.5 Hz, 1 H, $CH_A\underline{H_B}NO_2$), 5.14 (s, 2 H, $OC\underline{H_2}Ar$), 7.29 - 7.45 (m, 5 H, Ar$\underline{H}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 17.4 ($\underline{C}H_3CH$), 29.6 ($CH_3\underline{C}HCH_AH_BC(=O)$), 38.0 ($CH_3CH\underline{C}H_AH_BC(=O)$), 66.7 ($O\underline{C}H_2Ar$), 80.3 ($\underline{C}H_AH_BNO_2$), 128.4 (Ar$\underline{C}$H), 128.6 (Ar$\underline{C}$H), 128.8 (Ar$\underline{C}$H), 135.7 (Ar$\underline{C}$), 171.2 ($\underline{C}$=O); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{15}NNaO_4$) requires *m/z* 260.0893, found *m/z* 260.0893.

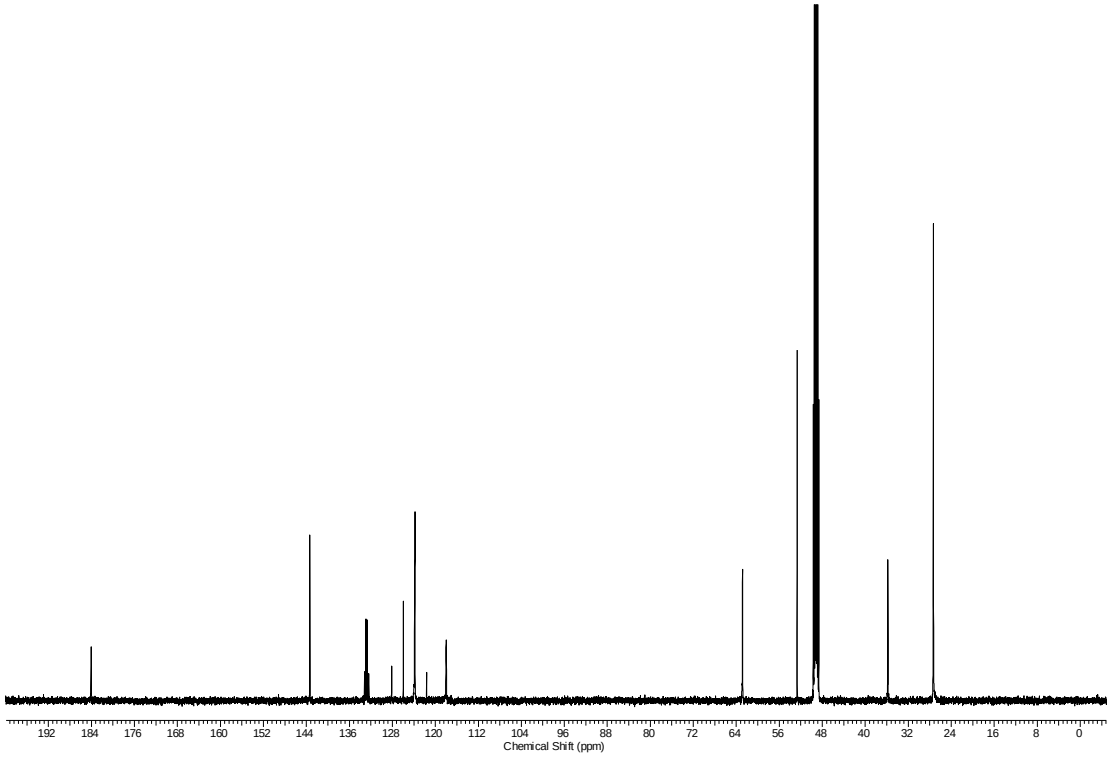
9 Appendices

9.1 Representative NMR Spectra

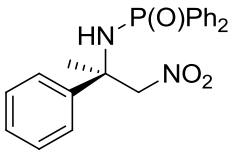
^{1}H NMR of compound **131** (500 MHz, CD_3OD)

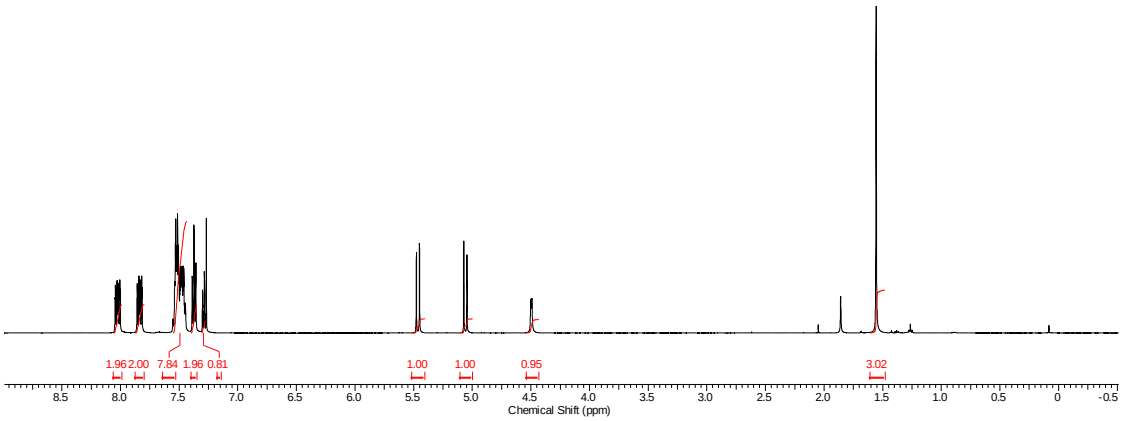


^{13}C NMR of compound **131** (125 MHz, CD_3OD)

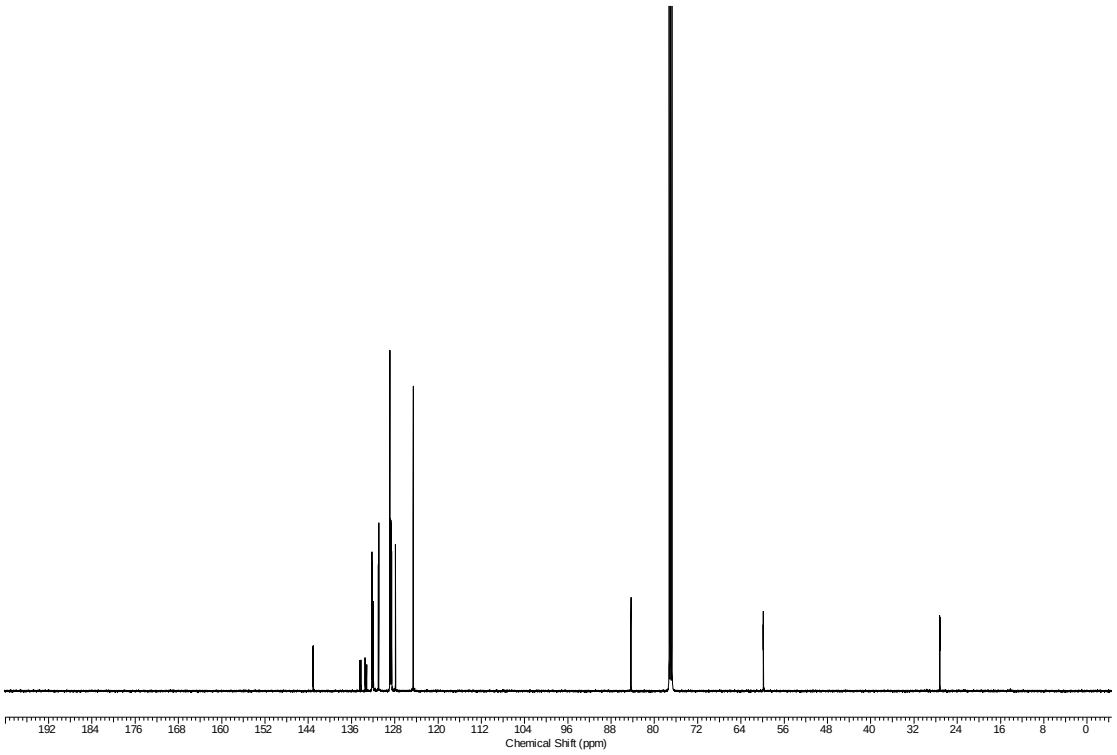


^{1}H NMR of compound **152a** (400 MHz, $CDCl_3$)

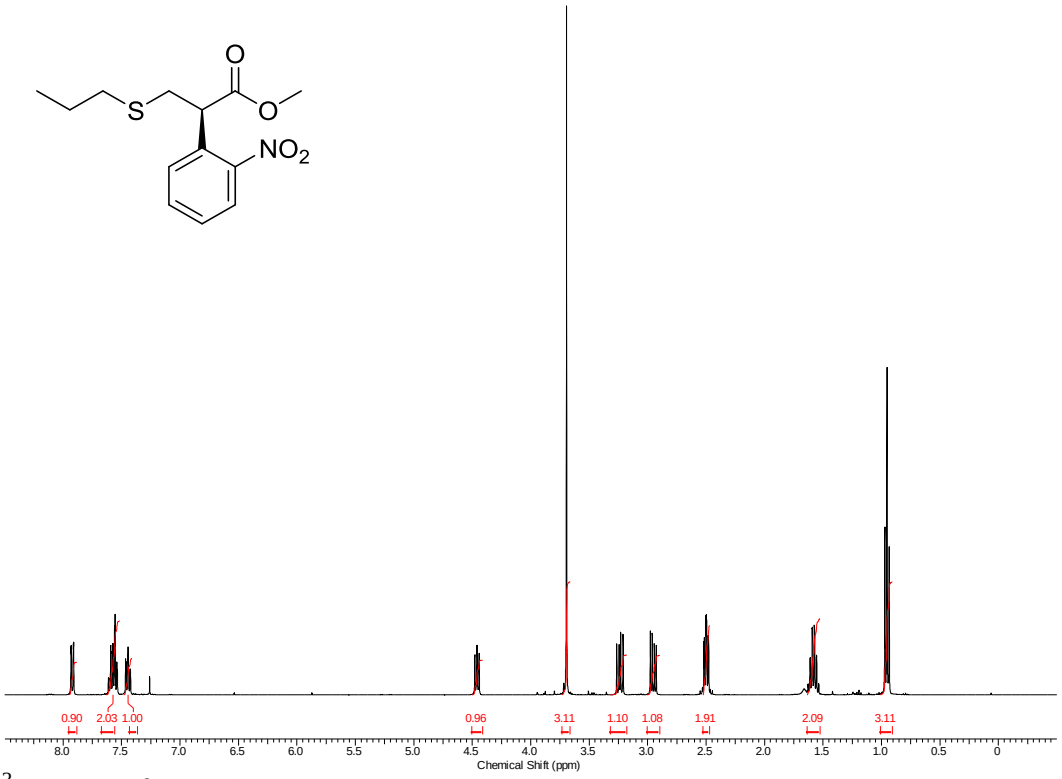




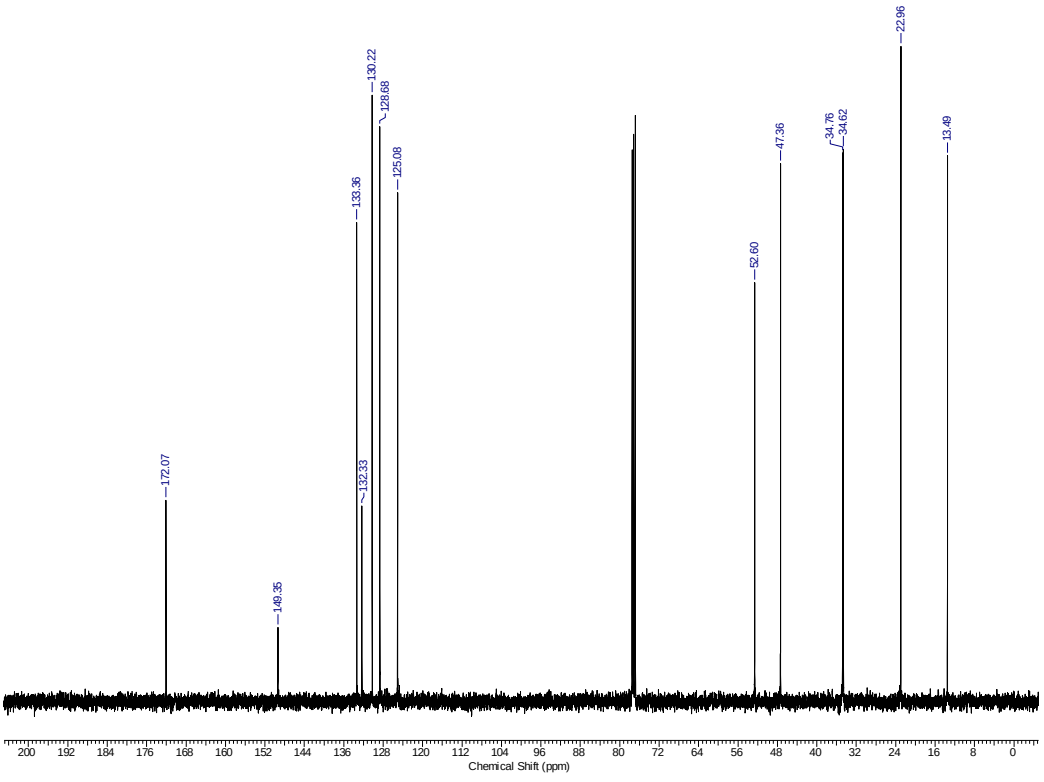
^{13}C NMR of compound **152a** (100 MHz, $CDCl_3$)



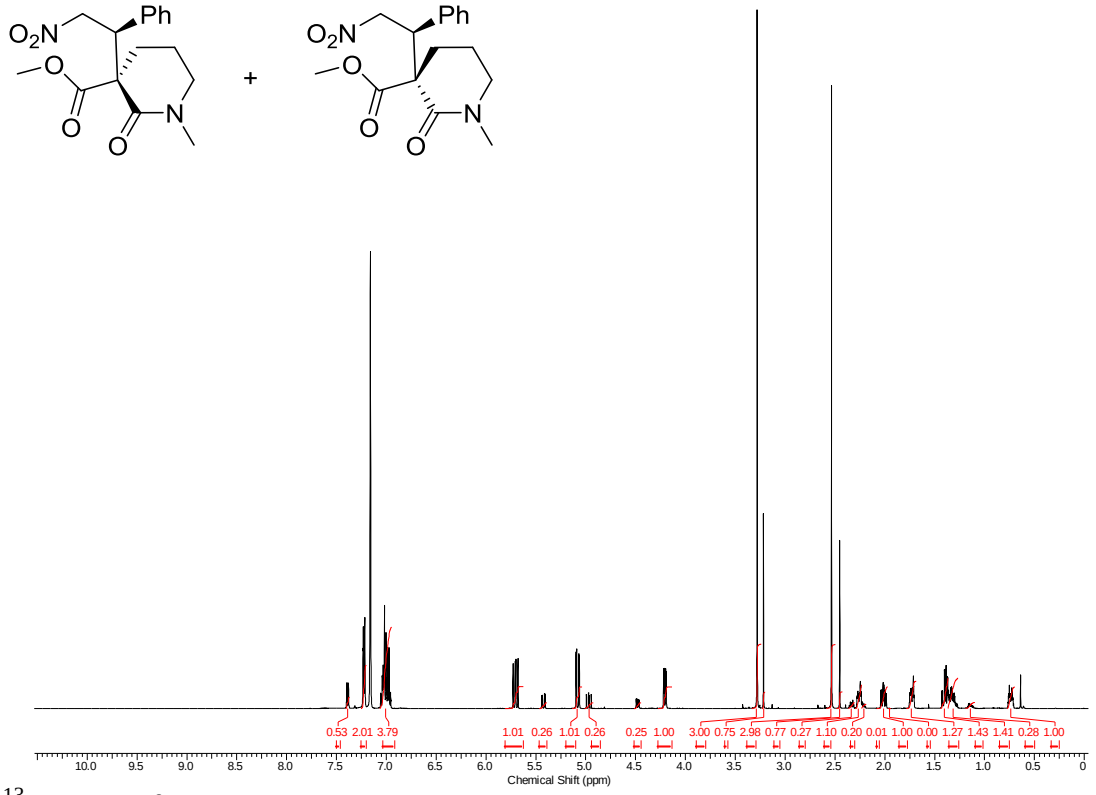
^{1}H NMR of **288ad** (400 MHz, $CDCl_3$)



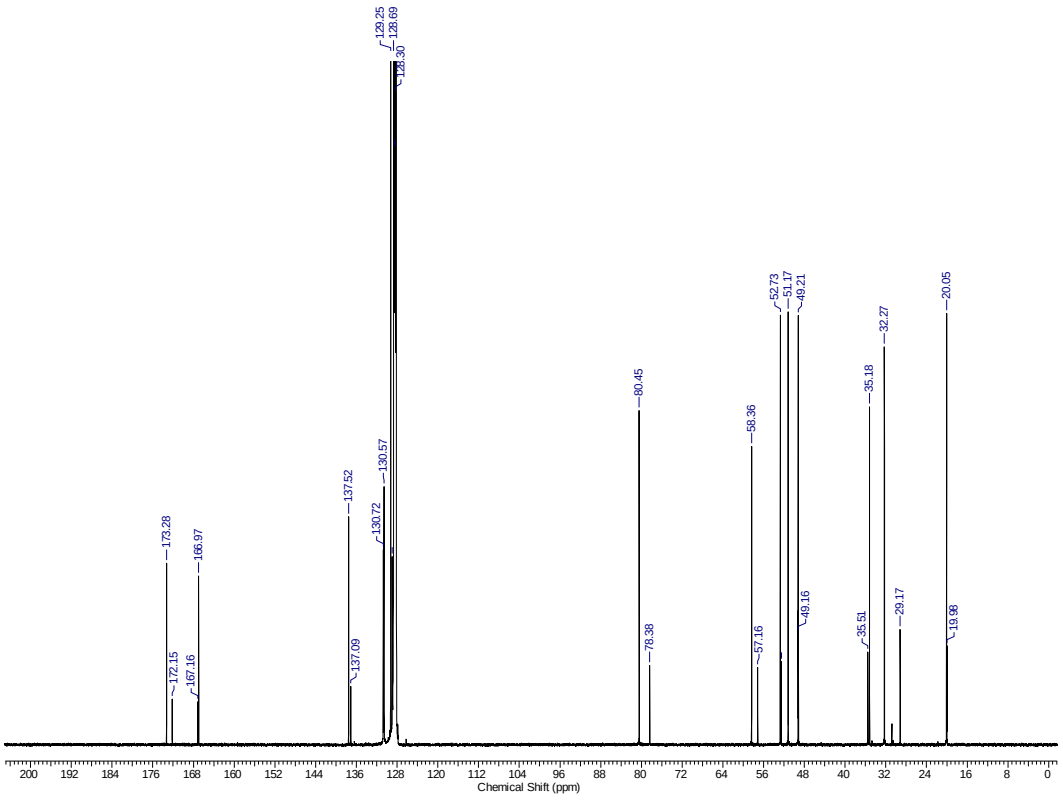
^{13}C NMR of **288ad** (100 MHz, $CDCl_3$)



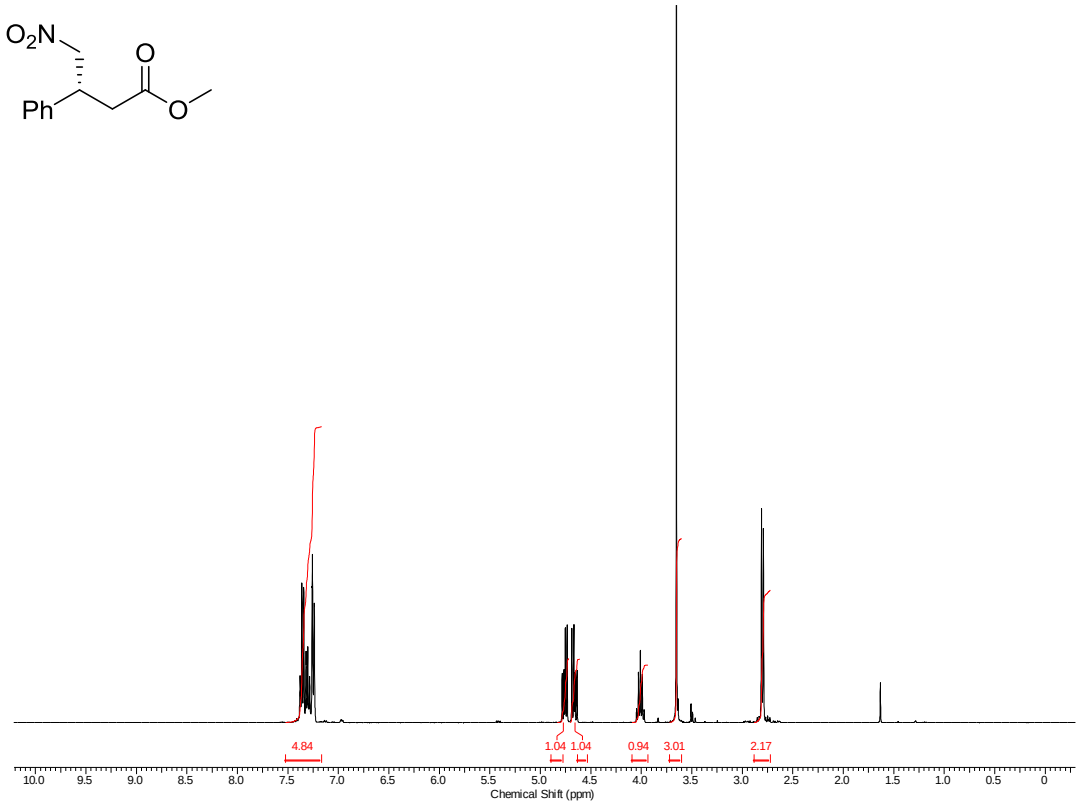
^{1}H NMR of **343** (500 MHz, C_6D_6)



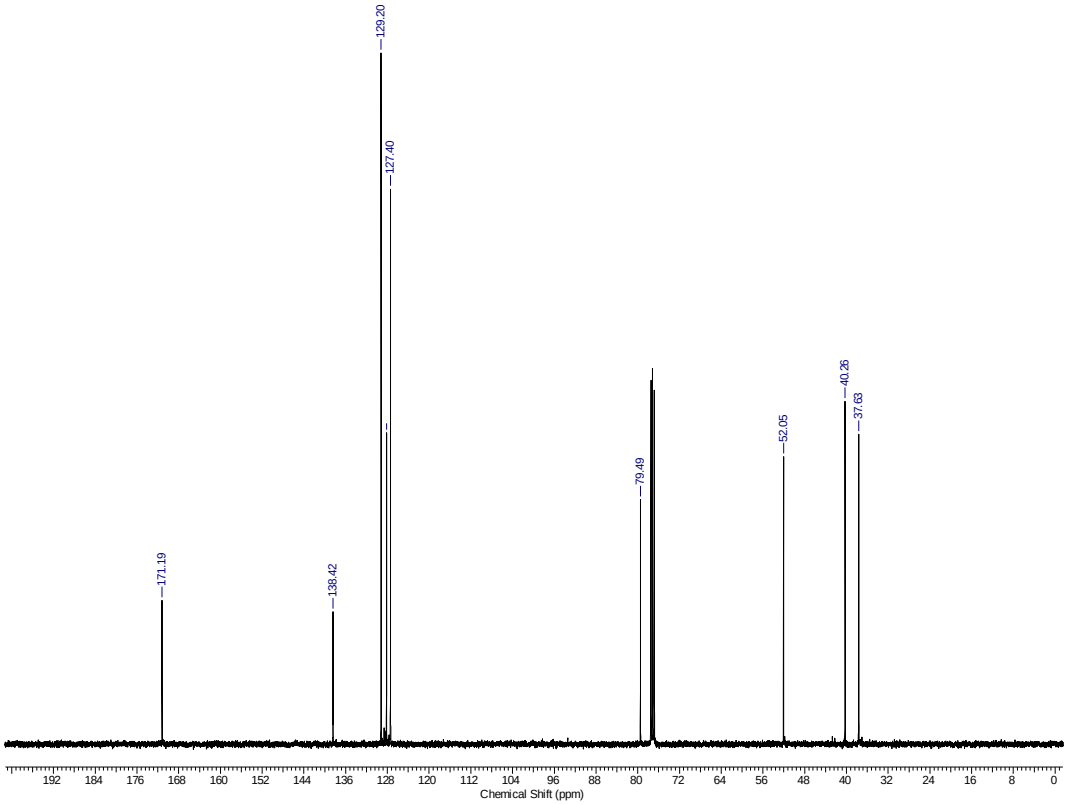
^{13}C NMR of **343** (125 MHz, C_6D_6)



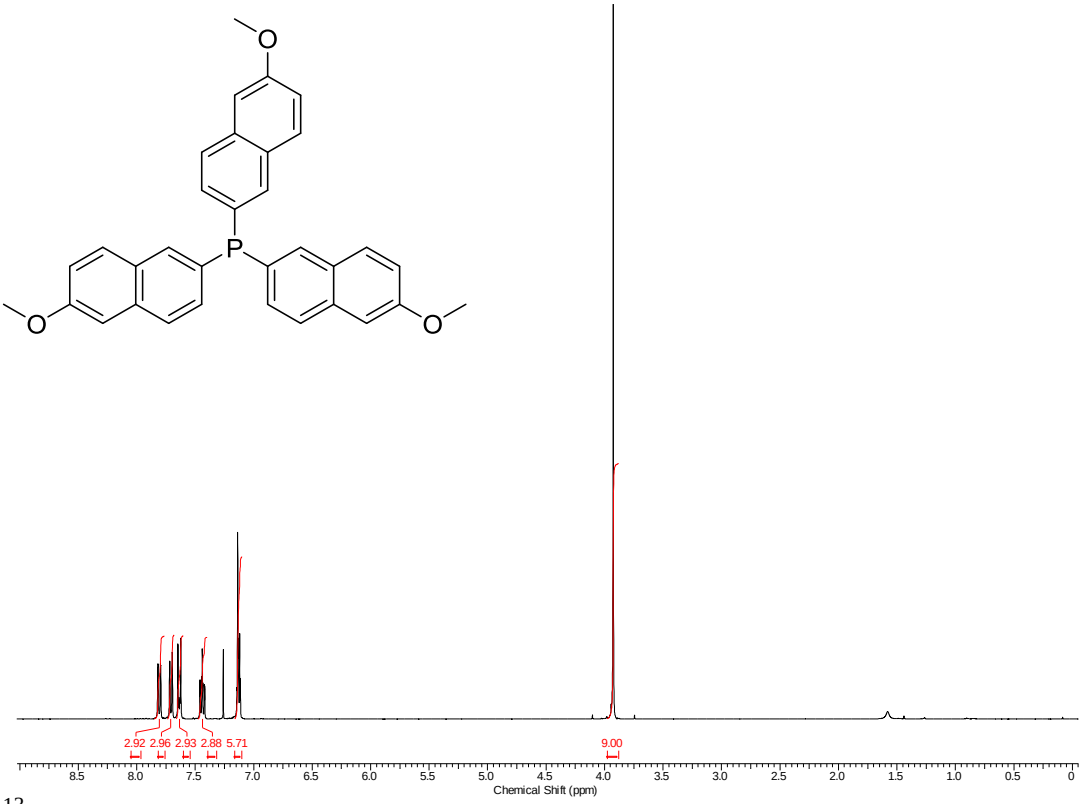
^{1}H NMR of **378b** (400 MHz, $CDCl_3$)



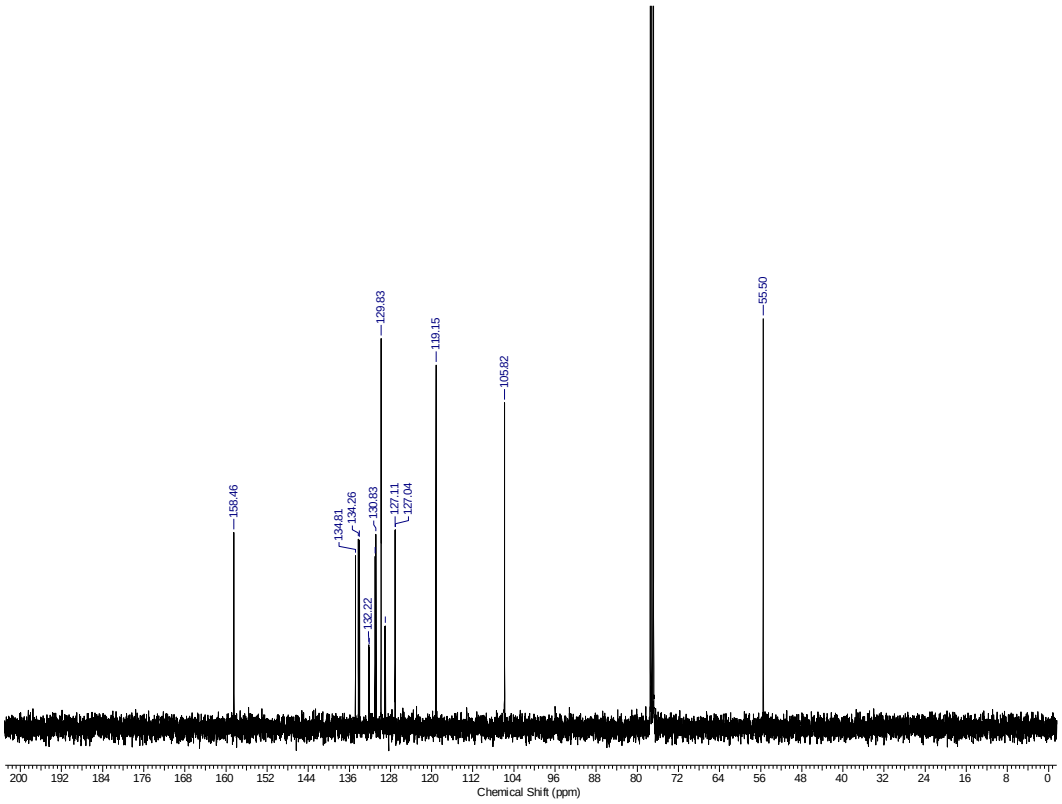
^{13}C NMR of **378b** (100 MHz, $CDCl_3$)



^{1}H NMR of **443** (400 MHz, $CDCl_3$)



^{13}C NMR of **443** (100 MHz, $CDCl_3$)



9.2 ^{1}H NMR Kinetic Experiment Data

9.2.1 Ketimine nitro-Mannich reaction (Figure 26)

Catalyst **147**

Expt Number	Time (minutes)	product $CH_AH_BNO_2$	CH_3 mesitylene	CH_3 starter	Internal standard conversion (%)	Conversion SM vs pdt (%)
0	0	0.00	0.00	1.00	0.00	**0.00**
1	9	1.00	28.75	6.79	31.30	**30.64**
2	19	1.00	16.47	3.08	54.64	**49.34**
3	29	1.00	13.69	2.06	65.74	**59.29**
4	39	1.00	12.37	1.56	72.76	**65.79**
5	49	1.00	11.28	1.24	79.79	**70.75**
6	59	1.00	10.82	1.06	83.18	**73.89**
7	69	1.00	10.19	0.89	88.32	**77.12**
8	79	1.00	10.19	0.82	88.32	**78.53**
9	89	1.00	10.43	0.78	86.29	**79.37**
10	99	1.00	9.76	0.69	92.21	**81.30**
11	109	1.00	10.35	0.67	86.96	**81.74**
12	119	1.00	9.81	0.63	91.74	**82.64**
13	129	1.00	9.66	0.59	93.17	**83.57**
14	139	1.00	9.56	0.57	94.14	**84.03**
15	149	1.00	9.39	0.55	95.85	**84.51**
16	159	1.00	9.79	0.54	91.93	**84.75**
17	169	1.00	9.26	0.53	97.19	**84.99**
18	179	1.00	9.26	0.51	97.19	**85.47**
19	189	1.00	9.27	0.52	97.09	**85.23**
20	199	1.00	9.21	0.48	97.72	**86.21**
21	209	1.00	9.28	0.50	96.98	**85.71**
22	219	1.00	9.24	0.51	97.40	**85.47**
23	229	1.00	9.19	0.48	97.93	**86.21**
24	239	1.00	9.13	0.50	98.58	**85.71**
25	249	1.00	9.11	0.47	98.79	**86.46**
26	259	1.00	9.14	0.48	98.47	**86.21**
27	269	1.00	9.13	0.48	98.58	**86.21**
28	279	1.00	8.98	0.49	100.22	**85.96**
29	289	1.00	9.42	0.49	95.54	**85.96**
30	299	1.00	9.03	0.48	99.67	**86.21**
31	309	1.00	8.87	0.45	101.47	**86.96**
32	319	1.00	8.85	0.44	101.69	**87.21**
33	329	1.00	8.85	0.44	101.69	**87.21**
34	339	1.00	8.86	0.44	101.58	**87.21**
35	349	1.00	8.9	0.46	101.12	**86.71**
36	359	1.00	8.83	0.46	101.93	**86.71**
37	369	1.00	9.36	0.46	96.15	**86.71**
38	379	1.00	8.92	0.45	100.90	**86.96**
39	389	1.00	8.94	0.44	100.67	**87.21**
40	399	1.00	8.8	0.46	102.27	**86.71**
41	409	1.00	8.8	0.45	102.27	**86.96**
42	419	1.00	8.94	0.47	100.67	**86.46**
43	429	1.00	8.79	0.45	102.39	**86.96**
44	439	1.00	8.81	0.46	102.16	**86.71**
45	449	1.00	8.92	0.46	100.90	**86.71**
46	459	1.00	8.97	0.47	100.33	**86.46**
47	469	1.00	9.11	0.46	98.79	**86.71**
48	479	1.00	8.99	0.47	100.11	**86.46**
49	489	1.00	9.35	0.45	96.26	**86.96**
50	499	1.00	9.09	0.46	99.01	**86.71**

Catalyst **145**

Expt Number	Time (minutes)	product $CH_AH_BNO_2$	CH_3 mesitylene	CH_3 starter	Internal standard conversion (%)	Conversion SM vs pdt (%)
0	0	0.00	0.00	1.00	0.00	**0.00**
1	9	1.00	41.66	11.59	21.60	**20.56**
2	19	1.00	22.63	4.98	39.77	**37.59**
3	29	1.00	17.88	3.31	50.34	**47.54**
4	39	1.00	15.12	2.37	59.52	**55.87**
5	49	1.00	13.44	1.85	66.96	**61.86**
6	59	1.00	12.76	1.55	70.53	**65.93**
7	69	1.00	12.16	1.30	74.01	**69.77**
8	79	1.00	11.89	1.17	75.69	**71.94**
9	89	1.00	11.13	1.00	80.86	**75.00**
10	99	1.00	10.99	0.92	81.89	**76.53**
11	109	1.00	10.62	0.81	84.75	**78.74**
12	119	1.00	10.47	0.76	85.96	**79.79**
13	129	1.00	10.39	0.71	86.62	**80.86**
14	139	1.00	10.30	0.67	87.38	**81.74**
15	149	1.00	10.10	0.63	89.11	**82.64**
16	159	1.00	10.07	0.60	89.37	**83.33**
17	169	1.00	10.05	0.58	89.55	**83.80**
18	179	1.00	9.96	0.55	90.36	**84.51**
19	189	1.00	10.01	0.55	89.91	**84.51**
20	199	1.00	9.93	0.54	90.63	**84.75**
21	209	1.00	9.85	0.51	91.37	**85.47**
22	219	1.00	9.71	0.49	92.69	**85.96**
23	229	1.00	9.71	0.49	92.69	**85.96**
24	239	1.00	9.66	0.48	93.17	**86.21**
25	249	1.00	9.76	0.48	92.21	**86.21**
26	259	1.00	9.83	0.48	91.56	**86.21**
27	269	1.00	9.56	0.46	94.14	**86.71**
28	279	1.00	9.58	0.47	93.95	**86.46**
29	289	1.00	9.49	0.46	94.84	**86.71**
30	299	1.00	9.52	0.46	94.54	**86.71**
31	309	1.00	9.55	0.45	94.24	**86.96**
32	319	1.00	9.55	0.45	94.24	**86.96**
33	329	1.00	9.57	0.45	94.04	**86.96**
34	339	1.00	9.55	0.44	94.24	**87.21**
35	349	1.00	9.63	0.45	93.46	**86.96**
36	359	1.00	9.64	0.44	93.36	**87.21**
37	369	1.00	9.66	0.44	93.17	**87.21**
38	379	1.00	9.55	0.43	94.24	**87.46**
39	389	1.00	9.64	0.44	93.36	**87.21**
40	399	1.00	9.49	0.45	94.84	**86.96**
41	409	1.00	9.49	0.43	94.84	**87.46**
42	419	1.00	9.47	0.43	95.04	**87.46**
43	429	1.00	9.35	0.42	96.26	**87.72**
44	439	1.00	9.46	0.42	95.14	**87.72**
45	449	1.00	9.38	0.44	95.95	**87.21**
46	459	1.00	9.64	0.43	93.36	**87.46**
47	469	1.00	9.62	0.44	93.56	**87.21**
48	479	1.00	9.58	0.44	93.95	**87.21**
49	489	1.00	9.61	0.43	93.65	**87.46**
50	499	1.00	9.60	0.41	93.75	**87.98**

Catalyst **229**

Expt Number	Time (minutes)	Conversion SM vs pdt (%)
0	0	**0.00**
1	9	**1.70**
2	19	**4.20**
3	29	**6.40**
4	39	**8.48**
5	49	**10.98**
6	59	**13.11**
7	69	**15.31**
8	79	**17.31**
9	89	**19.93**
10	99	**22.79**
11	109	**24.61**
12	119	**26.24**
13	129	**27.78**
14	139	**29.27**
15	149	**30.55**
16	159	**32.08**
17	169	**33.36**
18	179	**34.90**
19	189	**36.05**
20	199	**37.27**
21	209	**38.34**
22	219	**39.16**
23	229	**40.06**
24	239	**40.87**
25	249	**41.60**
26	259	**42.48**
27	269	**43.20**
28	279	**44.00**
29	289	**44.76**
30	299	**45.63**
31	309	**46.36**
32	319	**47.17**
33	329	**47.78**
34	339	**48.70**
35	349	**49.53**
36	359	**50.25**
37	369	**51.08**
38	379	**51.56**
39	389	**52.17**
40	399	**53.01**
41	409	**53.61**
42	419	**54.01**
43	429	**54.90**
44	439	**55.55**
45	449	**55.92**
46	459	**56.61**
47	469	**57.14**
48	479	**57.80**
49	489	**58.50**
50	499	**59.19**

Catalyst **53**

Time (minutes)	Conversion SM vs pdt (%)
0	**0.00**
600	**0.00**

9.2.2 Ketimine nitro-Mannich reaction (Figure 27)

Catalyst **207**

Expt Number	Time (minutes)	product $CH_AH_BNO_2$	CH_3 mesitylene	CH_3 starter	Internal standard conversion (%)	Conversion SM vs pdt (%)
0	0	0.00	0.00	1.00	0.00	**0.00**
1	15	1.00	671.25	197.24	1.34	**1.50**
2	35	1.00	63.6	15.58	14.15	**16.15**
3	55	1.00	34.53	7.11	26.06	**29.67**
4	75	1.00	25.67	4.51	35.06	**39.95**
5	95	1.00	20.77	3.13	43.33	**48.94**
6	115	1.00	18.35	2.4	49.05	**55.56**
7	135	1.00	16.46	1.86	54.68	**61.73**
8	155	1.00	15.32	1.53	58.75	**66.23**
9	175	1.00	14.17	1.25	63.51	**70.59**
10	195	1.00	13.34	1.06	67.47	**73.89**
11	215	1.00	12.76	0.91	70.53	**76.73**
12	235	1.00	12.68	0.82	70.98	**78.53**
13	255	1.00	12.3	0.72	73.17	**80.65**
14	275	1.00	12.26	0.73	73.41	**80.43**
15	295	1.00	11.92	0.68	75.50	**81.52**
16	315	1.00	11.8	0.63	76.27	**82.64**
17	335	1.00	11.57	0.57	77.79	**84.03**
18	355	1.00	11.3	0.53	79.65	**84.99**
19	375	1.00	11.24	0.49	80.07	**85.96**
20	395	1.00	11.17	0.45	80.57	**86.96**
21	415	1.00	11.03	0.42	81.60	**87.72**
22	435	1.00	10.97	0.41	82.04	**87.98**
23	455	1.00	10.83	0.39	83.10	**88.50**
24	475	1.00	10.92	0.39	82.42	**88.50**
25	495	1.00	10.76	0.36	83.64	**89.29**
26	515	1.00	10.79	0.41	83.41	**87.98**
27	535	1.00	10.6	0.38	84.91	**88.76**
28	555	1.00	10.64	0.36	84.59	**89.29**
29	575	1.00	10.61	0.32	84.83	**90.36**
30	595	1.00	10.67	0.32	84.35	**90.36**
31	615	1.00	10.57	0.31	85.15	**90.63**
32	635	1.00	10.63	0.31	84.67	**90.63**
33	655	1.00	10.56	0.3	85.23	**90.91**
34	675	1.00	10.64	0.3	84.59	**90.91**
35	695	1.00	10.51	0.31	85.63	**90.63**
36	715	1.00	10.57	0.32	85.15	**90.36**
37	735	1.00	10.51	0.32	85.63	**90.36**
38	755	1.00	10.61	0.32	84.83	**90.36**
39	775	1.00	10.57	0.31	85.15	**90.63**
40	795	1.00	10.56	0.31	85.23	**90.63**

Catalyst **148**

Expt Number	Time (minutes)	product $CH_AH_BNO_2$	CH_3 mesitylene	CH_3 starter	Internal standard conversion (%)	Conversion SM vs pdt (%)
0	0	0.00	0.00	1.00	0.00	**0.00**
1	9	1.00	37.93	9.98	23.73	**23.11**
2	19	1.00	20.24	3.97	44.47	**43.04**
3	29	1.00	16.15	2.53	55.73	**54.25**
4	39	1.00	14.02	1.81	64.19	**62.37**
5	49	1.00	12.93	1.41	69.61	**68.03**
6	59	1.00	12.27	1.12	73.35	**72.82**
7	69	1.00	11.87	0.94	75.82	**76.14**
8	79	1.00	11.14	0.78	80.79	**79.37**
9	89	1.00	11.07	0.70	81.30	**81.08**
10	99	1.00	10.81	0.65	83.26	**82.19**
11	109	1.00	10.79	0.59	83.41	**83.57**
12	119	1.00	10.43	0.50	86.29	**85.71**
13	129	1.00	10.43	0.51	86.29	**85.47**
14	139	1.00	10.16	0.46	88.58	**86.71**
15	149	1.00	10.24	0.43	87.89	**87.46**
16	159	1.00	10.08	0.38	89.29	**88.76**
17	169	1.00	10.19	0.39	88.32	**88.50**
18	179	1.00	9.94	0.35	90.54	**89.55**
19	189	1.00	9.95	0.38	90.45	**88.76**
20	199	1.00	9.92	0.37	90.73	**89.02**
21	209	1.00	10.09	0.36	89.20	**89.29**
22	219	1.00	10.00	0.33	90.00	**90.09**
23	229	1.00	10.12	0.37	88.93	**89.02**
24	239	1.00	9.92	0.35	90.73	**89.55**
25	249	1.00	9.99	0.37	90.09	**89.02**
26	259	1.00	9.94	0.34	90.54	**89.82**
27	269	1.00	10.06	0.36	89.46	**89.29**
28	279	1.00	9.96	0.36	90.36	**89.29**
29	289	1.00	9.96	0.34	90.36	**89.82**
30	299	1.00	9.86	0.35	91.28	**89.55**
31	309	1.00	9.86	0.33	91.28	**90.09**
32	319	1.00	9.75	0.35	92.31	**89.55**
33	329	1.00	9.83	0.34	91.56	**89.82**
34	339	1.00	9.80	0.34	91.84	**89.82**
35	349	1.00	9.90	0.36	90.91	**89.29**
36	359	1.00	9.76	0.33	92.21	**90.09**
37	369	1.00	9.96	0.34	90.36	**89.82**
38	379	1.00	9.79	0.34	91.93	**89.82**
40	399	1.00	9.60	0.31	93.75	**90.63**
45	449	1.00	9.73	0.32	92.50	**90.36**
50	499	1.00	9.79	0.31	91.93	**90.63**

Catalyst **230**

Expt Number	Time (minutes)	product $CH_AH_BNO_2$	CH_3 mesitylene	CH_3 starter	Internal standard conversion (%)	Conversion SM vs pdt (%)
0	0	0.00	0.00	1.00	0.00	**0.00**
1	9	1.00	63.09	17.07	14.27	**14.95**
2	19	1.00	26.65	5.42	33.77	**35.63**
3	29	1.00	19.1	3.02	47.12	**49.83**
4	39	1.00	15.41	1.92	58.40	**60.98**
5	49	1.00	13.75	1.39	65.45	**68.34**
6	59	1.00	12.97	1.08	69.39	**73.53**
7	69	1.00	12.23	0.92	73.59	**76.53**
8	79	1.00	11.62	0.75	77.45	**80.00**
9	89	1.00	11.33	0.64	79.44	**82.42**
10	99	1.00	11.21	0.56	80.29	**84.27**
11	109	1.00	10.92	0.49	82.42	**85.96**
12	119	1.00	11.03	0.46	81.60	**86.71**
13	129	1.00	10.88	0.41	82.72	**87.98**
14	139	1.00	10.69	0.39	84.19	**88.50**
15	149	1.00	10.56	0.40	85.23	**88.24**
16	159	1.00	10.56	0.36	85.23	**89.29**
17	169	1.00	9.71	0.45	92.69	**86.96**
18	179	1.00	10.58	0.34	85.07	**89.82**
19	189	1.00	10.63	0.42	84.67	**87.72**
20	199	1.00	10.61	0.39	84.83	**88.50**
21	209	1.00	10.65	0.39	84.51	**88.50**
22	219	1.00	10.81	0.37	83.26	**89.02**
23	229	1.00	10.68	0.40	84.27	**88.24**
24	239	1.00	10.5	0.39	85.71	**88.50**
29	289	1.00	10.71	0.38	84.03	**88.76**
39	389	1.00	10.55	0.35	85.31	**89.55**
50	499	1.00	9.79	0.31	91.93	**90.63**

Catalyst **231**

Expt Number	Time (minutes)	product $CH_AH_BNO_2$	CH_3 mesitylene	CH_3 starter	Internal standard conversion (%)	Conversion SM vs pdt (%)
0	0	0.00	0.00	1.00	0.00	**0.00**
1	7	1.00	134.24	40.76	6.70	**6.86**
2	17	1.00	34.66	8.27	25.97	**26.62**
3	27	1.00	21.79	4.11	41.30	**42.19**
4	37	1.00	17.15	2.60	52.48	**53.57**
5	47	1.00	15.11	1.91	59.56	**61.10**
6	57	1.00	13.29	1.41	67.72	**68.03**
7	67	1.00	12.50	1.13	72.00	**72.64**
8	77	1.00	12.10	0.95	74.38	**75.95**
9	87	1.00	11.87	0.80	75.82	**78.95**
10	97	1.00	11.48	0.77	78.40	**79.58**
11	107	1.00	11.13	0.67	80.86	**81.74**
12	117	1.00	10.98	0.62	81.97	**82.87**
13	127	1.00	10.98	0.58	81.97	**83.80**
14	137	1.00	10.88	0.55	82.72	**84.51**
15	147	1.00	10.78	0.51	83.49	**85.47**
16	157	1.00	10.75	0.49	83.72	**85.96**
17	167	1.00	10.75	0.49	83.72	**85.96**
18	177	1.00	10.82	0.49	83.18	**85.96**
19	187	1.00	10.83	0.48	83.10	**86.21**
20	197	1.00	10.65	0.47	84.51	**86.46**
21	207	1.00	10.87	0.46	82.80	**86.71**
22	217	1.00	10.78	0.46	83.49	**86.71**
23	227	1.00	10.84	0.46	83.03	**86.71**
24	237	1.00	10.72	0.47	83.96	**86.46**
25	247	1.00	10.74	0.47	83.80	**86.46**
26	257	1.00	10.87	0.49	82.80	**85.96**
27	267	1.00	10.66	0.47	84.43	**86.46**
28	277	1.00	10.87	0.47	82.80	**86.46**
29	287	1.00	11.03	0.49	81.60	**85.96**
30	297	1.00	10.50	0.46	85.71	**86.71**
31	307	1.00	10.53	0.47	85.47	**86.46**
32	317	1.00	10.56	0.46	85.23	**86.71**
33	327	1.00	10.59	0.45	84.99	**86.96**
34	337	1.00	10.80	0.49	83.33	**85.96**
35	347	1.00	11.14	0.48	80.79	**86.21**

9.2.3 Sulfa-Michael Kinetic Isotope Effect Experiment (Figure 51)

Protonated Thiol Expt

NI=Not able to integrate

			Product Peaks Int								**Peaks Int**			
		ppm	**2.74**	**2.54**	**2.4**	**2.26 (2H)**	**1.44 (2H)**	**1.14 (3H)**	**0.86 (3H)**		**1.36 (2H)**	**0.78 (3H)**		
			1	2	3	4	5	6	7	**AVERAGE**	1	2	Average	
Expt	**Time / s**	**Time/min**												**Conv (%)**
	0	**0.00**												**0.00**
3	210	**2.50**	0.04	0.05	0.07	NI	NI	NI	NI	0.0533	2.45	3.34	1.169	**4.36**
4	260	**3.33**	0.05	0.04	0.05			0.17		0.0492	2.11	3.19	1.059	**4.44**
5	310	**4.17**	0.08	0.06	0.08	0.17		0.34		0.0833	2.30	3.22	1.112	**6.97**
6	360	**5.00**	0.09	0.08	0.10	0.20		0.34		0.0958	2.30	3.20	1.108	**7.96**
7	410	**5.83**	0.11	0.11	0.14	0.25		0.39		0.1225	2.27	3.11	1.086	**10.14**
8	460	**6.67**	0.11	0.10	0.12	0.24	0.28	0.35	0.40	0.1200	1.99	3.04	1.004	**10.67**
9	510	**7.50**	0.14	0.13	0.15	0.30	0.61	0.51	0.57	0.1764	2.24	3.07	1.072	**14.14**
10	560	**8.33**	0.14	0.12	0.15	0.30	0.33	0.45	0.50	0.1488	1.92	2.97	0.975	**13.24**
11	610	**9.17**	0.17	0.15	0.18	0.36	0.59	0.61	0.61	0.1974	2.12	3.00	1.030	**16.08**
12	660	**10.00**	0.18	0.17	0.20	0.38	0.59	0.61	0.68	0.2093	2.10	2.94	1.015	**17.09**
13	710	**10.83**	0.20	0.18	0.21	0.41	0.65	0.70	0.69	0.2262	2.07	2.94	1.008	**18.33**
14	760	**11.67**	0.20	0.18	0.20	0.40	0.44	0.67	0.70	0.2081	1.79	2.84	0.921	**18.43**
15	810	**12.50**	0.21	0.19	0.22	0.43	0.46	0.74	0.71	0.2212	1.77	2.81	0.911	**19.54**
16	860	**13.33**	0.24	0.22	0.26	0.50	0.72	0.87	0.87	0.2729	1.95	2.79	0.953	**22.27**
17	910	**14.17**	0.25	0.23	0.28	0.52	0.71	0.92	0.91	0.2836	1.93	2.79	0.948	**23.03**
18	960	**15.00**	0.27	0.24	0.30	0.56	0.74	0.98	0.98	0.3019	1.93	2.71	0.934	**24.42**
19	1010	**15.83**	0.28	0.26	0.31	0.58	0.79	1.01	0.99	0.3145	1.87	2.73	0.923	**25.43**
20	1060	**16.67**	0.29	0.27	0.32	0.60	0.77	1.04	1.03	0.3221	1.84	2.69	0.908	**26.18**
21	1110	**17.50**	0.31	0.27	0.31	0.59	0.77	1.06	1.05	0.3248	1.79	2.65	0.889	**26.75**
22	1160	**18.33**	0.32	0.29	0.34	0.64	0.82	1.12	1.07	0.3443	1.81	2.64	0.893	**27.84**
23	1210	**19.17**	0.33	0.30	0.36	0.67	0.85	1.16	1.13	0.3590	1.77	2.60	0.876	**29.08**
24	1260	**20.00**	0.34	0.31	0.37	0.69	0.87	1.20	1.15	0.3690	1.75	2.57	0.866	**29.89**
25	1310	**20.83**	0.35	0.31	0.36	0.69	0.85	1.22	1.16	0.3690	1.69	2.54	0.846	**30.38**
29	1510	**24.17**	0.40	0.35	0.40	0.76	0.92	1.36	1.32	0.4119	1.60	2.40	0.800	**33.99**
33	1710	**27.50**	0.44	0.40	0.47	0.87	1.01	1.51	1.44	0.4619	1.55	2.31	0.773	**37.42**
37	1910	**30.83**	0.48	0.44	0.52	0.96	1.08	1.64	1.58	0.5048	1.48	2.21	0.738	**40.61**
41	2110	**34.17**	0.52	0.47	0.55	1.01	1.11	1.74	1.65	0.5329	1.41	2.14	0.709	**42.90**
45	2310	**37.50**	0.56	0.50	0.59	1.08	1.17	1.85	1.76	0.5683	1.34	2.02	0.672	**45.83**
49	2510	**40.83**	0.59	0.53	0.62	1.15	1.22	1.95	1.91	0.6017	1.23	1.90	0.624	**49.08**
53	2710	**44.17**	0.62	0.56	0.66	1.21	1.26	2.05	2.00	0.6321	1.17	1.80	0.593	**51.62**
57	2910	**47.50**	0.64	0.58	0.68	1.25	1.29	2.13	2.06	0.6524	1.11	1.74	0.568	**53.48**
61	3110	**50.83**	0.67	0.60	0.71	1.30	1.33	2.21	2.12	0.6769	1.06	1.69	0.547	**55.32**
65	3310	**54.17**	0.70	0.62	0.74	1.36	1.37	2.30	2.20	0.7036	1.03	1.64	0.531	**57.00**
69	3510	**57.50**	0.73	0.65	0.78	1.41	1.47	2.39	2.30	0.7376	0.97	1.58	0.506	**59.32**
73	3710	**60.83**	0.75	0.67	0.80	1.46	1.50	2.46	2.36	0.7581	0.94	1.54	0.492	**60.66**
77	3910	**64.17**	0.77	0.67	0.79	1.46	1.50	2.51	2.41	0.7643	0.88	1.47	0.465	**62.17**
81	4110	**67.50**	0.78	0.68	0.82	1.50	1.53	2.57	2.48	0.7826	0.84	1.42	0.447	**63.66**
85	4310	**70.83**	0.81	0.70	0.84	1.54	1.56	2.63	2.51	0.8019	0.81	1.38	0.433	**64.96**
89	4510	**74.17**	0.82	0.71	0.85	1.57	1.60	2.68	2.61	0.8183	0.77	1.29	0.408	**66.76**
93	4710	**77.50**	0.83	0.73	0.87	1.60	1.62	2.73	2.65	0.8333	0.74	1.25	0.393	**67.93**
97	4910	**80.83**	0.86	0.77	0.92	1.67	1.69	2.81	2.72	0.8676	0.74	1.19	0.383	**69.36**
101	5110	**84.17**	0.87	0.76	0.91	1.66	1.68	2.84	2.74	0.8671	0.68	1.15	0.362	**70.57**
105	5310	**87.50**	0.89	0.78	0.93	1.69	1.70	2.88	2.78	0.8831	0.66	1.11	0.350	**71.62**
109	5510	**90.83**	0.90	0.79	0.94	1.73	1.73	2.93	2.84	0.8976	0.65	1.06	0.339	**72.58**
113	5710	**94.17**	0.92	0.83	0.99	1.79	1.79	3.01	2.88	0.9276	0.66	1.04	0.338	**73.27**
117	5910	**97.50**	0.93	0.81	0.97	1.78	1.76	3.01	2.91	0.9219	0.61	1.02	0.323	**74.08**
121	6110	**100.83**	0.94	0.83	0.99	1.80	1.79	3.06	2.95	0.9369	0.60	0.98	0.313	**74.94**
125	6310	**104.17**	0.95	0.84	1.00	1.83	1.81	3.10	2.98	0.9481	0.58	0.98	0.308	**75.46**
129	6510	**107.50**	0.97	0.87	1.04	1.88	1.85	3.15	3.01	0.9712	0.58	0.94	0.302	**76.30**
133	6710	**110.83**	0.97	0.86	1.03	1.87	1.84	3.17	3.04	0.9693	0.54	0.89	0.283	**77.38**
137	6910	**114.17**	0.99	0.87	1.03	1.89	1.85	3.19	3.06	0.9776	0.52	0.89	0.278	**77.84**
141	7110	**117.50**	1.00	0.88	1.05	1.91	1.88	3.23	3.09	0.9902	0.51	0.86	0.271	**78.52**
145	7310	**120.83**	1.02	0.90	1.07	1.93	1.90	3.27	3.12	1.0050	0.50	0.82	0.262	**79.34**
149	7510	**124.17**	1.02	0.90	1.07	1.95	1.91	3.29	3.14	1.0090	0.48	0.81	0.255	**79.83**
152	7660	**126.67**	1.02	0.91	1.08	1.96	1.93	3.31	3.16	1.0160	0.47	0.79	0.249	**80.30**

Deuterated Thiol Expt

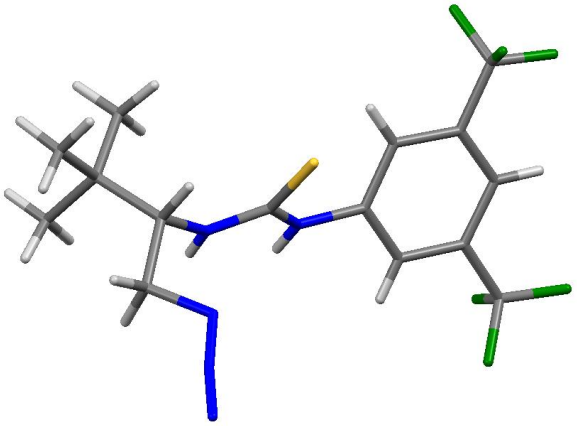
			Product Peaks Int								SM Peaks Int			
	ppm		2.74	Deut Peak	2.4	2.26 (2H)	1.44 (2H)	1.14 (3H)	0.86 (3H)		1.36 (2H)	0.78 (3H)		
			1	2	3	4	5	6	7	AVERAGE	2	3	Average	
Expt	**Time / s**	**Time / min**												**Conv (%)**
		0.00												**0.00**
2	171	**2.85**	0.06	0.00	0.07	0.14	0.14	0.2	0.28	0.0717	1.77	2.79	0.908	**7.32**
3	221	**3.68**	0.08	0.00	0.09	0.18	0.17	0.26	0.34	0.0908	1.68	2.75	0.878	**9.37**
4	271	**4.52**	0.12	0.01	0.14	0.26	0.27	0.36	0.44	0.1319	1.73	2.69	0.881	**13.03**
5	321	**5.35**	0.13	0.02	0.16	0.29	0.25	0.4	0.48	0.1422	1.61	2.62	0.839	**14.49**
6	371	**6.18**	0.17	0.03	0.18	0.33	0.33	0.48	0.55	0.1706	1.65	2.58	0.843	**16.84**
7	421	**7.02**	0.19	0.03	0.23	0.40	0.39	0.57	0.66	0.2042	1.62	2.50	0.822	**19.90**
8	471	**7.85**	0.22	0.03	0.24	0.43	0.45	0.74	0.74	0.2322	1.57	2.45	0.801	**22.48**
9	521	**8.68**	0.24	0.04	0.25	0.46	0.48	0.8	0.78	0.2478	1.53	2.40	0.783	**24.05**
10	571	**9.52**	0.26	0.03	0.27	0.50	0.48	0.82	0.81	0.2606	1.42	2.32	0.742	**26.00**
11	621	**10.35**	0.28	0.04	0.29	0.54	0.56	0.93	0.89	0.2878	1.46	2.31	0.750	**27.73**
12	671	**11.18**	0.30	0.05	0.32	0.58	0.59	0.99	0.93	0.3075	1.43	2.27	0.736	**29.47**
13	721	**12.02**	0.31	0.05	0.33	0.61	0.63	1.04	0.98	0.3222	1.39	2.22	0.718	**30.99**
14	771	**12.85**	0.33	0.05	0.36	0.65	0.66	1.10	1.03	0.3425	1.36	2.17	0.702	**32.80**
15	821	**13.68**	0.35	0.05	0.37	0.68	0.69	1.16	1.10	0.3597	1.34	2.11	0.687	**34.38**
16	871	**14.52**	0.37	0.06	0.39	0.71	0.73	1.21	1.16	0.3783	1.31	2.06	0.671	**36.06**
17	921	**15.35**	0.39	0.06	0.41	0.74	0.76	1.26	1.19	0.3944	1.27	2.03	0.656	**37.56**
18	971	**16.18**	0.4	0.06	0.43	0.78	0.78	1.32	1.27	0.4122	1.25	1.96	0.639	**39.21**
19	1021	**17.02**	0.42	0.07	0.44	0.81	0.82	1.38	1.35	0.4308	1.22	1.91	0.623	**40.87**
20	1071	**17.85**	0.44	0.07	0.46	0.84	0.85	1.43	1.39	0.4475	1.2	1.87	0.612	**42.25**
21	1121	**18.68**	0.45	0.07	0.48	0.87	0.88	1.48	1.42	0.4619	1.17	1.83	0.598	**43.60**
22	1171	**19.52**	0.47	0.07	0.49	0.90	0.91	1.53	1.46	0.4769	1.16	1.81	0.592	**44.63**
23	1221	**20.35**	0.48	0.08	0.51	0.93	0.93	1.58	1.49	0.4906	1.14	1.78	0.582	**45.75**
24	1271	**21.18**	0.50	0.08	0.53	0.96	0.96	1.63	1.56	0.5089	1.11	1.75	0.569	**47.20**
28	1471	**24.52**	0.56	0.09	0.59	1.07	1.06	1.82	1.75	0.5675	1.04	1.65	0.535	**51.47**
32	1671	**27.85**	0.62	0.10	0.65	1.19	1.20	2.02	1.93	0.6303	0.98	1.55	0.503	**55.60**
36	1871	**31.18**	0.67	0.10	0.70	1.28	1.27	2.16	2.05	0.6747	0.92	1.48	0.477	**58.60**
40	2071	**34.52**	0.7	0.11	0.74	1.35	1.34	2.29	2.17	0.7119	0.87	1.39	0.449	**61.32**
44	2271	**37.85**	0.74	0.11	0.78	1.42	1.40	2.41	2.27	0.7483	0.81	1.30	0.419	**64.10**
48	2471	**41.18**	0.77	0.12	0.82	1.48	1.46	2.52	2.37	0.7817	0.76	1.22	0.393	**66.52**
52	2671	**44.52**	0.81	0.13	0.86	1.54	1.51	2.61	2.43	0.8125	0.72	1.16	0.373	**68.52**
56	2871	**47.85**	0.84	0.13	0.87	1.59	1.56	2.69	2.51	0.8364	0.67	1.11	0.353	**70.35**
60	3071	**51.18**	0.86	0.14	0.91	1.64	1.61	2.78	2.57	0.8631	0.63	1.05	0.333	**72.19**
64	3271	**54.52**	0.89	0.15	0.94	1.69	1.65	2.87	2.65	0.8900	0.61	1.02	0.323	**73.40**
68	3471	**57.85**	0.90	0.14	0.95	1.71	1.66	2.92	2.70	0.9014	0.56	0.97	0.302	**74.92**
72	3671	**61.18**	0.92	0.15	0.98	1.76	1.71	2.99	2.76	0.9253	0.54	0.91	0.287	**76.35**
76	3871	**64.52**	0.95	0.15	0.99	1.79	1.75	3.04	2.81	0.9433	0.49	0.87	0.268	**77.91**
80	4071	**67.85**	0.97	0.16	1.02	1.83	1.8	3.11	2.88	0.9669	0.48	0.81	0.255	**79.13**
84	4271	**71.18**	0.98	0.17	1.04	1.85	1.84	3.15	2.97	0.9842	0.43	0.76	0.234	**80.78**
88	4471	**74.52**	1.00	0.16	1.05	1.88	1.86	3.21	3.04	1.0006	0.4	0.71	0.218	**82.09**
92	4671	**77.85**	1.01	0.17	1.06	1.90	1.88	3.26	3.08	1.0122	0.38	0.66	0.205	**83.16**
96	4871	**81.18**	1.02	0.17	1.08	1.93	1.9	3.31	3.12	1.0264	0.36	0.63	0.195	**84.03**
100	5071	**84.52**	1.04	0.17	1.09	1.95	1.93	3.35	3.17	1.0406	0.34	0.57	0.180	**85.25**
104	5271	**87.85**	1.05	0.17	1.1	1.97	1.95	3.39	3.21	1.0517	0.33	0.56	0.176	**85.68**
108	5471	**91.18**	1.06	0.18	1.12	2.00	1.97	3.42	3.23	1.0636	0.32	0.53	0.168	**86.34**
112	5671	**94.52**	1.07	0.18	1.13	2.01	1.99	3.45	3.26	1.0728	0.30	0.52	0.162	**86.90**
116	5871	**97.85**	1.08	0.18	1.15	2.03	2.01	3.48	3.29	1.0844	0.29	0.48	0.153	**87.67**
120	6071	**101.18**	1.09	0.18	1.15	2.04	2.02	3.51	3.32	1.0911	0.27	0.47	0.146	**88.21**
124	6271	**104.52**	1.10	0.18	1.16	2.06	2.04	3.54	3.34	1.1006	0.26	0.44	0.138	**88.83**
128	6471	**107.85**	1.10	0.19	1.16	2.07	2.05	3.57	3.36	1.1050	0.25	0.43	0.134	**89.17**
132	6671	**111.18**	1.11	0.19	1.17	2.08	2.05	3.58	3.37	1.1103	0.24	0.42	0.130	**89.52**
136	6871	**114.52**	1.11	0.19	1.18	2.10	2.06	3.60	3.39	1.1167	0.23	0.41	0.126	**89.87**
140	7071	**117.85**	1.12	0.19	1.18	2.10	2.08	3.63	3.41	1.1228	0.23	0.38	0.121	**90.28**
144	7271	**121.18**	1.13	0.19	1.19	2.12	2.09	3.64	3.42	1.1297	0.22	0.39	0.120	**90.40**
148	7471	**124.52**	1.14	0.20	1.20	2.14	2.11	3.66	3.42	1.1375	0.21	0.38	0.116	**90.76**
152	7671	**127.85**	1.14	0.18	1.19	2.14	2.12	3.69	3.45	1.1400	0.18	0.32	0.098	**92.06**
156	7871	**131.18**	1.15	0.20	1.21	2.15	2.12	3.70	3.46	1.1469	0.20	0.36	0.110	**91.25**
158	7971	**132.85**	1.15	0.19	1.22	2.16	2.11	3.68	3.46	1.1475	0.14	0.31	0.087	**92.98**

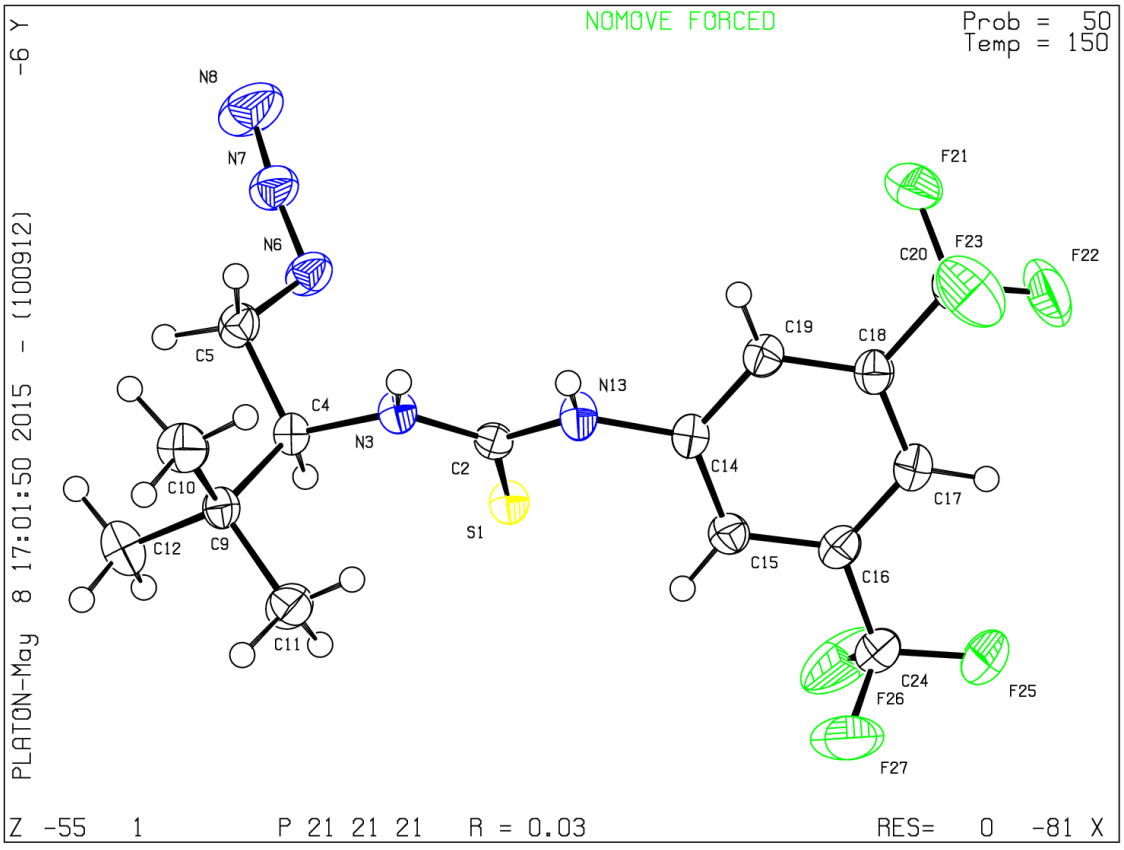
9.2.4 Nitro-olefin Michael Addition Reaction (Figure 72)

Expt	Time (min)	mesitylene CH3	pdt 5.5 ppm	pdt 4.8-5.3 ppm	pdt 4-4.5 ppm	conv1 (%)	conv 2 (%)	conv 3 (%)
0	0	9.00	0.00	0.00	0.00	0.0	0.0	0.0
1	4	9.00	0.18	0.16	0.20	18.0	16.0	20.0
2	6	9.00	0.37	0.41	0.54	37.0	41.0	54.0
3	8	9.00	0.44	0.47	0.56	44.0	47.0	56.0
4	10	9.00	0.49	0.52	0.59	49.0	52.0	59.0
5	12	9.00	0.55	0.59	0.64	55.0	59.0	64.0
6	14	9.00	0.58	0.62	0.67	58.0	62.0	67.0
7	16	9.00	0.61	0.63	0.68	61.0	63.0	68.0
8	18	9.00	0.64	0.68	0.72	64.0	68.0	72.0
9	20	9.00	0.65	0.69	0.72	65.0	69.0	72.0
10	22	9.00	0.67	0.71	0.75	67.0	71.0	75.0
11	24	9.00	0.69	0.74	0.79	69.0	74.0	79.0
12	26	9.00	0.71	0.77	0.82	71.0	77.0	82.0
13	28	9.00	0.71	0.75	0.79	71.0	75.0	79.0
14	30	9.00	0.73	0.78	0.83	73.0	78.0	83.0
15	32	9.00	0.73	0.77	0.82	73.0	77.0	82.0
16	34	9.00	0.74	0.77	0.82	74.0	77.0	82.0
17	36	9.00	0.75	0.79	0.83	75.0	79.0	83.0
18	38	9.00	0.76	0.82	0.86	76.0	82.0	86.0
19	40	9.00	0.76	0.82	0.87	76.0	82.0	87.0
20	42	9.00	0.76	0.81	0.85	76.0	81.0	85.0
21	44	9.00	0.77	0.83	0.87	77.0	83.0	87.0
22	46	9.00	0.78	0.85	0.89	78.0	85.0	89.0
23	48	9.00	0.78	0.85	0.89	78.0	85.0	89.0
24	50	9.00	0.79	0.85	0.90	79.0	85.0	90.0
25	52	9.00	0.81	0.90	0.94	81.0	90.0	94.0
26	54	9.00	0.79	0.85	0.89	79.0	85.0	89.0
27	56	9.00	0.80	0.88	0.92	80.0	88.0	92.0
28	58	9.00	0.80	0.88	0.92	80.0	88.0	92.0
29	60	9.00	0.80	0.86	0.90	80.0	86.0	90.0
30	62	9.00	0.80	0.86	0.91	80.0	86.0	91.0

9.3 X-ray Diffraction Data

9.3.1 X-ray Diffraction Data for 131





Crystal data	
Chemical formula	$C_{15}H_{17}F_6N_5S$

M_r	413.39
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	150
a, *b*, *c* (Å)	8.1384 (1), 9.2254 (1), 25.1063 (3)
V (Å^3)	1884.98 (4)
Z	4
Radiation type	Mo *K*α
μ (mm^{-1})	0.24
Crystal size (mm)	0.2 × 0.2 × 0.2
Data collection	
Diffractometer	Nonius KappaCCD diffractometer
Absorption correction	Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	1.00, 1.00
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	4281, 4281, 3759
R_{int}	0.000
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.649
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.034, 0.078, 0.96
No. of reflections	4281
No. of parameters	297
H-atom treatment	Only H-atom coordinates refined
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.29, −0.25
Absolute structure	Flack (1983), 1828 Friedel-pairs
Absolute structure parameter	−0.04 (6)

Computer programs: *COLLECT* (Nonius, 2001)., *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997), USER DEFINED *STRUCTURE* SOLUTION,*CRYSTALS* (Betteridge *et al.*, 2003), *CAMERON* (Watkin *et al.*, 1996).

Table 2 Selected geometric parameters (Å, º)

S1—C2	1.6926 (16)	C14—C19	1.389 (3)
C2—N3	1.332 (2)	C15—C16	1.388 (3)
C2—N13	1.361 (2)	C16—C17	1.381 (3)
N3—C4	1.461 (2)	C16—C24	1.496 (3)
C4—C5	1.527 (2)	C17—C18	1.387 (3)
C4—C9	1.552 (2)	C18—C19	1.385 (2)
C5—N6	1.482 (2)	C18—C20	1.500 (3)
N6—N7	1.228 (2)	C20—F21	1.325 (2)
N7—N8	1.126 (2)	C20—F22	1.313 (2)
C9—C10	1.524 (3)	C20—F23	1.337 (3)
C9—C11	1.529 (3)	C24—F25	1.325 (2)

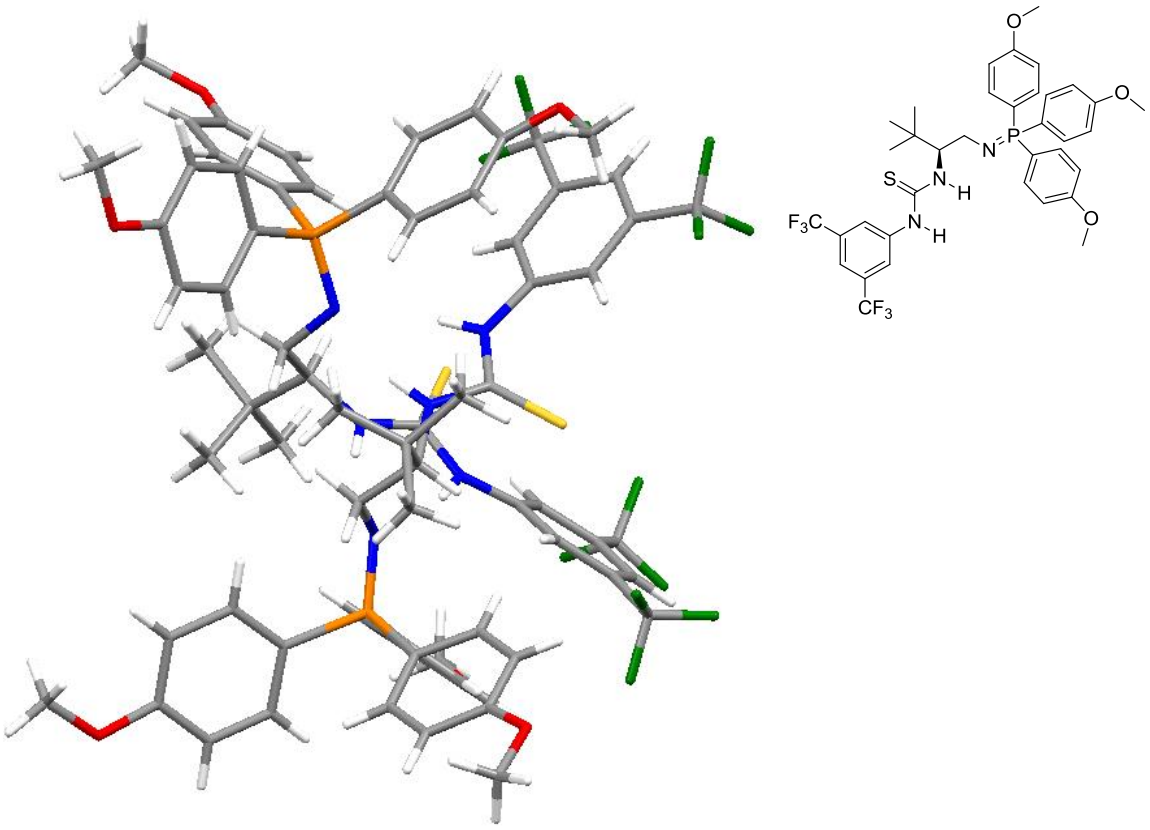
C9—C12	1.528 (3)	C24—F26	1.331 (3)
N13—C14	1.416 (2)	C24—F27	1.315 (3)
C14—C15	1.392 (2)		
S1—C2—N3	123.39 (12)	C15—C16—C17	121.40 (17)
S1—C2—N13	123.04 (12)	C15—C16—C24	117.86 (17)
N3—C2—N13	113.56 (15)	C17—C16—C24	120.74 (17)
C2—N3—C4	126.16 (14)	C16—C17—C18	118.74 (17)
N3—C4—C5	108.33 (14)	C17—C18—C19	120.79 (17)
N3—C4—C9	111.28 (13)	C17—C18—C20	120.04 (16)
C5—C4—C9	114.17 (13)	C19—C18—C20	119.16 (17)
C4—C5—N6	106.49 (14)	C14—C19—C18	120.00 (17)
C5—N6—N7	114.60 (15)	C18—C20—F21	112.41 (15)
N6—N7—N8	172.6 (2)	C18—C20—F22	113.12 (17)
C4—C9—C10	111.68 (15)	F21—C20—F22	108.38 (18)
C4—C9—C11	108.42 (14)	C18—C20—F23	111.55 (17)
C10—C9—C11	109.39 (17)	F21—C20—F23	105.38 (18)
C4—C9—C12	109.02 (15)	F22—C20—F23	105.47 (17)
C10—C9—C12	109.83 (16)	C16—C24—F25	113.22 (17)
C11—C9—C12	108.42 (17)	C16—C24—F26	111.50 (16)
C2—N13—C14	128.11 (15)	F25—C24—F26	105.22 (18)
N13—C14—C15	122.44 (16)	C16—C24—F27	113.29 (18)
N13—C14—C19	117.81 (15)	F25—C24—F27	105.88 (16)
C15—C14—C19	119.70 (16)	F26—C24—F27	107.16 (19)
C14—C15—C16	119.29 (17)		

Table 3 Hydrogen-bond geometry (Å, º)

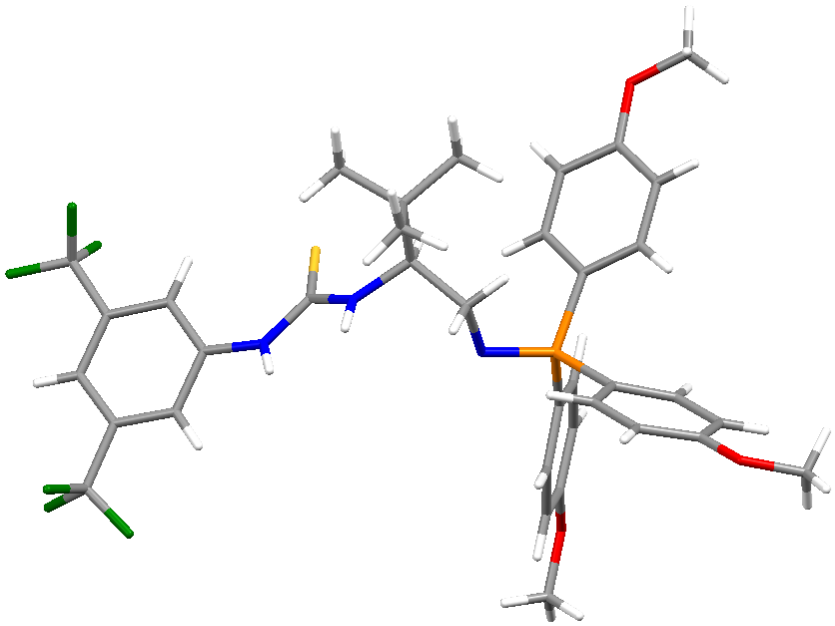
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N13—H131···N6^{i}	0.783	2.516	3.093 (3)	132 (2)

Symmetry code: (i) −*x*, *y*+1/2, −*z*+1/2.

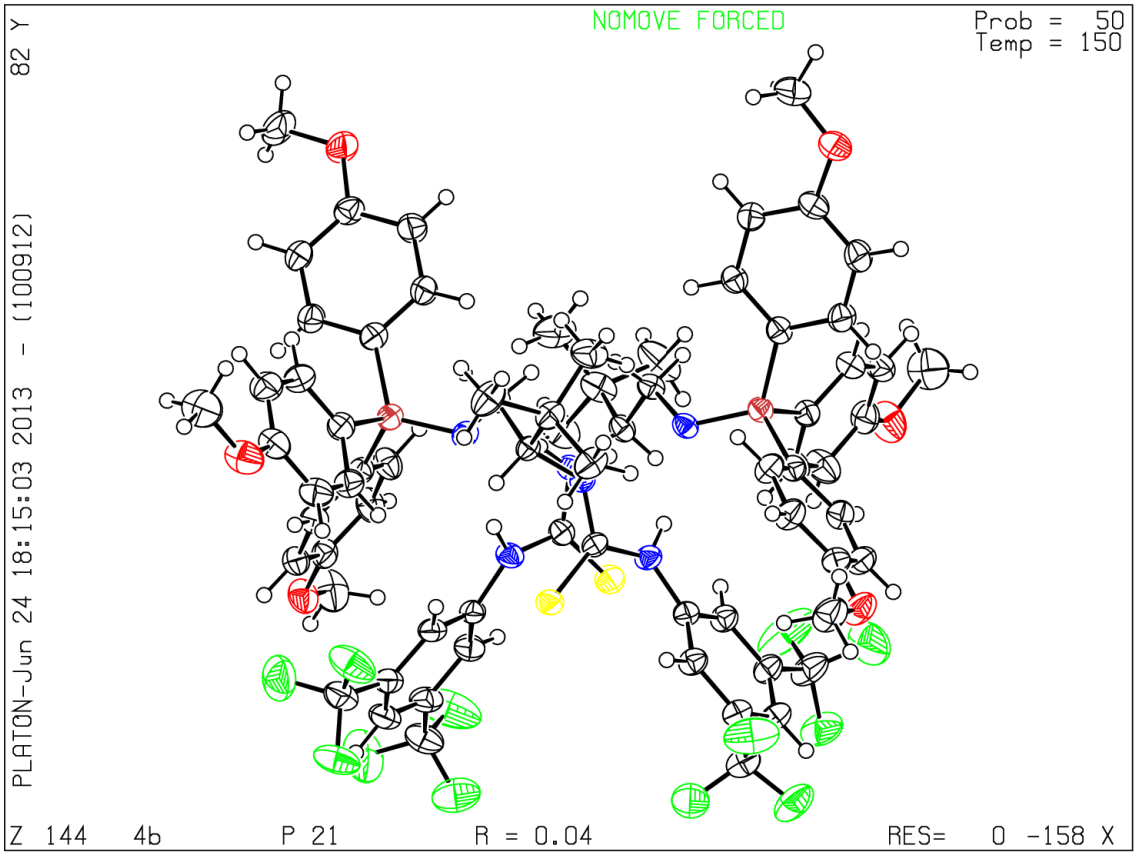
9.3.2 X-ray Diffraction Data for 147



Compound **147** shown in its dimer form as solved by Crystals.



Compound **147** shown as a monomer for clarity.



(147)

Crystal data

$C_{36}H_{38}F_6N_3O_3PS$
M_r = 737.74
Monoclinic, $P2_1$
a = 12.8838 (1) Å
b = 19.4546 (2) Å
c = 15.0458 (2) Å
β = 102.5816 (4)°
V = 3680.66 (7) Å^3
Z = 4
Mo $K\alpha$ radiation, λ = 0.71073 Å
μ = 0.20 mm^{-1}
T = 150 K
0.58 × 0.46 × 0.22 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min} = 0.63, T_{max} = 0.96
98019 measured reflections
16705 independent reflections
14629 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.057

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.039$	H-atom parameters constrained
$wR(F^2) = 0.089$	$\Delta\rho_{max} = 0.37$ e Å^{-3}
$S = 0.97$	$\Delta\rho_{min} = -0.27$ e Å^{-3}
16705 reflections	Absolute structure: Flack (1983), 8111 Friedel-pairs
902 parameters	Flack parameter: −0.04 (4)
1 restraint	

Table 1

Selected geometric parameters (Å, º)

S1—C2	1.6802 (19)	S51—C52	1.679 (2)
C2—N3	1.344 (2)	C52—N53	1.345 (3)
C2—N36	1.370 (2)	C52—N86	1.379 (3)
N3—C4	1.457 (2)	N53—C54	1.456 (2)
C4—C5	1.533 (3)	C54—C55	1.529 (3)
C4—C32	1.556 (3)	C54—C82	1.557 (3)
C5—N6	1.479 (2)	C55—N56	1.476 (2)
N6—P7	1.5935 (17)	N56—P57	1.5896 (16)
P7—C8	1.794 (2)	P57—C58	1.794 (2)
P7—C16	1.802 (2)	P57—C66	1.810 (2)
P7—C24	1.814 (2)	P57—C74	1.813 (2)
C8—C9	1.395 (3)	C58—C59	1.398 (3)
C8—C15	1.389 (3)	C58—C65	1.391 (3)
C9—C10	1.386 (3)	C59—C60	1.381 (3)
C10—C11	1.385 (3)	C60—C61	1.393 (3)
C11—O12	1.370 (3)	C61—O62	1.367 (3)
C11—C14	1.385 (3)	C61—C64	1.390 (3)
O12—C13	1.423 (3)	O62—C63	1.432 (3)
C14—C15	1.396 (3)	C64—C65	1.388 (3)
C16—C17	1.396 (3)	C66—C67	1.386 (3)
C16—C23	1.398 (3)	C66—C73	1.406 (3)
C17—C18	1.386 (3)	C67—C68	1.396 (3)
C18—C19	1.393 (3)	C68—C69	1.389 (3)
C19—O20	1.371 (3)	C69—O70	1.366 (3)
C19—C22	1.384 (3)	C69—C72	1.384 (3)
O20—C21	1.428 (3)	O70—C71	1.422 (3)
C22—C23	1.391 (3)	C72—C73	1.374 (3)
C24—C25	1.390 (3)	C74—C75	1.393 (3)
C24—C31	1.398 (3)	C74—C81	1.398 (3)

C25—C26	1.393 (3)	C75—C76	1.398 (3)
C26—C27	1.381 (3)	C76—C77	1.375 (3)
C27—O28	1.369 (3)	C77—O78	1.368 (3)
C27—C30	1.398 (3)	C77—C80	1.383 (3)
O28—C29	1.427 (3)	O78—C79	1.438 (3)
C30—C31	1.380 (3)	C80—C81	1.379 (3)
C32—C33	1.539 (3)	C82—C83	1.536 (4)
C32—C34	1.523 (3)	C82—C84	1.521 (4)
C32—C35	1.523 (3)	C82—C85	1.531 (3)
N36—C37	1.388 (3)	N86—C87	1.396 (2)
C37—C38	1.397 (3)	C87—C88	1.392 (3)
C37—C42	1.396 (3)	C87—C92	1.401 (3)
C38—C39	1.378 (3)	C88—C89	1.381 (3)
C39—C40	1.387 (3)	C89—C90	1.394 (3)
C39—C47	1.493 (3)	C89—C97	1.480 (3)
C40—C41	1.380 (3)	C90—C91	1.372 (3)
C41—C42	1.400 (3)	C91—C92	1.388 (3)
C41—C43	1.494 (3)	C91—C93	1.490 (3)
C43—F44	1.336 (3)	C93—F94	1.331 (3)
C43—F45	1.330 (3)	C93—F95	1.347 (3)
C43—F46	1.337 (3)	C93—F96	1.310 (3)
C47—F48	1.329 (3)	C97—F98	1.337 (3)
C47—F49	1.319 (3)	C97—F99	1.328 (3)
C47—F50	1.348 (4)	C97—F100	1.365 (3)

S1—C2—N3	124.94 (15)	S51—C52—N53	124.71 (15)
S1—C2—N36	124.28 (14)	S51—C52—N86	124.20 (15)
N3—C2—N36	110.73 (17)	N53—C52—N86	111.04 (17)
C2—N3—C4	126.60 (16)	C52—N53—C54	125.50 (17)
N3—C4—C5	107.74 (15)	N53—C54—C55	107.50 (15)
N3—C4—C32	111.93 (15)	N53—C54—C82	112.41 (16)
C5—C4—C32	113.50 (16)	C55—C54—C82	113.15 (17)
C4—C5—N6	112.51 (15)	C54—C55—N56	112.96 (16)
C5—N6—P7	115.62 (13)	C55—N56—P57	116.40 (13)
N6—P7—C8	107.10 (9)	N56—P57—C58	108.19 (9)
N6—P7—C16	115.87 (10)	N56—P57—C66	116.51 (9)
C8—P7—C16	104.44 (10)	C58—P57—C66	105.87 (9)
N6—P7—C24	112.61 (9)	N56—P57—C74	112.16 (9)
C8—P7—C24	110.09 (10)	C58—P57—C74	109.02 (10)
C16—P7—C24	106.39 (10)	C66—P57—C74	104.75 (9)
P7—C8—C9	124.58 (16)	P57—C58—C59	123.04 (16)

P7—C8—C15	117.08 (16)	P57—C58—C65	118.44 (16)
C9—C8—C15	118.3 (2)	C59—C58—C65	118.51 (19)
C8—C9—C10	120.9 (2)	C58—C59—C60	120.6 (2)
C9—C10—C11	119.7 (2)	C59—C60—C61	120.1 (2)
C10—C11—O12	115.45 (19)	C60—C61—O62	115.3 (2)
C10—C11—C14	120.7 (2)	C60—C61—C64	120.1 (2)
O12—C11—C14	123.9 (2)	O62—C61—C64	124.5 (2)
C11—O12—C13	117.65 (19)	C61—O62—C63	116.76 (18)
C11—C14—C15	119.0 (2)	C61—C64—C65	119.2 (2)
C14—C15—C8	121.4 (2)	C58—C65—C64	121.5 (2)
P7—C16—C17	120.26 (16)	P57—C66—C67	121.49 (15)
P7—C16—C23	121.46 (17)	P57—C66—C73	120.16 (16)
C17—C16—C23	118.2 (2)	C67—C66—C73	118.23 (19)
C16—C17—C18	121.0 (2)	C66—C67—C68	121.23 (19)
C17—C18—C19	119.6 (2)	C67—C68—C69	119.3 (2)
C18—C19—O20	115.2 (2)	C68—C69—O70	124.1 (2)
C18—C19—C22	120.4 (2)	C68—C69—C72	120.0 (2)
O20—C19—C22	124.4 (2)	O70—C69—C72	115.90 (19)
C19—O20—C21	116.95 (19)	C69—O70—C71	118.13 (19)
C19—C22—C23	119.4 (2)	C69—C72—C73	120.4 (2)
C16—C23—C22	121.2 (2)	C66—C73—C72	120.8 (2)
P7—C24—C25	124.11 (17)	P57—C74—C75	123.74 (16)
P7—C24—C31	117.77 (17)	P57—C74—C81	118.49 (16)
C25—C24—C31	118.0 (2)	C75—C74—C81	117.52 (19)
C24—C25—C26	121.4 (2)	C74—C75—C76	121.4 (2)
C25—C26—C27	119.8 (2)	C75—C76—C77	119.5 (2)
C26—C27—O28	124.9 (2)	C76—C77—O78	124.4 (2)
C26—C27—C30	119.8 (2)	C76—C77—C80	120.0 (2)
O28—C27—C30	115.4 (2)	O78—C77—C80	115.6 (2)
C27—O28—C29	117.3 (2)	C77—O78—C79	116.6 (2)
C27—C30—C31	119.9 (2)	C77—C80—C81	120.3 (2)
C24—C31—C30	121.3 (2)	C74—C81—C80	121.2 (2)
C4—C32—C33	107.99 (17)	C54—C82—C83	108.4 (2)
C4—C32—C34	111.19 (17)	C54—C82—C84	111.11 (18)
C33—C32—C34	109.6 (2)	C83—C82—C84	111.0 (2)
C4—C32—C35	110.20 (17)	C54—C82—C85	110.19 (18)
C33—C32—C35	108.24 (18)	C83—C82—C85	107.2 (2)
C34—C32—C35	109.51 (19)	C84—C82—C85	108.8 (2)
C2—N36—C37	130.38 (17)	C52—N86—C87	129.50 (17)
N36—C37—C38	115.58 (18)	N86—C87—C88	116.75 (17)
N36—C37—C42	125.69 (18)	N86—C87—C92	124.35 (19)

C38—C37—C42	118.55 (18)	C88—C87—C92	118.71 (18)
C37—C38—C39	120.9 (2)	C87—C88—C89	120.77 (19)
C38—C39—C40	121.2 (2)	C88—C89—C90	120.7 (2)
C38—C39—C47	118.2 (2)	C88—C89—C97	120.6 (2)
C40—C39—C47	120.6 (2)	C90—C89—C97	118.6 (2)
C39—C40—C41	118.1 (2)	C89—C90—C91	118.3 (2)
C40—C41—C42	121.9 (2)	C90—C91—C92	122.1 (2)
C40—C41—C43	120.7 (2)	C90—C91—C93	118.8 (2)
C42—C41—C43	117.37 (19)	C92—C91—C93	119.1 (2)
C41—C42—C37	119.38 (19)	C87—C92—C91	119.3 (2)
C41—C43—F44	112.0 (2)	C91—C93—F94	112.5 (2)
C41—C43—F45	113.3 (2)	C91—C93—F95	111.8 (2)
F44—C43—F45	106.2 (2)	F94—C93—F95	104.2 (2)
C41—C43—F46	112.8 (2)	C91—C93—F96	114.3 (2)
F44—C43—F46	106.5 (2)	F94—C93—F96	106.5 (2)
F45—C43—F46	105.5 (2)	F95—C93—F96	106.9 (2)
C39—C47—F48	112.9 (2)	C89—C97—F98	113.4 (2)
C39—C47—F49	113.5 (2)	C89—C97—F99	114.0 (2)
F48—C47—F49	109.1 (2)	F98—C97—F99	108.0 (2)
C39—C47—F50	112.0 (2)	C89—C97—F100	111.2 (2)
F48—C47—F50	104.6 (2)	F98—C97—F100	104.8 (2)
F49—C47—F50	103.9 (3)	F99—C97—F100	104.7 (2)

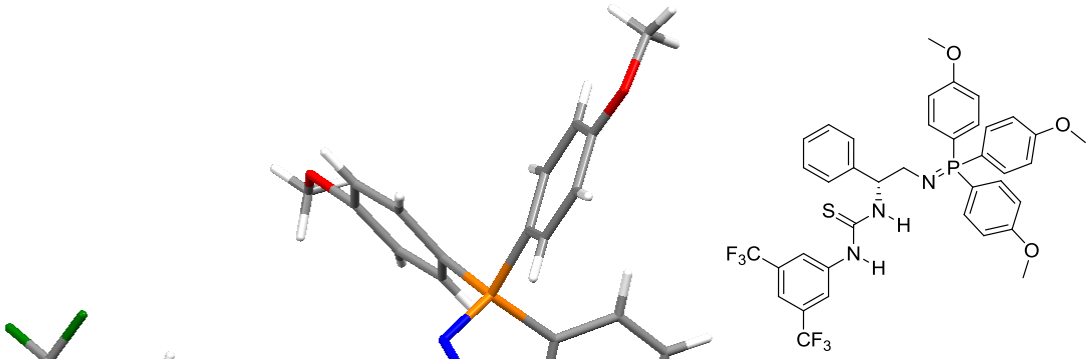
Table 2

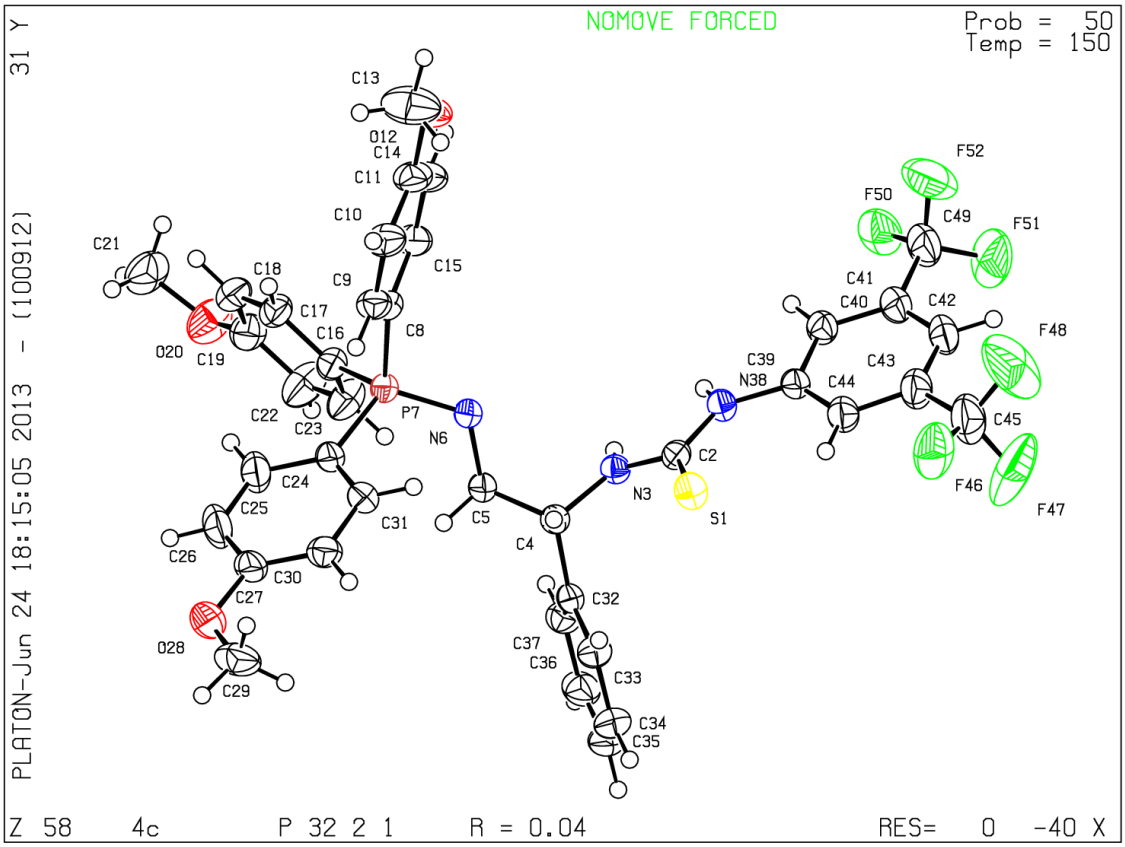
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C13—H132···O20^{i}	0.97	2.51	3.228 (3)	131
N86—H861···N6	0.88	2.16	3.008 (3)	160
N3—H31···N56	0.87	2.19	3.031 (3)	162
N53—H531···N6	0.91	2.15	3.010 (3)	158
N36—H361···N56	0.88	2.14	2.995 (3)	162

Symmetry code: (i) −*x*, *y*−1/2, −*z*+1.

9.3.3 X-ray Diffraction Data for 148





(148)

Crystal data

$C_{38}H_{34}F_6N_3O_3PS$	Z = 6
M_r = 757.73	Mo $K\alpha$ radiation, λ = 0.71073 Å
Trigonal, $P3_221$	μ = 0.17 mm^{-1}
a = 22.8761 (1) Å	T = 150 K
c = 14.2626 (1) Å	0.44 × 0.40 × 0.34 mm
V = 6463.88 (6) $Å^3$	

Data collection

Nonius KappaCCD diffractometer	9789 independent reflections
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	9025 reflections with $I > 2.0\sigma(I)$
T_{min} = 0.88, T_{max} = 0.94	R_{int} = 0.062
177140 measured reflections	

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042	H-atom parameters constrained
$wR(F^2)$ = 0.106	$\Delta\rho_{max}$ = 0.25 e $Å^{-3}$
S = 0.91	$\Delta\rho_{min}$ = −0.24 e $Å^{-3}$
9787 reflections	Absolute structure: Flack (1983), 4540 Friedel-pairs
470 parameters	Flack parameter: −0.076 (8)
0 restraints	

Table 3

Selected geometric parameters (Å, º)

S1—C2	1.6798 (18)	C24—C31	1.386 (3)
C2—N3	1.340 (2)	C25—C26	1.373 (3)
C2—N38	1.374 (2)	C26—C27	1.380 (4)
N3—C4	1.461 (2)	C27—O28	1.364 (2)
C4—C5	1.530 (2)	C27—C30	1.396 (3)
C4—C32	1.528 (2)	O28—C29	1.420 (3)
C5—N6	1.479 (2)	C30—C31	1.389 (3)
N6—P7	1.5914 (15)	C32—C33	1.389 (3)
P7—C8	1.7960 (19)	C32—C37	1.396 (3)
P7—C16	1.809 (2)	C33—C34	1.396 (3)
P7—C24	1.8030 (18)	C34—C35	1.373 (4)
C8—C9	1.391 (3)	C35—C36	1.383 (4)
C8—C15	1.404 (3)	C36—C37	1.391 (3)
C9—C10	1.397 (3)	N38—C39	1.397 (2)

C10—C11	1.384 (3)	C39—C40	1.407 (3)
C11—O12	1.366 (3)	C39—C44	1.385 (3)
C11—C14	1.394 (3)	C40—C41	1.390 (3)
O12—C13	1.430 (3)	C41—C42	1.372 (3)
C14—C15	1.383 (3)	C41—C49	1.497 (3)
C16—C17	1.393 (3)	C42—C43	1.392 (3)
C16—C23	1.400 (3)	C43—C44	1.395 (3)
C17—C18	1.394 (3)	C43—C45	1.497 (4)
C18—C19	1.376 (3)	C45—F46	1.331 (3)
C19—O20	1.373 (3)	C45—F47	1.311 (4)
C19—C22	1.391 (3)	C45—F48	1.329 (4)
O20—C21	1.429 (3)	C49—F50	1.333 (3)
C22—C23	1.374 (3)	C49—F51	1.313 (3)
C24—C25	1.401 (3)	C49—F52	1.351 (4)

S1—C2—N3	123.14 (13)	C25—C26—C27	120.8 (2)
S1—C2—N38	125.79 (14)	C26—C27—O28	115.5 (2)
N3—C2—N38	111.01 (15)	C26—C27—C30	120.29 (19)
C2—N3—C4	125.80 (15)	O28—C27—C30	124.2 (2)
N3—C4—C5	107.81 (14)	C27—O28—C29	117.7 (2)
N3—C4—C32	111.11 (14)	C27—C30—C31	118.4 (2)
C5—C4—C32	112.91 (15)	C30—C31—C24	121.86 (19)
C4—C5—N6	110.06 (15)	C4—C32—C33	119.93 (18)
C5—N6—P7	118.95 (12)	C4—C32—C37	121.31 (17)
N6—P7—C8	106.41 (8)	C33—C32—C37	118.72 (18)
N6—P7—C16	116.04 (9)	C32—C33—C34	120.2 (2)
C8—P7—C16	106.38 (9)	C33—C34—C35	120.5 (2)
N6—P7—C24	112.83 (8)	C34—C35—C36	120.0 (2)
C8—P7—C24	108.61 (9)	C35—C36—C37	119.9 (2)
C16—P7—C24	106.22 (9)	C32—C37—C36	120.7 (2)
P7—C8—C9	123.78 (14)	C2—N38—C39	131.75 (16)
P7—C8—C15	117.37 (14)	N38—C39—C40	114.83 (16)
C9—C8—C15	118.61 (18)	N38—C39—C44	126.28 (17)
C8—C9—C10	121.02 (18)	C40—C39—C44	118.84 (17)
C9—C10—C11	119.48 (19)	C39—C40—C41	120.24 (19)
C10—C11—O12	125.2 (2)	C40—C41—C42	121.4 (2)
C10—C11—C14	120.2 (2)	C40—C41—C49	120.0 (2)
O12—C11—C14	114.5 (2)	C42—C41—C49	118.5 (2)
C11—O12—C13	117.9 (2)	C41—C42—C43	118.07 (19)
C11—C14—C15	120.1 (2)	C42—C43—C44	121.9 (2)
C8—C15—C14	120.52 (19)	C42—C43—C45	117.7 (2)

P7—C16—C17	121.51 (15)	C44—C43—C45	120.4 (2)
P7—C16—C23	120.62 (15)	C43—C44—C39	119.49 (19)
C17—C16—C23	117.86 (19)	C43—C45—F46	113.5 (2)
C16—C17—C18	121.11 (19)	C43—C45—F47	112.4 (3)
C17—C18—C19	119.34 (19)	F46—C45—F47	106.1 (3)
C18—C19—O20	124.2 (2)	C43—C45—F48	112.4 (3)
C18—C19—C22	120.8 (2)	F46—C45—F48	105.4 (3)
O20—C19—C22	115.0 (2)	F47—C45—F48	106.5 (3)
C19—O20—C21	116.9 (2)	C41—C49—F50	113.9 (2)
C19—C22—C23	119.2 (2)	C41—C49—F51	112.6 (2)
C16—C23—C22	121.6 (2)	F50—C49—F51	108.9 (3)
P7—C24—C25	122.52 (16)	C41—C49—F52	112.1 (3)
P7—C24—C31	119.05 (14)	F50—C49—F52	104.6 (2)
C25—C24—C31	118.41 (18)	F51—C49—F52	104.1 (2)
C24—C25—C26	120.3 (2)		

Table 4

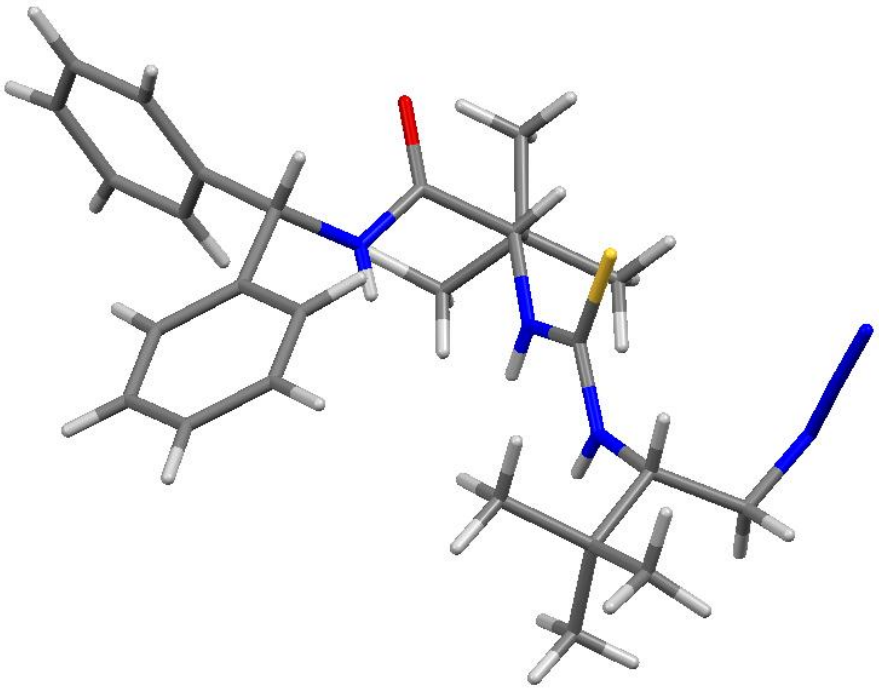
Hydrogen-bond geometry (Å, º)

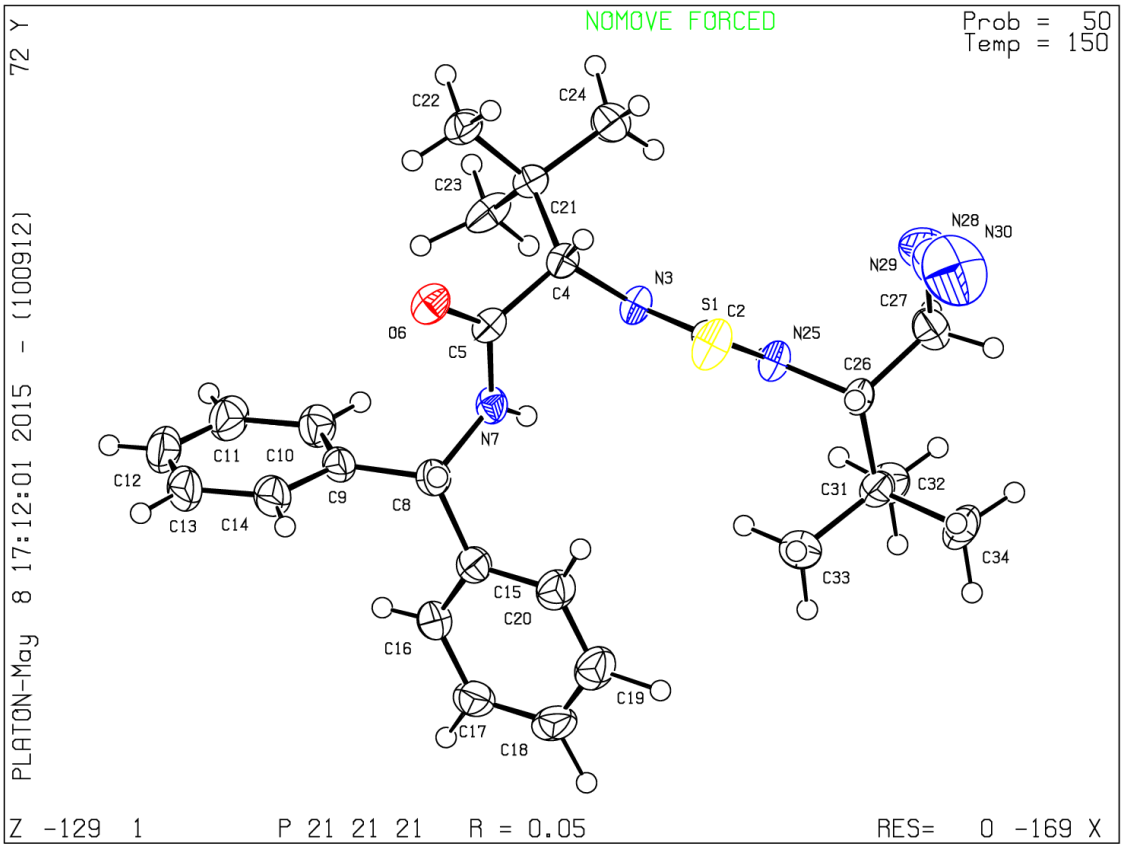
D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C15—H151···C37^{i}	0.97	2.54	3.483 (4)	163
C17—H171···O28^{ii}	0.94	2.46	3.293 (4)	147
N3—H31···N6^{i}	0.84	2.17	2.975 (4)	161
N38—H381···N6^{i}	0.85	2.17	2.987 (4)	161

Symmetry codes: (i) *y*, *x*, −*z*; (ii) *y*, *x*, −*z*+1.

Low temperature single crystal X-ray diffraction data were collected for **4b** and **4c** using a Nonius Kappa CCD diffractometer. Intensity data were reduced using Denzo-SMN (with SCALEPACK) [348] including unit cell refinement, inter-frame scaling and corrections for absorption. The structures were solved with SuperFlip[349] and refined with CRYSTALS.[350,351] Although it was necessary to model disordered solvent in **4b** with PLATON/SQUEEZE,[352,353] the final Flack *x* parameter[354,355] and Bayesian analysis the Bijvoet pairs[356,357] for both compounds was in agreement with the assignment from the initial amino acid.

9.3.4 X-ray Diffraction Data for 306





Crystal data	
Chemical formula	$C_{26}H_{36}N_6OS$
M_r	480.68
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	150
a, *b*, *c* (Å)	10.3102 (1), 24.4640 (3), 10.7881 (1)
V (Å^3)	2721.07 (5)
Z	4
Radiation type	Mo *K*α
μ (mm^{-1})	0.15
Data collection	
Diffractometer	Nonius KappaCCD diffractometer
Absorption correction	Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	1.00, 1.00
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	9852, 4936, 4602
R_{int}	0.018
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.603
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.045, 0.117, 0.94
No. of reflections	4936
No. of parameters	451
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.68, −0.30

Selected geometric parameters (Å, º)			
S1—C2	1.678 (2)	C15—C20	1.403 (4)
C2—N3	1.354 (3)	C16—C17	1.382 (4)
C2—N25	1.349 (3)	C17—C18	1.380 (4)
N3—C4	1.451 (3)	C18—C19	1.386 (5)
C4—C5	1.532 (3)	C19—C20	1.383 (4)
C4—C21	1.560 (3)	C21—C22	1.528 (3)
C5—O6	1.243 (3)	C21—C23	1.527 (3)
C5—N7	1.327 (3)	C21—C24	1.535 (4)
N7—C8	1.478 (3)	N25—C26	1.459 (3)
C8—C9	1.507 (3)	C26—C27	1.527 (3)
C8—C15	1.523 (3)	C26—C31	1.546 (3)

C9—C10	1.379 (4)	C27—N28	1.469 (4)
C9—C14	1.393 (4)	N28—N29	1.208 (4)
C10—C11	1.395 (4)	N29—N30	1.169 (5)
C11—C12	1.376 (5)	C31—C32	1.536 (4)
C12—C13	1.373 (5)	C31—C33	1.527 (4)
C13—C14	1.386 (4)	C31—C34	1.538 (4)
C15—C16	1.386 (4)		
S1—C2—N3	122.18 (17)	C15—C16—C17	121.1 (3)
S1—C2—N25	123.79 (17)	C16—C17—C18	120.4 (3)
N3—C2—N25	114.00 (19)	C17—C18—C19	119.4 (3)
C2—N3—C4	124.13 (19)	C18—C19—C20	120.4 (3)
N3—C4—C5	111.91 (19)	C15—C20—C19	120.4 (3)
N3—C4—C21	110.52 (18)	C4—C21—C22	109.9 (2)
C5—C4—C21	113.61 (19)	C4—C21—C23	111.2 (2)
C4—C5—O6	121.1 (2)	C22—C21—C23	109.1 (2)
C4—C5—N7	117.2 (2)	C4—C21—C24	107.8 (2)
O6—C5—N7	121.6 (2)	C22—C21—C24	108.5 (2)
C5—N7—C8	122.2 (2)	C23—C21—C24	110.4 (2)
N7—C8—C9	112.54 (19)	C2—N25—C26	125.45 (19)
N7—C8—C15	108.23 (19)	N25—C26—C27	108.9 (2)
C9—C8—C15	114.5 (2)	N25—C26—C31	111.99 (18)
C8—C9—C10	122.2 (2)	C27—C26—C31	113.9 (2)
C8—C9—C14	118.4 (2)	C26—C27—N28	113.6 (2)
C10—C9—C14	119.4 (2)	C27—N28—N29	112.5 (3)
C9—C10—C11	120.1 (3)	N28—N29—N30	173.7 (4)
C10—C11—C12	119.8 (3)	C26—C31—C32	111.1 (2)
C11—C12—C13	120.7 (3)	C26—C31—C33	108.4 (2)
C12—C13—C14	119.6 (3)	C32—C31—C33	110.2 (2)
C9—C14—C13	120.5 (3)	C26—C31—C34	109.2 (2)
C8—C15—C16	123.1 (2)	C32—C31—C34	109.6 (2)
C8—C15—C20	118.7 (2)	C33—C31—C34	108.2 (2)
C16—C15—C20	118.2 (2)		

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Bifunctional Iminophosphorane Organocatalysts for Enantioselective Synthesis: Application to the Ketimine Nitro-Mannich Reaction

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Supporting Information

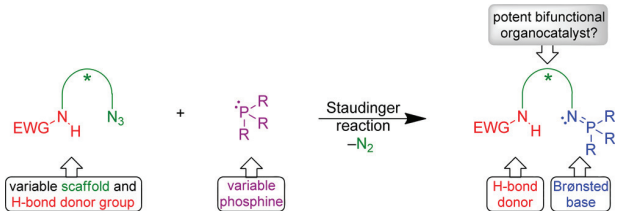
ABSTRACT: The design, synthesis, and development of a new class of modular, strongly basic, and tunable bifunctional Brønsted base/H-bond-donor organocatalysts are reported. These catalysts incorporate a triarylimino-phosphorane as the Brønsted basic moiety and are readily synthesized via a last step Staudinger reaction of a chiral organoazide and a triarylphosphine. Their application to the first general enantioselective organocatalytic nitro-Mannich reaction of nitromethane to unactivated ketone-derived imines allows the enantioselective construction of β-nitroamines possessing a fully substituted carbon atom. The reaction is amenable to multigram scale-up, and the products are useful for the synthesis of enantiopure 1,2-diamine and α-amino acid derivatives.

The addition of a carbon- or heteroatom-centered acid to an electron-deficient carbon−carbon (C═C) or carbon−heteroatom (C═X) double bond is a reaction of fundamental importance in organic synthesis. Such reactions offer perfect atom economy, are often energetically favorable, and can generate products that are chiral.[1] Brønsted basic reagents can be employed to catalyze the addition by generating the ion-paired conjugate base as the key nucleophilic entity, and asymmetry in the Brønsted base can relay through to the product via energetically discriminated transition states.[2] To this end, a plethora of chiral single-enantiomer Brønsted bases have been developed for a wide range of enantioselective addition reactions. These range from relatively weak chiral tertiary amines to organic superbases[3] such as amidines,[4] guanidines,[5] phosphazenes,[6] and cyclopropenimines.[7]

Within the past decade, one particular class of base that has received considerable attention is that of the bifunctional Brønsted base/H-bond donor organocatalyst.[8] These catalysts typically possess both a tertiary amine group and a hydrogen-bond donor group appropriately positioned on a chiral scaffold. Additional organization of the transition structure through stabilization of developing negative charge by the H-bond donor can result in increased reaction rates and/or enantioselectivity relative to H-bond donor free analogues.[9] Although this class continues to demonstrate synthetic utility, it is not without its limitations; reaction times are often long even with the most reactive reagent combinations, and arguably the range of pro-nucleophiles and electrophiles amenable to asymmetric union is relatively narrow. This low catalytic activity often stems from the relatively weak Brønsted basicity of the tertiary amine moiety, providing insufficient activation of the pro-nucleophile. To address some of these limitations, we proposed to develop a new class of bifunctional organocatalysts that possessed a much stronger and tunable Brønsted basic group. Our hope was that through the synergistic effects of the stronger Brønsted base and the H-bond donor, good reactivity and selectivity in new and challenging enantioselective organocatalytic addition reactions would be obtained. Herein we report our findings.

From the outset, we wanted a design that relied on a clean and efficient last step generation of the Brønsted basic moiety of the catalyst; this would greatly simplify their synthesis and handling. To this end we considered the Staudinger reaction[10] of a triarylphosphine and an enantiopure organoazide possessing an effective H-bond donor group (Scheme 1). Our hope was that

Scheme 1. Concept and Design of a New Class of Bifunctional Iminophosphorane (BIMP) Organocatalysts



the strong nucleophilicity of the triarylphosphine would create a strongly Brønsted basic iminophosphorane moiety through favorable loss of dinitrogen gas.[11] As many triarylphosphine reagents are readily available, this simple design could allow the synthesis of a range of bifunctional catalysts with electronic and/or steric variations at the iminophosphorane moiety. Further variations to the chiral scaffold and the H-bond donor group would add favorably to the diversity of catalysts accessible through this design.

The premise of our catalyst design was the enhanced Brønsted basicity of the triaryliminophosphorane functionality relative to the weak tertiary amine group. Interestingly, whereas the basicities of triaminoiminophosphoranes are reported—such as P_1-^{t}Bu with a pK_{BH+} (MeCN) of 26.98 (Figure 1)—the Brønsted basicities of triaryliminophosphoranes are not. Accordingly, to quantify the basicity of triaryliminophosphoranes, pK_{BH+} measurements were carried out on a model triphenylphosphine-derived iminophosphorane, **1a** (derived from cyclohexyl azide; see Supporting Information). Indeed its pK_{BH+} (MeCN) of 22.7 was determined to be 4 orders of magnitude greater than

Received: September 3, 2013
Published: October 9, 2013

   dx.doi.org/10.1021/ja409121s | J. Am. Chem. Soc. 2013, 135, 16348−16351

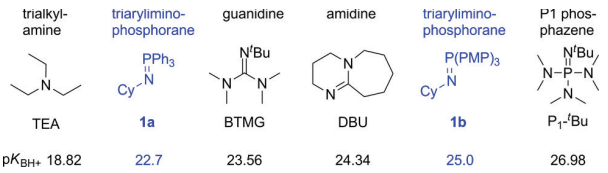
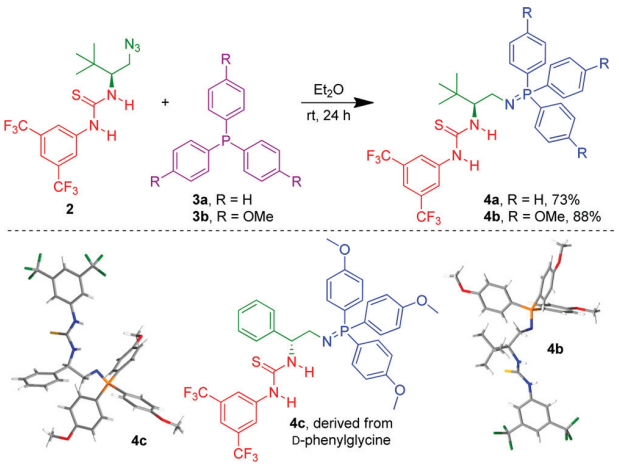


Figure 1. pK_{BH+} (MeCN) measurements of a tertiary amine and some common organic superbases and two triaryliminophosphorane superbases **1a** and **1b**. PMP = *para*-methoxyphenyl.

that of triethylamine and comparable to that of guanidines and other organic superbases, thus validating our design concept.[3,12] Importantly, tris(4-methoxyphenyl)phosphine-derived iminophosphorane **1b** was found to be a further hundred-fold more basic (pK_{BH+} (MeCN) of 25.0), thus demonstrating that the basicity of the triaryliminophosphorane moiety can be readily modified by varying the electronics of the triarylphosphine component.

L-*tert*-Leucine-derived azide **2** was then prepared on a gram scale (see Supporting Information) and reacted separately with equimolar quantities of both triphenylphosphine and tris(4-methoxyphenyl)phosphine in anhydrous diethyl ether (Scheme 2). In both cases after stirring for 24 h bifunctional

Scheme 2. Synthesis of Two Representative BIMPs and Single-Crystal X-ray Structures of 4b and 4c (P, orange; N, blue; S, yellow; O, red; F, green; H, white)

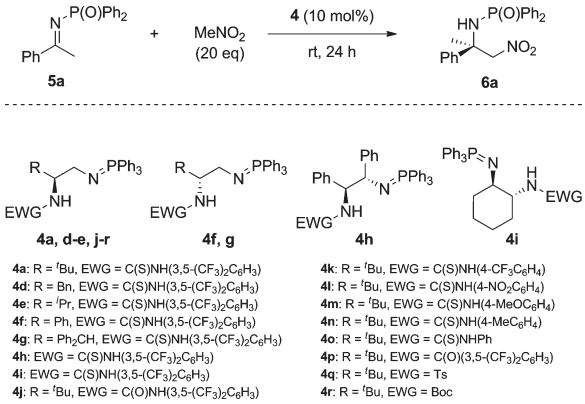


iminophosphoranes **4a** and **4b** were isolated as bench-stable solids by precipitation and filtration.[13] In the case of tris(4-methoxyphenyl)phosphine-derived catalyst **4b**, crystals of suitable quality for single-crystal X-ray diffraction were obtained (Scheme 2), allowing the unambiguous determination of its solid-state structure. Furthermore, in the enantiomeric series, the single-crystal X-ray structure of D-phenylglycine-derived iminophosphorane **4c** was also obtained.

To demonstrate the synthetic potential of this new class of bifunctional organocatalysts, we selected the challenging enantioselective organocatalytic nitro-Mannich (or aza-Henry) reaction of nitromethane with unactivated ketone-derived imines (ketimines). Unlike the many variations of the well-developed organocatalytic enantioselective nitro-Mannich reaction of aldehyde-derived imines (aldimines),[14] the corresponding ketimine variant has no reported general solution.[15] We believed that the strong Brønsted basicity of the triaryliminophosphorane and the appropriate positioning of an effective H-bond donor group over a suitable chiral scaffold could provide both the potency and control required.[16]

To expedite screening, a library of BIMP catalysts (**4a**, **4d**–**i**) was made *in situ* from the corresponding catalytically inactive azides and triphenylphosphine by simply stirring equimolar amounts in diethyl ether at rt for 24 h (see Supporting Information). This library was assessed for performance in the reaction of nitromethane with acetophenone-derived *N*-diphenylphosphinoyl (DPP) ketimine **5a** (Table 1).[17] Pleasingly,

Table 1. Proof of Concept and Optimization Studies in the Nitro-Mannich Reaction of Nitromethane with *N*-Diphenylphosphinoyl Ketimine 5a[a]



entry	catalyst	conversion,[b] ee[c] (%)	entry	catalyst	conversion,[b] ee[c] (%)
1	**4a**	98, *85*	9	**4k**	98, *79*
2	**4d**	93, *78*	10	**4l**	98, *84*
3	**4e**	94, *77*	11	**4m**	98, *70*
4	**4f**	95, *77*[d]	12	**4n**	99, *68*
5	**4g**	93, *70*[d]	13	**4o**	98, *73*
6	**4h**	48, *34*[d]	14	**4p**	98, *11*
7	**4i**	98, *20*[d]	15	**4q**	92, *0*
8	**4j**	97, *79*	16	**4r**	99, *0*

[a]Reactions performed using 0.2 mmol of ketimine **5a** in 0.2 mL of $MeNO_2$ at rt. [b]Conversion was determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]Enantiomeric excess (ee) was determined by HPLC analysis on a chiral stationary phase. [d]Enantiomer (*S*)-**6a** was obtained.

using neat nitromethane (20 equiv) and 10 mol % catalyst, all BIMPs demonstrated excellent reactivity in the formation of addition product **6a**; conversion after 24 h was near full with all but catalyst **4h**. Furthermore, enantioselectivities were good except with catalysts **4h** and **4i** (Table 1, entries 6, 7). L-*tert*-Leucine-derived catalyst **4a** outperformed the other catalysts in terms of enantioselectivity (85% ee at rt, Table 1, entry 1) and was therefore selected as the scaffold of choice for the remainder of the optimization studies.

BIMPs **4j**–**r** possessing a range of H-bond donor groups including thiourea, urea, amide, sulfonamide, and carbamate were investigated for performance. In all cases good conversion to addition product **6a** was observed after 24 h at rt (Table 1, entries 8–16). Pleasingly both urea and thioureas with electron-donating or electron-withdrawing substituents (**4a**, **4j**–**o**) attached to the aromatic ring imparted high levels of enantioselectivity in the reaction (Table 1, entries 1, 8–13). However, electron-deficient aryl amide **4p** afforded the product

dx.doi.org/10.1021/ja409121s | J. Am. Chem. Soc. 2013, 135, 16348–16351

with poor enantiocontrol (Table 1, entry 14), and both sulfonamide **4q** and carbamate **4r** yielded the product in racemic form (Table 1, entries 15, 16). From these results, it was clear that the H-bond donor group was playing a key role in controlling the stereochemical outcome of the reaction and that the Schreiner-type 3,5-bis(trifluoromethyl)phenyl thiourea moiety of catalyst **4a** was optimal.[18]

With the best scaffold and H-bond donor group identified, we turned our attention to the Brønsted base moiety and studied how the reaction rate varied as a function of the electronics of the triarylphosphine component. Catalyst **4a** (R = H) and its analogues **4b** (R = MeO) and **4s** (R = Cl) were used in the reaction of ketimine **5a** with nitromethane, and conversion to addition product **6a** was measured by ^{1}H NMR analysis (Figure 2). The reaction rate was indeed governed by the aryl

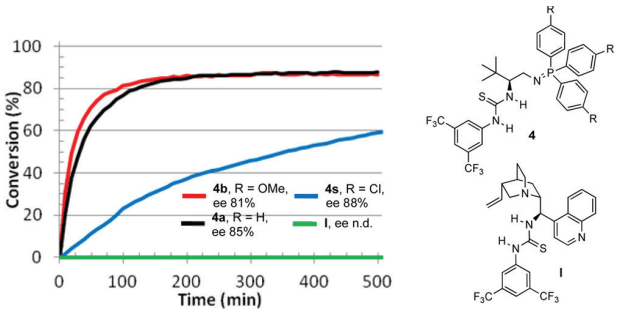


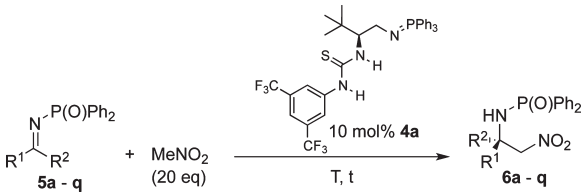
Figure 2. Comparison of reaction rates with BIMP catalysts **4a**, **4b**, and **4s** and cinchonine-derived bifunctional organocatalyst **I**.

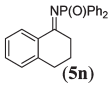
substituents of the iminophosphorane moiety. The reaction with catalyst **4s** was slower than that with **4a** or **4b**, in line with a more electron-deficient triarylphosphine generating a weaker base. As a direct comparison, when cinchonine-derived bifunctional organocatalyst **I** was used as the catalyst in the same ^{1}H NMR kinetic experiment, *no product was detected even after a prolonged* reaction *time of 32 h*. The above experiments clearly demonstrate that the enhanced basicity of iminophosphoranes compared to tertiary amines is responsible for the increase in catalytic activity.

Although catalyst **4b** was marginally superior to **4a** in terms of reaction rate, **4a** was more enantioselective and was therefore chosen as the catalyst to investigate the substrate scope in the nitro-Mannich addition of nitromethane to ketimines. To maximize enantioselectivity, reactions were performed in chilled (0 or −15 °C) nitromethane. Good to excellent enantioselectivities were obtained with aromatic ketone-derived imines bearing either electron-withdrawing or electron-donating substitutents (up to 95% yield, up to 95% ee; Table 2, entries 1−12). Phenyl ethyl ketone-derived imine **5m** also afforded the product with high enantioselectivity, as did the tetralone-derived imine substrate **5n** albeit in lower yield in the latter case (Table 2, entries 13, 14). Heteroaromatic ketimines **5o** and **5p** gave the desired products in near quantitative yields and with good enantioselectivities (Table 2, entries 15, 16). Pleasingly, the reaction was also applicable to aliphatic ketimine **5q** (Table 2, entry 17).[19]

The performance of our new BIMP catalysts for enantioselective catalysis on a preparative scale was investigated next. To minimize reaction time, the most active catalyst, **4b**, was selected for this purpose. Using 1 mol % **4b**, 10 g of ketimine **5a** was reacted with 10 equiv of nitromethane at rt over 21 h to afford the

Table 2. Scope of Asymmetric Nitro-Mannich Reaction of Ketimines[a]



Entry	R^1	R^2	T/°C	t/h	Yield (%)	ee (%)[b]
1	C_6H_5 (**5a**)	Me	−15	96	86	95
2	4-MeC_6H_4 (**5b**)	Me	0	48	93	89
3	4-MeOC_6H_4 (**5c**)	Me	0	48	95	91
4	3-MeOC_6H_4 (**5d**)	Me	0	48	88	91
5	2-MeOC_6H_4 (**5e**)	Me	0	48	62	93
6	4-PhC_6H_4 (**5f**)	Me	0	24	92	90
7	4-$NO_2C_6H_4$ (**5g**)	Me	−15	48	92	86
8	2-FC_6H_4 (**5h**)	Me	−15	96	89	94
9	4-ClC_6H_4 (**5i**)	Me	0	20	90	90
10	4-BrC_6H_4 (**5j**)	Me	0	48	84	90
11	3,4-$Cl_2C_6H_3$ (**5k**)	Me	0	20	92	87
12	3,5-$(CF_3)_2C_6H_3$ (**5l**)	Me	−15	96	95	90
13	C_6H_5 (**5m**)	Et	0	48	95	92
14	 (**5n**)		−15	96	40*	92
15	2-furyl (**5o**)	Me	0	48	97	84
16	3-pyridyl (**5p**)	Me	0	48	97	82
17	cyclohexyl (**5q**)	Me	0	48	71	78

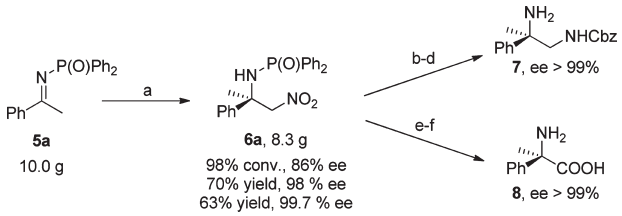
[a]Reactions were carried out on 0.2 mmol of **5** at the indicated temperature. [b]Enantiomeric excess (ee) was determined by HPLC analysis on a chiral stationary phase. *Conversion was 50%.

crude product in 98% conversion and 86% ee. After recrystallization, 8.3 g of addition product **6a** (70% yield) was obtained in 98% ee, and a further recrystallization afforded **6a** in >99% ee. In a short demonstration of synthetic utility this enantiopure β-nitroamine was converted to the corresponding 1,2-diamine derivative **7**[20] via a nickel boride-mediated reduction of the nitro group followed by Cbz protection and then DPP removal. Furthermore, **6a** was transformed into fully substituted α-amino acid **8**[21] by a two-step sequence involving a Nef oxidation followed by DPP removal (Scheme 3).

In summary, we have designed and developed a new and effective class of modular bifunctional iminophosphorane superbase organocatalysts and have applied it to the first metal-free catalytic enantioselective addition of nitromethane to unreactive ketone-derived imines, a reaction where existing tertiary amine organocatalysts are impotent. The synthesis of the catalysts from catalytically inactive and readily synthesized azide precursors and triarylphosphines allows for rapid catalyst screening and optimization. The nitro-Mannich reaction of ketimines can be performed on a multigram scale and allows ready access to synthetically relevant, nitrogen-containing chiral building blocks possessing a fully substituted carbon atom. Work to uncover the full capabilities of this new catalyst design is ongoing, and the results will be disclosed in due course.

dx.doi.org/10.1021/ja409121s | J. Am. Chem. Soc. 2013, 135, 16348−16351

Scheme 3. Preparative-Scale Synthesis of 6a and Derivatization into Enantiopure Diamine 7 and Quaternary α-Amino Acid 8[a]



5a 10.0 g

6a, 8.3 g
98% conv., 86% ee
70% yield, 98 % ee
63% yield, 99.7 % ee

7, ee > 99%

8, ee > 99%

[a]Reagents and conditions: (a) 1 mol % **4b** (231 mg), 17 mL of $MeNO_2$ (10 equiv), 21 °C, 21 h, recrystallization (propan-2-ol), 70%; (b) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 84%; (c) CbzCl, Na_2CO_3, H_2O/dioxane, 90%; (d) HCl, MeOH, 73%; (e) $KMnO_4$, KOH, KH_2PO_4, ^{t}BuOH; (f) HCl, MeOH, 57% over 2 steps.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the EPSRC (Leadership Fellowship to D.J.D., Postdoctoral Fellowship to M.G.N., and Studentship to A.J.M.F.), the EC (IEF to M.G.N. [PIEF-GA-2009-254637]), and AstraZeneca (Studentship to A.J.M.F.). We also thank Alison Hawkins for X-ray structure determination and the Oxford Chemical Crystallography Service for use of the instrumentation. X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under accession code **966013-966014**.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 May 2014 (01.05.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/064466 A3

(51) International Patent Classification:
B01J 31/02 (2006.01)

(21) International Application Number:
PCT/GB2013/052808

(22) International Filing Date:
28 October 2013 (28.10.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1219300.9 26 October 2012 (26.10.2012) GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
12 June 2014

(54) Title: BIFUNCTIONAL ORGANIC CATALYSTS

$$(R^1)_3P{=}N\text{-}Z\text{-}NH\text{-}EWG \qquad (1)$$

(57) Abstract: The present invention provides a bifunctional catalyst of the formula (1): wherein: each R^1 is independently selected from an optionally substituted alkyl group, an optionally substituted cycloalkyl group, an optionally substituted aryl group, an optionally substituted heteroaryl group, an optionally substituted aralkyl group and an optionally substituted alkaryl group; Z represents a divalent organic linking moiety optionally containing one or more stereocentres; and EWG represents an electron-withdrawing group.

WO 2014/064466 A3