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Enantioselective Rhodium-Catalysed Addition of Allylboron Reagents to Cyclic Imines

and

Enantioselective Nickel-Catalysed Michael Additions of 2-Acetylazaarenes to Nitroalkenes

Thesis Submitted in Accordance with the Requirement of the University of Edinburgh for the Degree of Doctor of Philosophy

By

Nawasit Chotsaeng

Supervised by
Prof. Guy C. Lloyd-Jones

EaStCHEM School of Chemistry
College of Science and Engineering

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Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in October 2011, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Signed

Nawasit Chotsaeng

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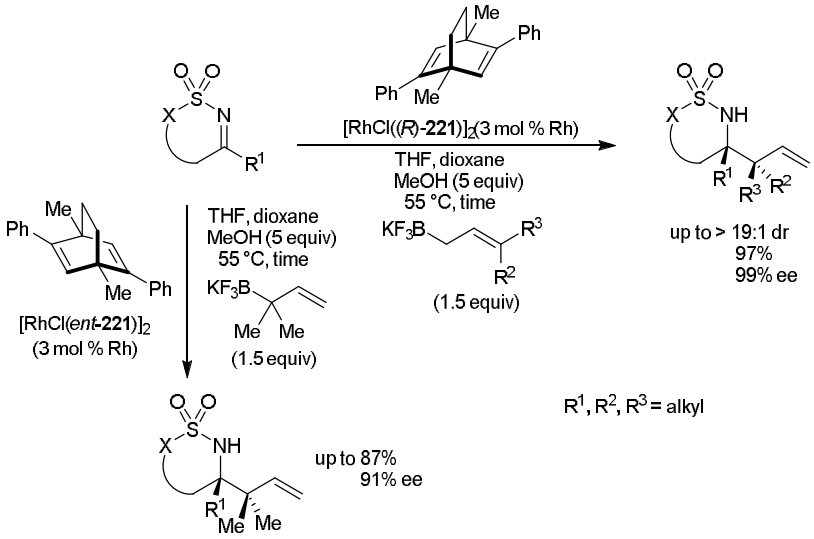
Abstract

I. Enantioselective Rhodium-Catalysed Addition of Allylboron Reagents to Cyclic Imines

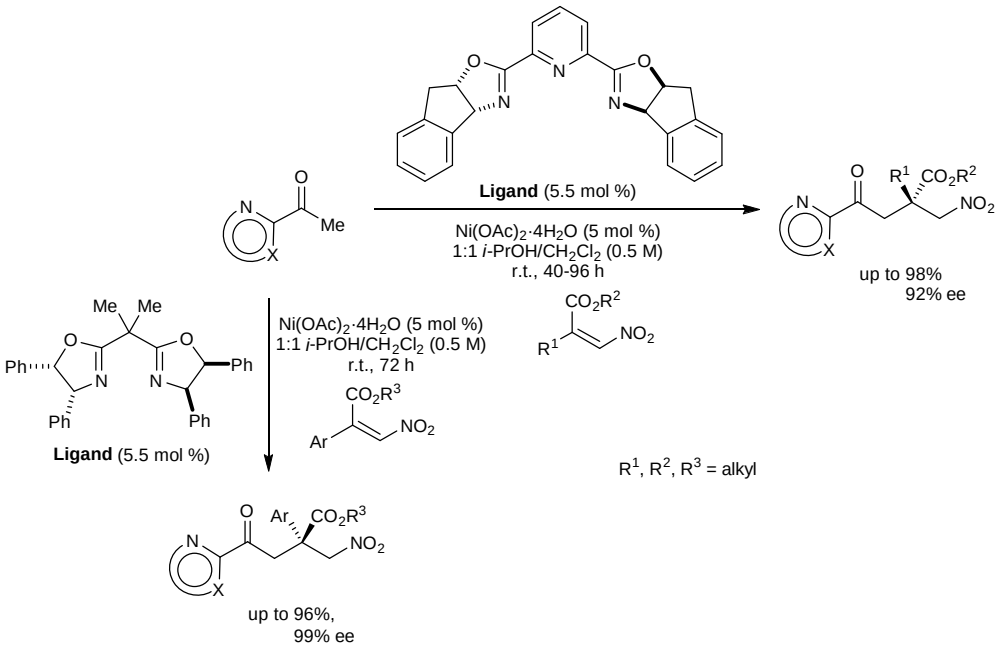
Rhodium-catalysed enantioselective allylation reaction of imines in the presence of chiral diene ligands has been investigated. Under the optimised conditions, cyclic imines provided homoallylic amines in high yield and excellent enantioselectivities. The reaction most likely proceeds *via* allylrhodium(I) intermediates, and represents the first rhodium-catalysed enantioselective nucleophilic allylation of π-electrophiles with allylboron compounds. Furthermore, the allylations display a strong preference for carbon–carbon bond formation at the more substituted terminus of the allyl fragment of the allyltrifluoroborate. To demonstrate the utility of the allylation products, representative manipulations were conducted.



II. Enantioselective Nickel-Catalysed Michael Additions of 2-Acetylazaarenes to Nitroalkenes

An enantioselective Michael addition of acylazaarenes with *α*-substituted *β*-nitroacrylates in the presence of a chiral Ni(II)–*bis*(oxazoline) complexes has been developed. A range of azaaryl nucleophiles were shown to react with a variety of nitroalkenes to construct highly functionalised Michael addition products which contain

a stereogenic all-carbon quaternary stereocentre with moderate to high yields and enantioselectivities. A possible mechanism for this reaction has been proposed.



List of Abbreviations

[α]	specific rotation
Ac	acetyl
acac	acetylacetonate
ACAT	acyl coenzyme A, cholesterol *O*-acyltransferase
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
9-BBN	9-borabicyclo[3.3.1]nonane
Binap	2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl
Binol	2,2′-dihydroxy-1,1′-binaphthyl
Bn	benzyl
Boc	*t*-butyloxycarbonyl
bod	bicyclo[2.2.2]octadiene
Box	*bis*(oxazoline)
br	broad
BSTFA	*N*,*O*-*bis*(trimethylsilyl)trifluoroacetamide
Bu	butyl

Bz	benzoyl
Calcd	calculated
cat.	catalytic
cod	1,5-cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
ºC	Celsius
δ	chemical shift (NMR)
D	deuterium
D	dextrorotatory
d	doublet
DCE	dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
ddt	doublet of doublet of triplets
DEAD	diethyl azodicarboxylate

DIBAL-H	diisobutylaluminium hydride
DKR	dynamic kinetic resolution
DMA	dimethylacetamide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dpp	diphenylphosphinoyl
dppe	1,2-*bis*(diphenylphosphino)ethane
dppf	1,1′-*bis*(diphenylphosphino)ferrocene
dq	doublet of quartets
dr	diastereomeric ratio
dt	doublet of triplets
dtd	doublet of triplet of doublets
E	electrophile
E	entgegen (opposite)
ee	enantiomeric excess
EI	electron impact
ent	entgegen (opposite)
equiv	equivalent

er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
FG	functional group
Fmoc	fluorenylmethyloxycarbonyl
FT	Fourier transform
g	grams
GC	gas chromatography
h	hour(s)
hept	heptets
HMDS	hexamethyldisilazide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	iso
IC_{50}	the half maximal inhibitory concentration
IR	infrared
KR	kinetic resolution
L	ligand

L	laevorotary
m	multiplet
m	meta
M	metal (complex) *or* mol L^{-1} *or* molecular ion
Me	methyl
mg	milligram
MHz	megaHertz
MIDA	*N*-methyliminodiacetic acid
min	minute(s)
mL	millilitre
mM	millimolar
MOP	monodentate phosphine ligand
m.p.	melting point
Ms	mesyl (methanesulfonyl)
MS	mass spectrometry *or* molecular sieves
mW	milliWatt
NHC	*N*-heterocyclic carbene
nM	nanomolar
NMR	nuclear magnetic resonance spectroscopy

Ns	nosyl
Nu	nucleophile
o	ortho
Ox	oxazoline
p	para
Ph	phenyl
Pin	pinacol
ppm	parts per million
Pr	propyl
Py	pyridine
q	quartet
qd	quartet of doublets
R	rectus (right)
rac	racemic
R_f	retention factor
r.t.	room temperature
S	sinister (left)
s	singlet
SDS	sodium dodecyl sulfate

T	triplet
t	tert(iary)
TBAB	tetrabutyl ammonium bromide
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenylsilyldifluorosilicate
TCA	trichloroacetic acid
td	triplet of doublets
tdd	triplet of doublet of doublets
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
t_r	retention time
Troc	trichloroethoxycarbonyl
TS	transition state
Ts	tosyl
US	United States
UV	ultraviolet spectroscopy

wt.%	weight percent
w/v	weight per volume
Z	zusammen (together)

Table of Contents

1. Enantioselective Rhodium-Catalysed Addition of Allylboron Reagents to Cyclic Imines

1.1 The Importance of Chiral Amines in Organic Chemistry

Chiral amines are widespread structural units in both natural and synthetic bioactive molecules, such as those shown in **Figure 1.1**.[1,2] These unique biological activities have resulted in them gaining much attention within chemical industries where they are powerful pharmacophores for defining new pharmaceutical drugs. Nowadays, a number of drugs are amines or contain functional groups derived from amines, and an increasing number of these molecules feature a non-racemic stereocentre. The development of such enantioenriched biologically active molecules, whether from natural or synthetic sources, relies on the development of general and efficient synthetic methods to prepare chiral amines.

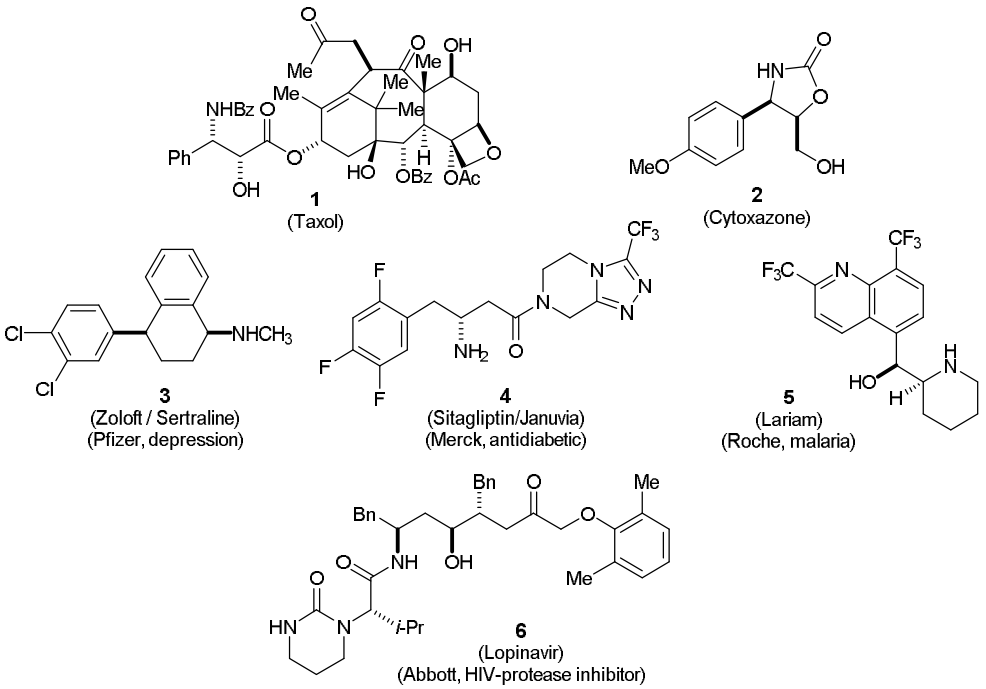


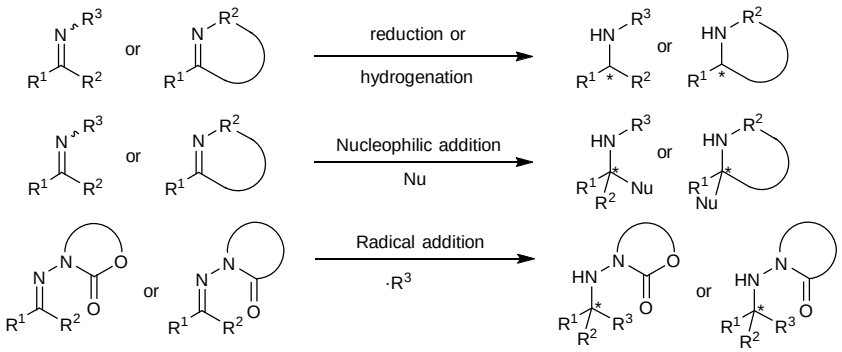
Figure 1.1: Amine containing natural and synthetic chiral compounds.

As mentioned above, chiral amines are crucially important, therefore, the following section was to understand the general approaches to obtain enantioenriched amines.

1.1.1 The Synthesis of Enantioenriched Amines

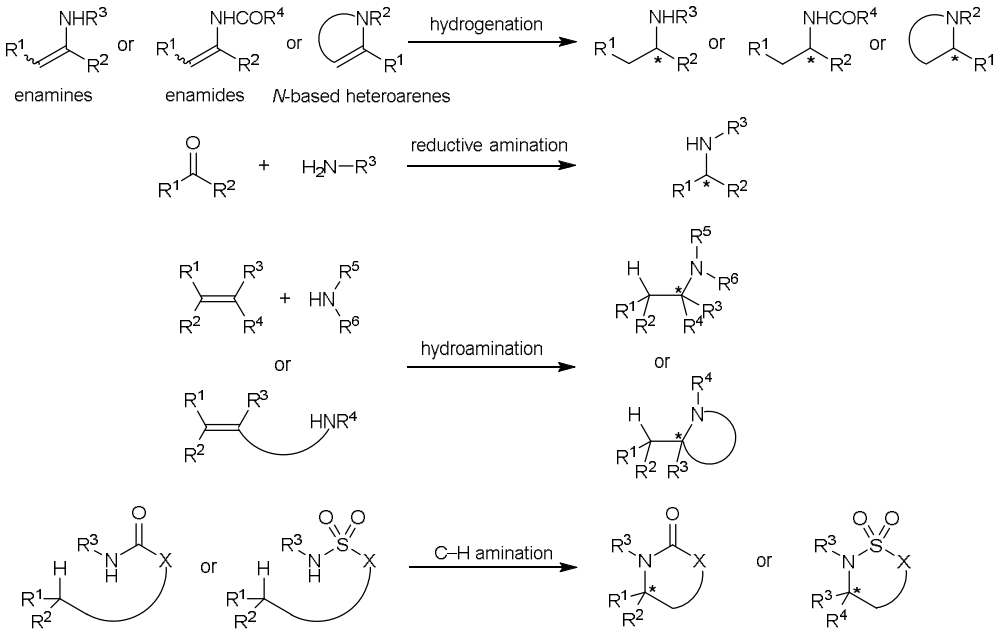
Chiral amine synthesis is a huge area and there are numerous routes to prepare enantioenriched amines using both metal catalysts and organocatalysts as well as biocatalysts.[1] These numerous methods are too vast to concisely summarise within this text, thus, only chiral amines prepared from imines, racemic amines, enamines, enamides, and *N*-based heteroarenes will be discussed.

The transformation of imines into chiral amines has been thoroughly investigated. Amongst several reduction pathways, asymmetric hydrogenation and transfer hydrogenation are a favoured due to atom economy and a straightforward protocol for the preparation of chiral α-secondary amines.[3] Another useful method involves the addition of nucleophiles to imines which generates both chiral α-secondary amines and chiral α-tertiary amines as desired products.[4] This method is possibly considered to be the widest studied process because it covers various types of nucleophiles such as stabilised and unstabilised carbanion reagents. In terms of stabilised carbanion reagents, Aza-Morita-Baylis-Hillman reactions,[5] Mannich reactions[6] and related reactions are a very common example. On the contrary, alkylation,[7] allylation,[8] alkenylation, arylation[9] and alkynylation[10] are well-known reactions using sp^3, sp^2 and sp unstabilised carbanion reagents. Although ionic reaction is a major approach of chiral amine syntheses radical reaction is also investigated currently which uses hydrazone prochiral starting materials[11] (**Scheme 1.1**).



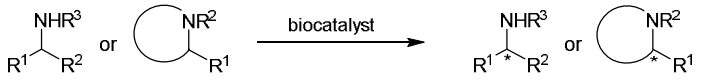
Scheme 1.1: Chiral amine synthesis using imine substrates.

In terms of other compounds aside from imines and racemic amines, asymmetric hydrogenation is a clean and convenient way to achieve chiral *α*-secondary amines. Many efficient metal catalysts and organocatalysts for this chemistry have been explored and developed by using simple starting materials such as enamines, enamides and *N*-based heterocyclic compounds.[12,13] Another option, reductive amination, the conversion of a ketone to an amine, has been gaining more and more attention in recent years.[14] However, this approach is still fairly undeveloped compared with the field of imine reduction. The addition of an amine N−H bond across an unsaturated C−C, called hydroamination, also gives chiral amines.[15] Nevertheless, the majority of catalysts for this transformation are currently confined to a limited set of substrates, requiring activated multiple C−C bonds. The last major approach to achieve chiral amines is a C−H activation process.[16] Even though a number of the intramolecular C−H amination have been reported successfully the intermolecular pathway is still challenging (**Scheme 1.2**).



Scheme 1.2: Chiral amine synthesis using carbonyl compounds, alkenes, enamines, enanmides and related substrates.

The preparation of chiral amines from racemic amines has also been reported recently. There are a few general methods that have been developed in the field, namely, kinetic resolution (KR), dynamic kinetic resolution (DKR), deracemisation, and asymmetric synthesis using enzymes, respectively.[17,18] Although some metal-catalysed reactions have been reported, most of them use enzymes or biocatalysts to convert racemic amines to chiral amines (**Scheme 1.3**).[19]



Scheme 1.3: Chiral amine synthesis from racemic amine substrates.

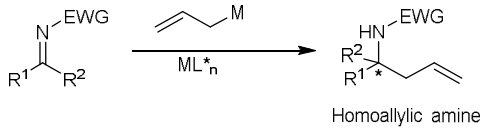
In summary, chiral amines can be synthesised from both racemic amines and prochiral compounds such as imines, enamines etc. The addition of nucleophiles to prochiral imines is regarded as one of the most important pathways to afford enantioenriched amines. In the Lam group we are interested in the allylation of imines using rhodium

catalysts. Thus, in the next section, the advantages and previously reported scopes of this transformation are discussed (**Section 1.2**).

1.2 Introduction to the Allylation of Imines

As a significant class of chiral amines, homoallylic amines are particularly important structures. They are useful building blocks for organic synthesis which allow further possible synthetic transformations due to the presence of a double bond, for examples; ozonolysis, epoxidation, dihydroxylation, hydroboration, hydrogenation, hydroformylation, cycloaddition and olefin metathesis respectively.[20] Therefore, in the last two decades, there have been many reported publications focused on developing a methodology to construct these amines.[8,21] Unsurprisingly, enantioselective nucleophilic allylation to prochiral imines is one of the most common approaches for forming this important class of compounds. A range of allylmetal nucleophiles can undergo nucleophilic addition to an activated imine in a stereoselective manner to prepare chiral homoallylic amines. Thanks to this easy way to access amines by deprotection of activating groups, together with the efficiency of this route, various complex molecules have been synthesised by utilising this methodology.[8,22,23]

As shown in the following sections, there are several straightforward ways to receive a high yield of enantiomerically pure homoallylic amines. Whereas most of methods are activated by transition metal catalysts such as Cu, Zn, Pd, Ag and In etc. (**Scheme 1.4**) some of them are mediated by chiral promoters along with either allylsilanes, allylic alcohols, allylstannanes, allylhalides, or allylborons as the allylating agent.

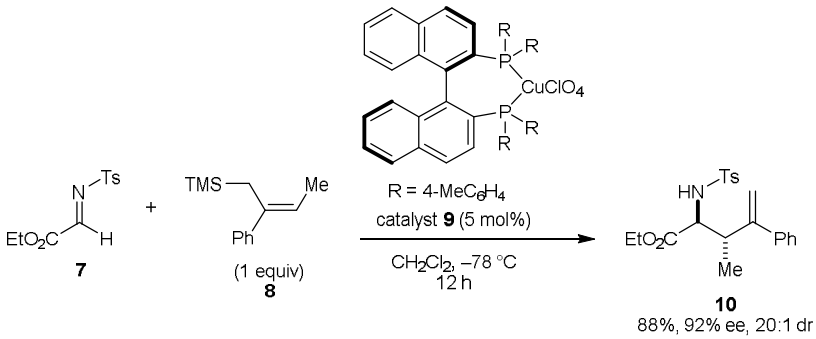


Scheme 1.4: Metal-catalysed enantioselective allylation of imines.

1.2.1 Allylation Using Allylsilanes

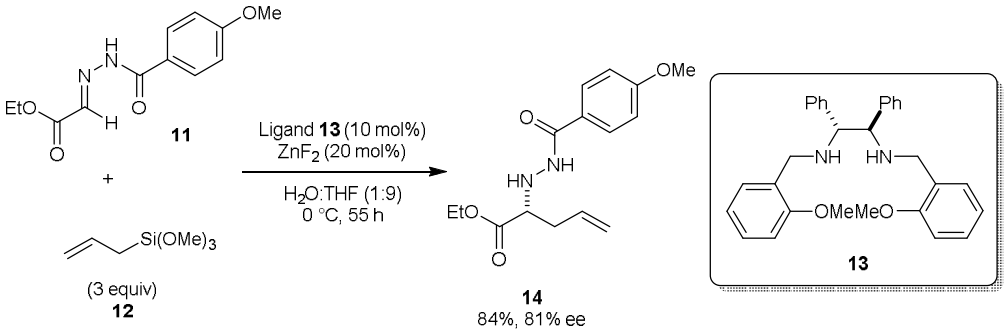
Allylsilanes have been widely used in organic synthesis for a long time.[24] As silicon is more electropositive than carbon, it exerts an electronic effect on both α- and β-carbons. In terms of activated α-carbon (or α-carbanion), silanes can stabilise this position by its partial positive charge, known as the α-effect. On the contrary, activated β-carbon (or β-carbocation) can be stabilised by hyperconjugation, called the β-effect, which involves the overlap between the empty p-orbital of the carbocation and the filled sigma molecular orbital of the C−Si bond. The weak polarisation of the C−Si bond together with the unique α- and β-effects allows an easier handling of these stable organometallic-type reagents, which, therefore becomes a useful source of functional group transformations. There are several reports that demonstrate that allylsilanes are a good allylating reagent in enantioselective allylation of imines. However, most of these reported reactions require a strong Lewis acid catalyst in order for the reaction to proceed efficiently and more detailed discussions on this topic will commence in the following sections.

Lectka and co-workers developed a methodology for the synthesis of non-natural amino acids *via* the catalytic, asymmetric alkyl- and allylations of (*R*)-imino esters by enol silanes, ketene acetals, alkenes, and allylsilanes using chiral copper(I)-phosphine complexes (**Scheme 1.5**).[25] It was found that, alkylation and allylation products were obtained with high yields (up to 97%), high enantioselectivities (up to 99% ee) and *anti*-diastereoselectivities (up to 25:1/*anti*:*syn*). Interestingly, according to the kinetic studies, the reaction was believed to proceed *via* a concerted, closed transition state and classical Lewis acidic activation of the imino ester.

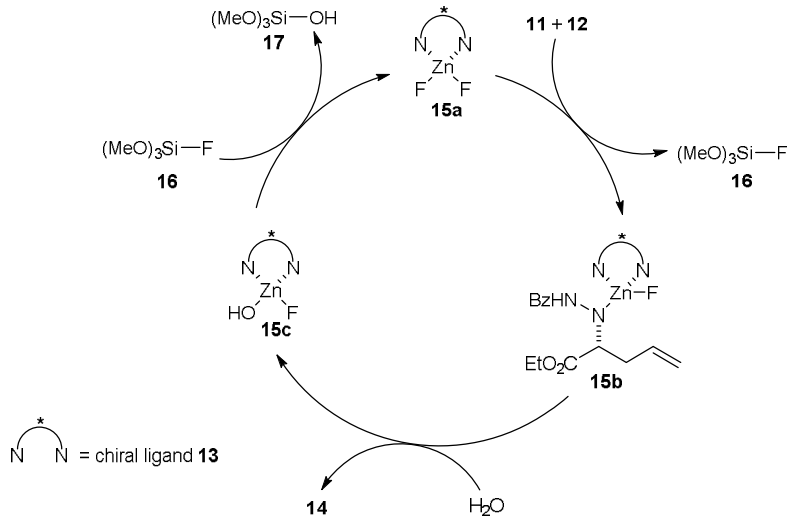


Scheme 1.5: Copper-catalysed enantioselective allylation of imino ester **7** with allylsilane **8**.

In 2003, the catalytic enantioselective allylation of acylhydrazono esters in aqueous media was reported by Kobayashi and co-workers (**Scheme 1.6**). By using ZnF_2 (20 mol%) and chiral diamine ligand **13** (10 mol%), the product **14** was obtained in good yield and enantioselectivity. The proposed mechanism suggests that zinc(II) **15a** acts as a Lewis acid to activate the hydrazone electrophile and the fluoride anion acts as Lewis base to activate the silicon atom of allyltrimethoxysilane (**12**) (**Scheme 1.7**). In addition, the methoxy substituent in the ligand **13** was found to have an essential role in attaining high yields and enantioselectivities.[26]

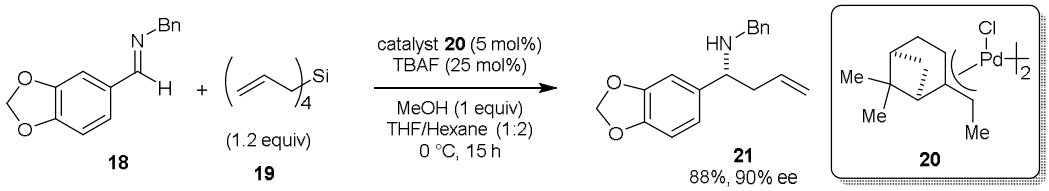


Scheme 1.6: Zinc-catalysed enantioselective allyllation of acylhydrazono ester **11**.



Scheme 1.7: Proposed mechanism for zinc-catalysed enantioselective allyllation of acylhydrazono ester **11**.

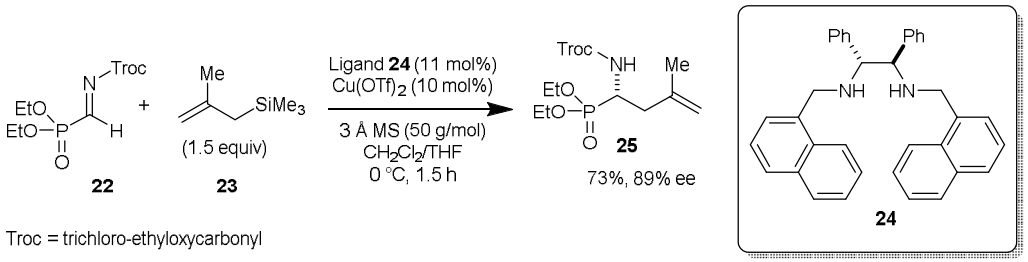
A year later, Fernandes and Yamamoto reported the allylation of aldimines with tetraallylsilane (**19**) catalysed by palladium complex **20** (**Scheme 1.8**).[27] Interestingly, the mechanism proposed also involved the fluoride anion from TBAF facilitatating the C−Si bond cleavage to form an allylpalladium complex. Methanol then promotes the protonation of the palladium amide to provide the chiral amine.



Scheme 1.8: Palladium-catalysed enantioselective allylation of aryl imine **18** in the presence of TBAF.

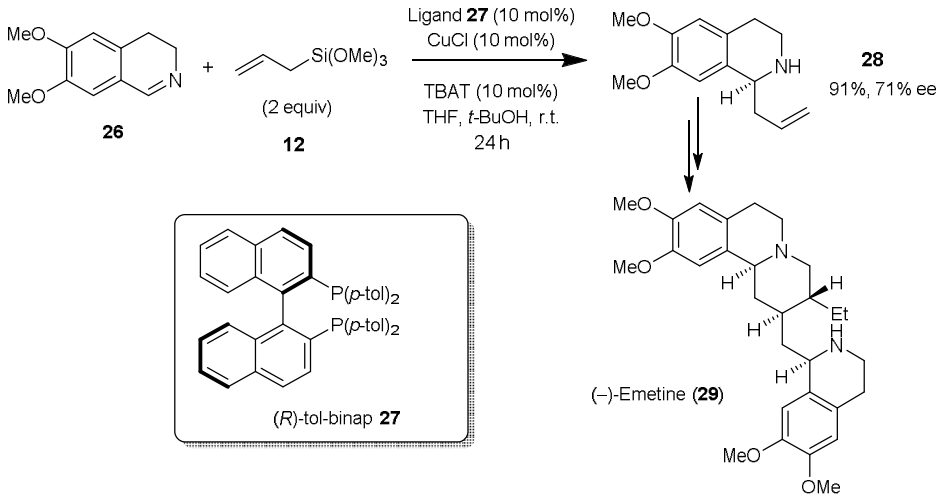
The first example of catalytic enantioselective allylations of iminophosphonates with allylsilanes using a copper catalyst with a diamine ligand was reported in 2006 (**Scheme 1.9**). Both yields and selectivities of the reaction were high, especially when

3 Å molecular sieves were employed to ensure anhydrous conditions as water was believed to partially hydrolyse the nucleophile. The slow addition of the substrate suppressed an uncatalysed background reaction allowing good results to be obtained.[28]



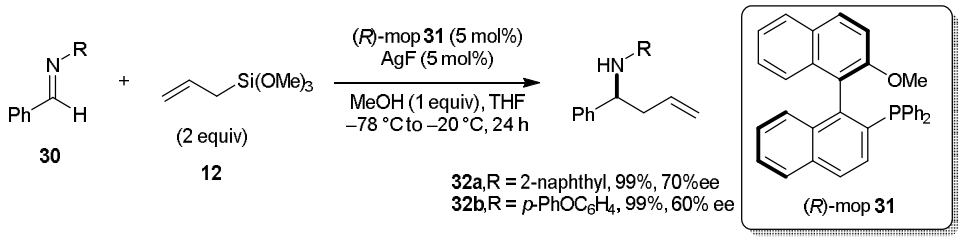
Scheme 1.9: Copper-catalysed enantioselective allylation of iminophosphonate **22**.

Itoh and co-workers reported the total synthesis of an *iso*quinoline alkaloid, (–)-emetine (**29**). In the formal synthesis, the key step was a copper-catalysed enantioselective allylation of an unactivated cyclic imine **26** with allyltrimethoxysilane (**12**) (**Scheme 1.10**). Various phosphine-based ligands were investigated and it was found that (*R*)-tol-binap **27** in THF at room temperature afforded the best result with high yield and moderate selectivity.[29]



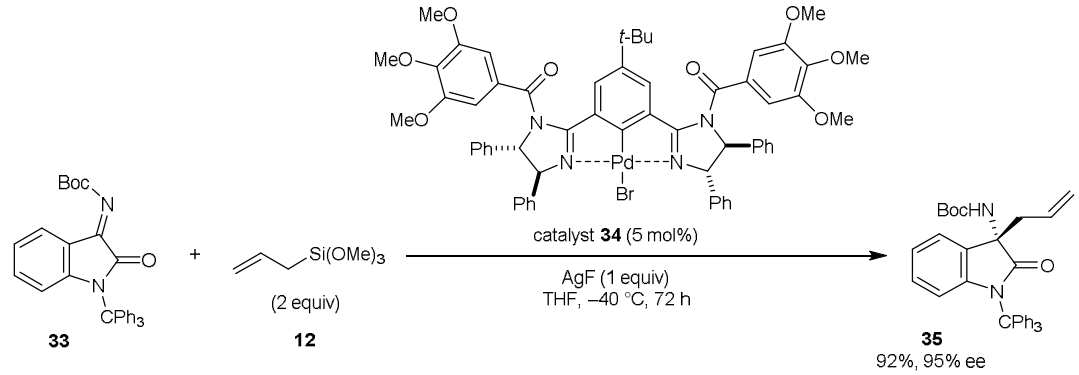
Scheme 1.10: Enantioselective allylation of dihydroisoquinoline **26**.

An enantioselective synthesis of homoallylic amines, using allyltrimethoxysilane **12** and a AgI–monophosphine catalyst was studied by Yamamoto and co-workers (**Scheme 1.11**).[30] Under mild conditions and low catalyst loadings, chiral amines were produced with high yields and modest to high ee values (up to 80%). Moreover, it was shown that the methodology could be efficiently expanded to include crotylsilane nucleophiles to afford *α*-branched products with highly diastereoselectivy and modest enantioselectivities.



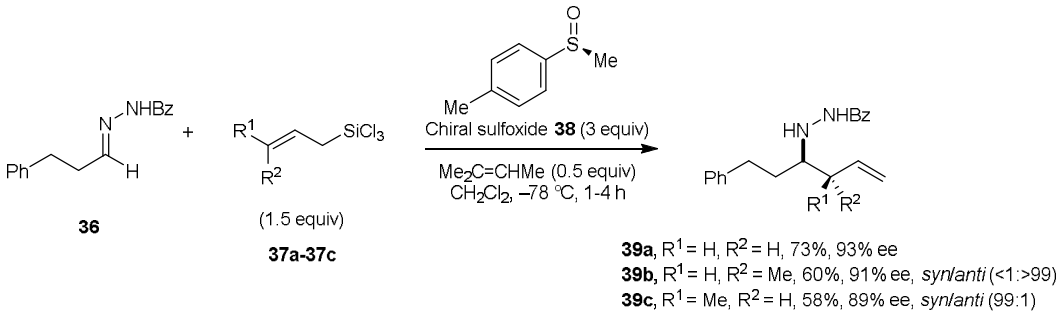
Scheme 1.11: Enantioselective allylation of imine **30**.

Expanding the scope of this reaction, Nakamura and co-workers[31] investigated the first enantioselective allylation of ketimines derived from isatins using *bis*(imidazoline)–palladium pincer complex **34** as a catalyst. The results showed that homoallylic amines containing a tetrasubstituted stereocentre could be obtained in high yields and very high stereoselectivities (**Scheme 1.12**).



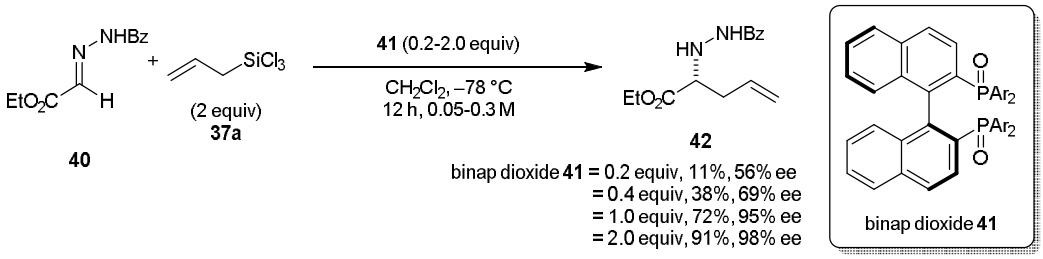
Scheme 1.12: Enantioselective allylation of isatin-derived imine **33**.

Aside from metal-catalysed allylation, organic compound promoted-allylation has also been widely studied. Many research groups have reported the asymmetric allylation of imines using chiral promoters. In 2003, the group of Kobayashi studied the allylation of hydrazones with allyltrichlorosilane using chiral sulfoxide **38** (**Scheme 1.13**). Both aromatic and aliphatic hydrazones gave moderate yields and good enantioselectivities, and *E*- and *Z*-crotyltrichlorosilanes were found to produce the *syn*- and *anti*-products respectively.[32]



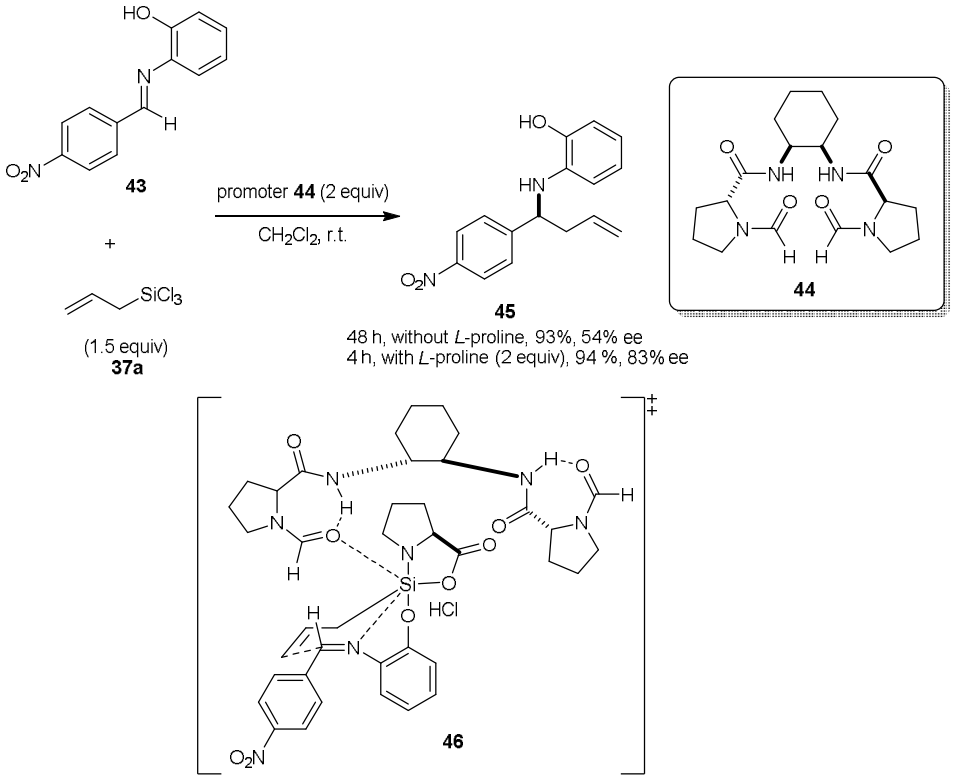
Scheme 1.13: Chiral sulfoxide-mediated enantioselective allylation of hydrazone **36**.

Inspired by their previous work[32], Kobayashi and co-workers investigated the allylation of α-hydrazono esters where chiral binap dioxide **41** was used as the source of inducing chirality. It was noted the yields and selectivities of products relied upon the concentration of the chiral ligand **41**. When lower quantities of ligands were used, lower yields were obtained (**Scheme 1.14**).[33]



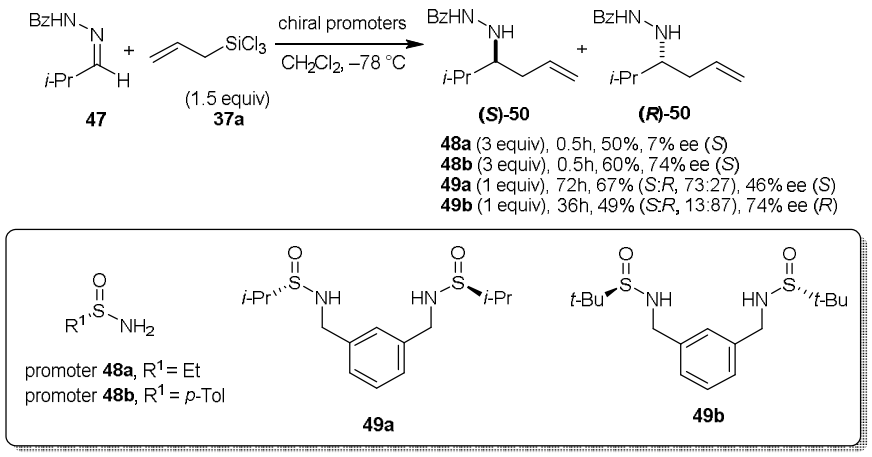
Scheme 1.14: Chiral binap dioxide-mediated enantioselective allylation of hydrazono ester **40**.

Jagtap and Tsogoeva reported the first stereoselective allylation of aldimines in the presence of *N*-formylproline promoters.[34] It was shown that the amide **44** was the best activator in terms of both yields and selectivities (**Scheme 1.15**). Although in all cases the yields were high, the enantioselectivity of the products were moderate. Interestingly, the enantioselectivities and the rate of the reaction were improved by adding *L*-proline. Moreover, based on MS and ^{1}H NMR results, a plausible transition-state model was proposed. It was postulated that the formation of two covalent bonds between the nucleophilic atoms (N and O) in *L*-proline and a silicon atom of allyltrichlorosilane (**37a**), provides a chiral allylating reagent. The second formamide moiety of chiral *bis*-formamide **44** enhances the nucleophilicity of allylic complex by coordinating to the silicon atom.

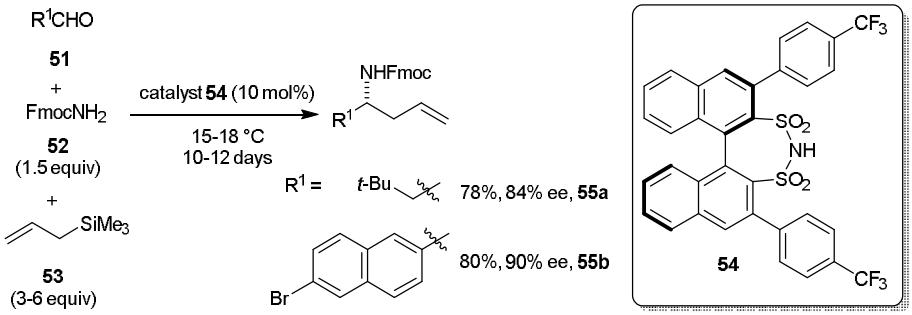


Scheme 1.15: Chiral *N*-formylproline-mediated enantioselective allylation of imine **43**.

Fernández and co-workers evaluated the allylation of hydrazones with screening both monosulfinamide and disulfinamide organic chiral promoters. The results indicated that the size of alkyl substituents on the promoters determined the enantioselective outcome, the bulkier the alkyl group the higher the enantioselectivity (**Scheme 1.16**).[35]



Scheme 1.16: Chiral mono- and disulfinamide-mediated enantioselective allylation of hydrazone **47**.



Scheme 1.17: Chiral disulfonimide-based Lewis acid catalysed enantioselective allylation of aldehydes.

Gandhi and List recently reported the first catalytic asymmetric three-component synthesis of chiral homoallylic amines starting directly from aldehyde **51**, carbamate **52**, and allyltrimethylsilane (**53**).[36] After screening different chiral acid motifs for example

phosphoric acid, phosphoramides, sulfonic acid and disulfonamides it was found that chiral disulfonimide-based Lewis acid catalyst **54** gave the best result (**Scheme 1.17**).

Concerning the mechanism of this reaction, two distinct pathways were envisioned (**Figure 1.2**). Accordingly, the disulfonimide promoter may act as a Brønsted acid which activates the *in situ* generated imine by protonation (a). Alternatively, the catalyst species in turn may activate the imine by silicon-based Lewis acid catalysis (b). However, the authors suggested that Lewis acid catalysis pathway tends to be the promising route according to the preliminary experiments utilising a preformed imine and the preformed silylated catalyst which gave nearly identical enantioselectivity as those obtained in the corresponding three-component reaction.

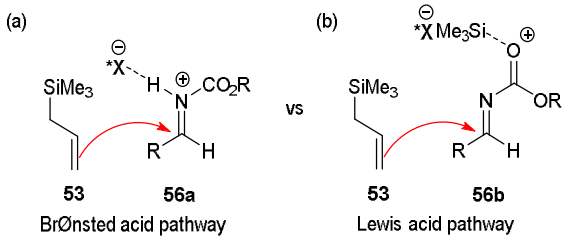
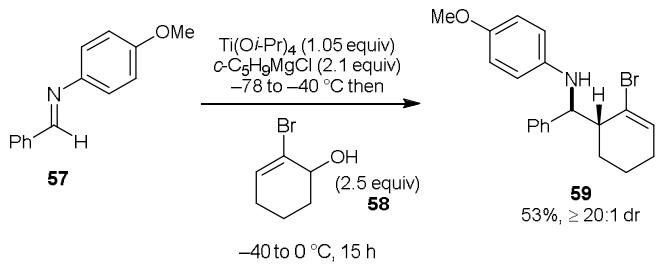


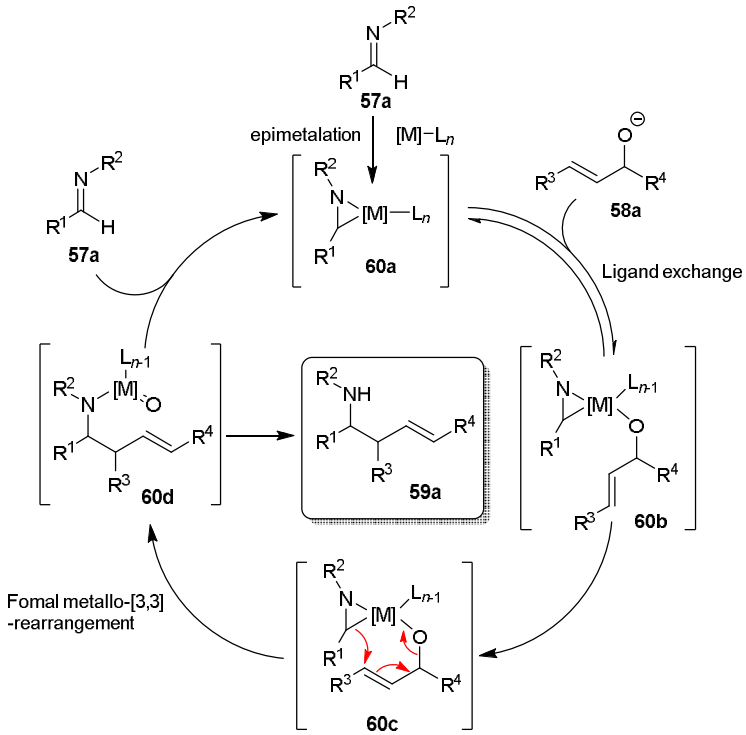
Figure 1.2: Modes of activation of asymmetric three component allylation.

1.2.2 Allylation Using Allylic Alcohols

Allyl alcohols are widely used as a raw material or a precursor in various chemical industries.[37] Furthermore, several research groups have recently developed the reaction using allylic alcohols as a source of inexpensive and stable starting materials in an asymmetric allyation process. In 2009 Micalizio reported a convergent coupling reaction between allylic alcohols and imines that delivered complex homoallylic amines without the requirement of allylic organometallic reagents (**Scheme 1.18**).[38]



Scheme 1.18: Complex allylation without an allylic organometallic reagent.

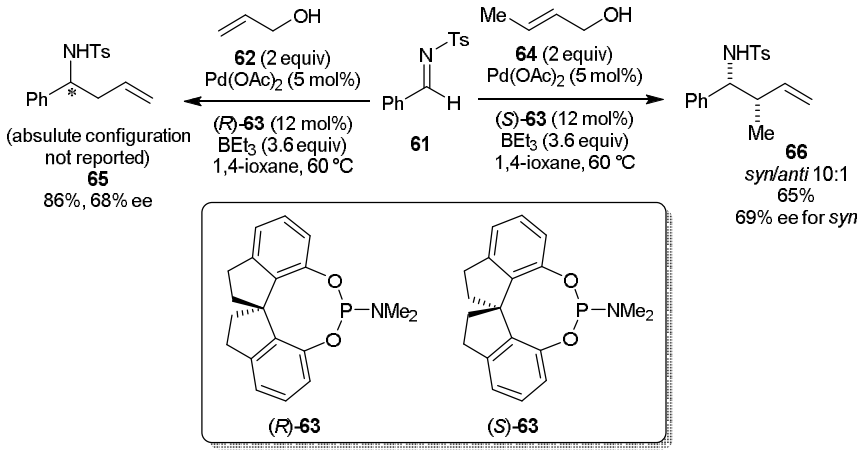


Scheme 1.19: Designed mechanism of the direct cross-coupling of imines with unactivated allylic alcohols.

It was proposed that the reaction mechanism involved the treatment of imine **57a** with a low-valent metal-reagent resulting in the formation of intermediate azametallocyclopropane **60a**. The addition of allylic alkoxide **58a** to complex **60a** led to a rapid and reversible ligand exchange to deliver **60b**. Formal metallo-[3,3]-rearrangement **60c** brought about the formation of the C–C bond of homoallylic

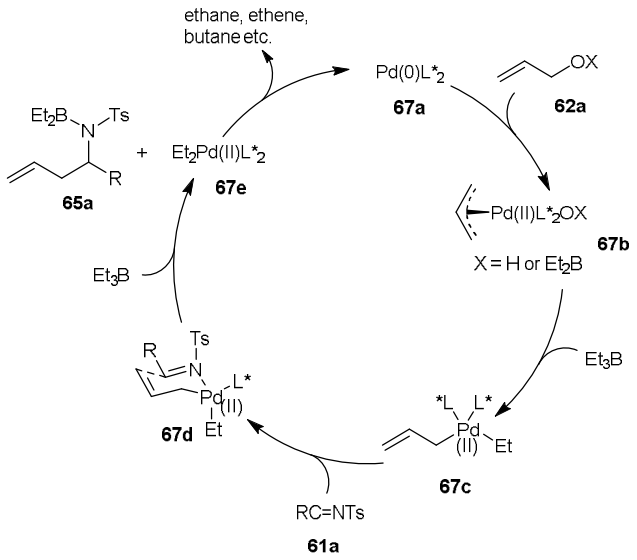
metalated amine **60d**. Finally, simple hydrolysis provided the complex homoallylic amine **59a** (**Scheme 1.19**).[38]

In 2010, the group of Zhou published the enantioselective allylation of arylimines with allylic alcohols by activating the alcohol with palladium-chiral spiro ligand catalyst **63**.[39] This work was successful with allyl alcohols and crotyl and cinnamyl alcohols to obtain homoallylic amines in reasonable yields and average enantioselectivities (**Scheme 1.20**).



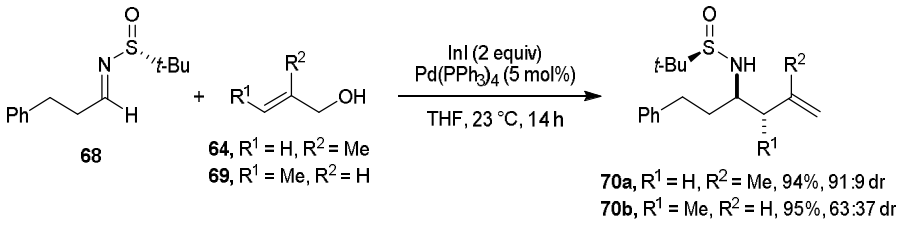
Scheme 1.20: Palladium-catalysed enantioselective allylation of imine **61**.

The mechanism was proposed as shown in **Scheme 1.21** to rationalise the 'Umpolung' of the π-allylpalladium.[40] The transfer of the electron-rich ethyl group from boron to η^3-allylpalladium species **67b** promotes the formation of η^1-allylpalladium species **67c** which was thought to change the electronic property of the palladium centre to become a stronger nucleophile. Then the reaction proceeds further in enantioselective fashion *via* transition state **67d** to generate homoallylic amine **65a**.[39]



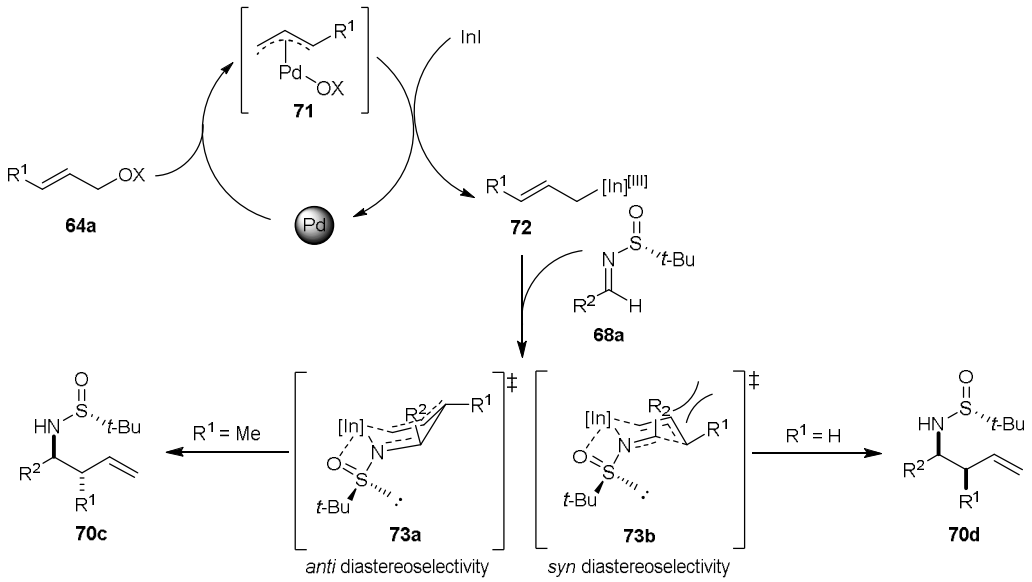
Scheme 1.21: Proposed mechanism of palladium-catalysed enantioselective allylation of aryl *N*-tosylated imines.

Although catalytic asymmetric allylation reactions have been widely studied, there are also reports of using a chiral auxiliary reagent to induce stereoselectivity. Recently, Yus reported the palladium-catalysed allylation of *N-tert*-butanesulfinyl imines with allylic alcohols in the presence of InI as a reducing reagent. The reaction took place with modest diastereoselectivity in reasonable yields for both *β*-substituted allylic alcohols and crotyl alcohol (**Scheme 1.22**).[41]



Scheme 1.22: Palladium-catalysed allylation of *N-tert*-butanesulfinyl imines with allylic alcohols.

From a mechanistic point of view (**Scheme 1.23**),[41] first, π-allylpalladium complex **71** is formed, then, it undergoes reductive transmetalation with indium(I) salts to give allylindium(III) species **72**. The allylation proceeds *via* a six-membered cyclic transition state **73a** or **73b** where the indium is coordinated to both the nitrogen and the oxygen atoms of the imine **68a**, and then a Si-face attack takes place with the imine. Regarding the crotylation reactions, the *E*-crotylindium species reacts at the *γ*-position through a cyclic boat-like six-membered transition state **73a** (preferred over the chair-like transition state **73b** due to the steric repulsion between the methyl group of crotylindium and the substituent of the aldimine) to produce the *anti*-product **70c**.

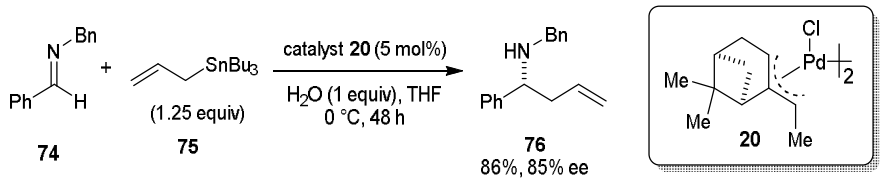


Scheme 1.23: Proposed mechanism of the addition of allylic alcohol to chiral substrates *via* allylindium species.

1.2.3 Allylation Using Allyl Stannanes

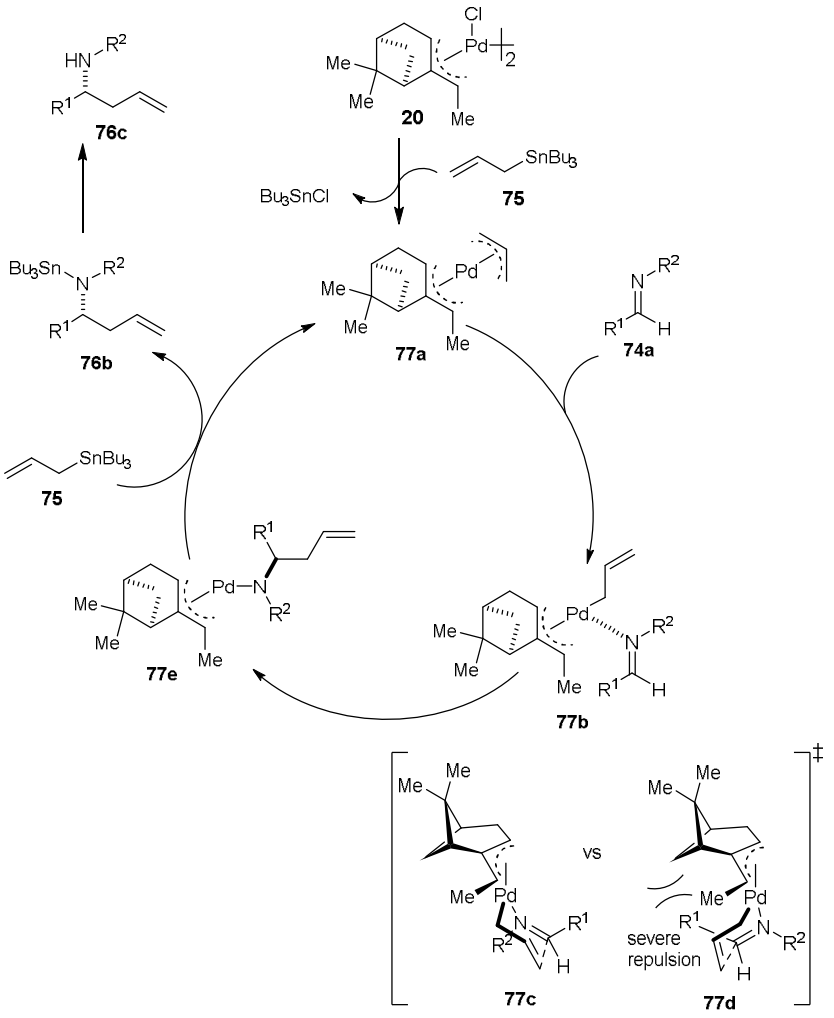
Also, the additions of organotin compounds to electrophiles are a very useful methodology in organic synthesis. Although organotin reagents are highly toxic, they are still widely used in the synthesis of organic molecules due to their stability, and selective reactivity.

The first enantioselective allylation of aryl imines with allylstananes using a palladium complex catalyst was reported by Yamamoto and co-workers in 1998.[42] The result demonstrated that the chiral amine products were achieved in modest to high yields and enantioselectivities (**Scheme 1.24**).[43]



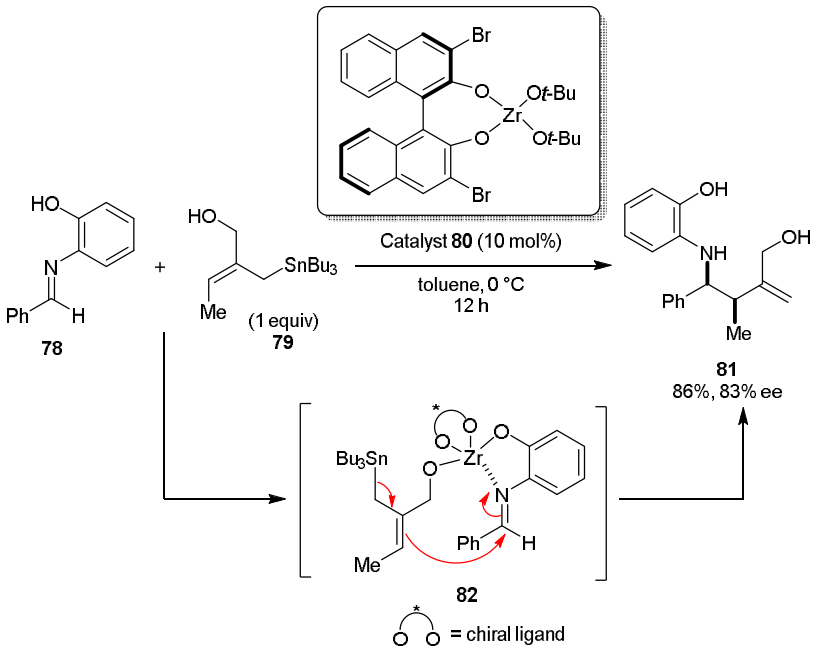
Scheme 1.24: Palladium-catalysed enantioselective allylation of aryl imines.

A plausible mechanism for allylation was proposed. The transmetalation between **20** and allyltributylstannane (**75**) produces the *bis*-π-allylpalladium complex **77a**. The key step for chiral induction was believed to be the coordination of imine **74a** to the intermediate **77a** to give **77b**. The allylation proceeds through a six-membered chair-like transition state **77c** to generate **77e**. Subsequently, the transmetalation of **75** to palladium produces the stannyl homoallylamide **76b** and regenerate *bis*-π-allylpalladium complex **77a**. Hydrolysis of **76b** then affords the chiral homoallylamine **76c**. The authors also suggested that the role of water is to form the pentacoordinate allylstannate, in which water facilitates the C−Sn bond cleavage and enhances the transmetalation step in giving **77a** and **76b** (**Scheme 1.25**).[43]



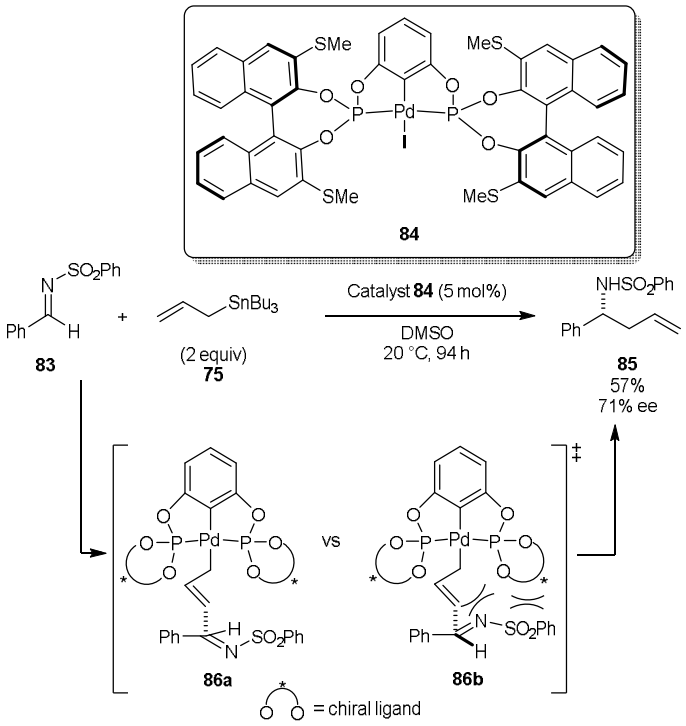
Scheme 1.25: Proposed mechanism.

In 2001, the zirconium-catalysed allylation of arylimines with allylstannanes was reported by Kobayashi and co-workers.[44] The authors suggested that a hydroxyl group substituted at the *o*-position of the arylimine **78** and an unprotected hydroxyl group on the stannane nucleophile **79** were required to coordinate to the zirconium catalyst, without this functionality, high enantioselectivities were not achieved. The mechanism was proposed involved the bonding of zirconium (Lewis acid) with the hydroxyl group of the imine results in the active catalyst, then the allylstannane attacks the imine in an intramolecular ene-like fashion.



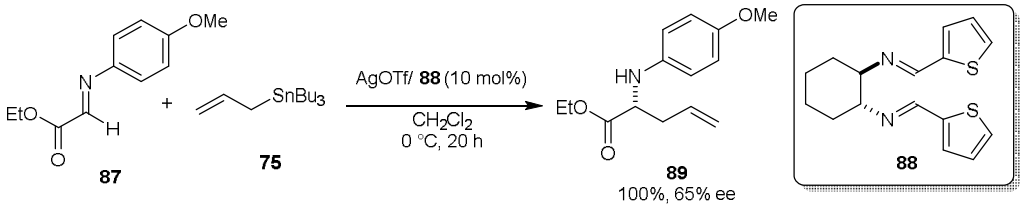
Scheme 1.26: Zirconium-catalysed enantioselective allylation of arylimine **78**.

Szabó's group studied the asymmetric allylation of sulfonimines using pincer complex catalysts (**Scheme 1.27**). It was believed that the reaction proceeded *via* transition state **86** in which the nitrogen atom of the sulfonylimine cannot coordinate to the palladium. Therefore the stereoselectivity of the product is determined by steric interactions between the sulfonyl group and ligands.[45,46]



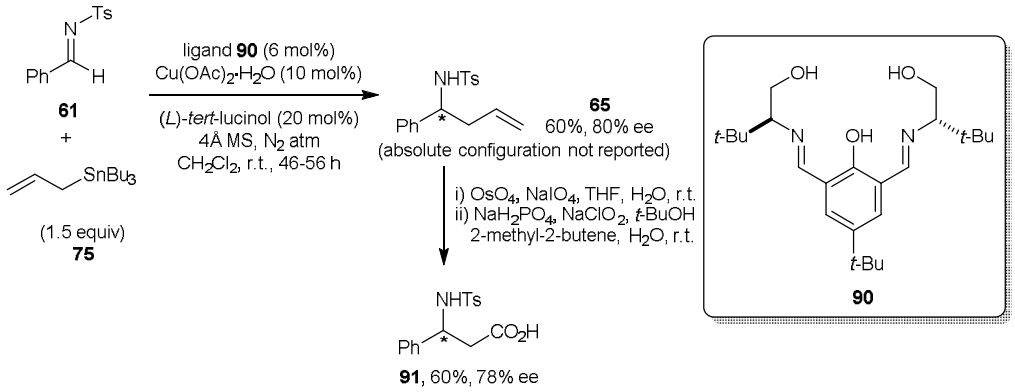
Scheme 1.27: Palladium-catalysed enantioselective allylation of aryl sulfonimines.

Benaglia and co-workers studied the catalytic enantioselective addition of allyltributylstannane **75** to *N*-protected α-imino esters promoted by silver(I) trifluoromethanesulfonate in the presence of imine ligands.[47] After testing several chiral ligands derived from 1,2-diaminocyclohexane and binaphthyl diamine, a very simple experimental procedure was developed that allowed them to obtain homoallylic amines in excellent yields and modest enantioselectivities (**Scheme 1.28**).



Scheme 1.28: Silver-catalysed enantioselective allylation of aryl imino ester **87**.

Recently, Abdi and co-workers investigated an enantioselective copper(II)-catalysed allylation of aryl and alkenyl-substituted *N*-sulfonylimines with allylstannane **75**.[48] With the use of a simple *in situ* generated copper(II)-amino alcohol based Schiff base complex, desired homoallyl amines were obtained up to 90% yield and 98% enantioselectivity. Moreover, to demonstrate the utility of this process, the transformation of homoallylic amine **65** to *β*-phenylalanine (**91**) was conducted (**Scheme 1.29**).



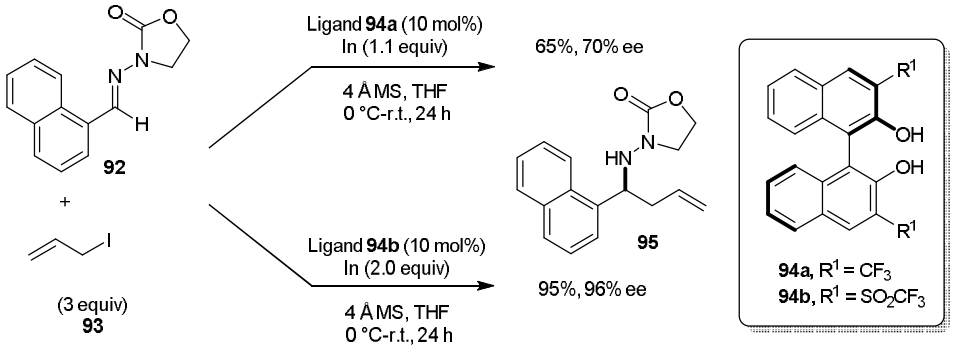
Scheme 1.29: Copper(II)-Schiff base catalysed enantioselective allylation of imines toward the synthesis of *β*-phenylalanine (**91**).

1.2.4 Allylation Using Allyl Halides

Allyl halides have gained much attention from organic chemists for a long time because they are synthetically useful and relatively cheap reagents. There are numerous examples of allyl halides used as an allylating reagent in Barbier-type reaction in the presence of metals such as Mg, Al, Zn, In and Sn etc.[8a,49,50]

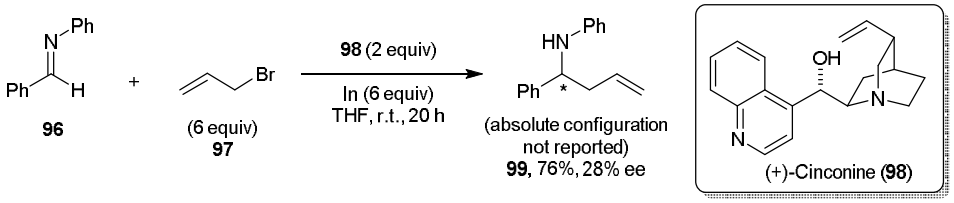
Cook and co-workers investigated the indium-mediated allylation of hydrazones. By varying ligands it was found that (*R*)-binol **94a** provided chiral product **95** in moderate yields and ee (**Scheme 1.30**).[51] Moreover, further investigation by Cook, Lloyd-Jones and co-workers showed that (*R*)-binol ligand **94b** could afford superior results. This new

reaction conditions provided good results when aliphatic imines were used as a starting material as well as aromatic imines.[52]



Scheme 1.30: Indium-mediated enantioselective allylation of hydrazone **92**.

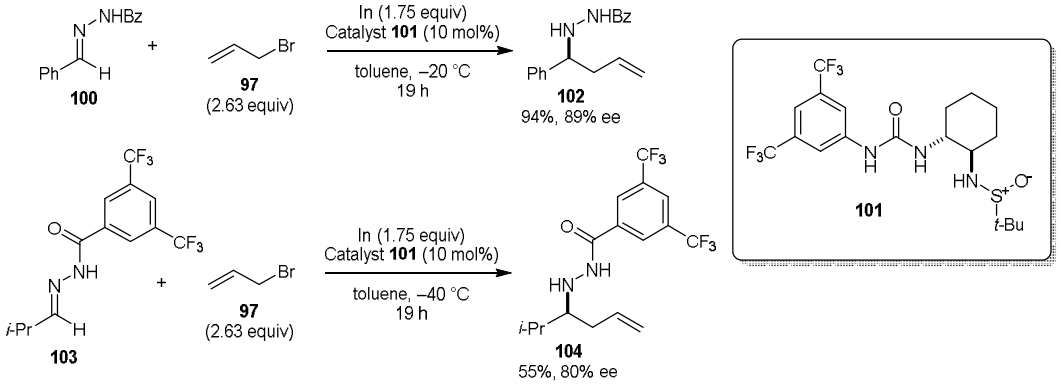
During the same period of time, Kim and co-workers attempted an allylation of aldimines with allyl bromide (**97**) in the presence of an indium-(+)-cinchonine complex.[53] Unfortunately, although the isolated yields were high, the enantioselectivities were very poor (**Scheme 1.31**).



Scheme 1.31: Indium-mediated enantioselective allylation of aryl imine **95**.

In 2007, Tan and Jacobsen studied the allylation of arylhydrazones using indium and sulfinamide-urea catalysts.[54] After screening various types of these catalysts it was shown that sulfinamide-urea **101** promoted the allylation of acylhydrazones with high levels of both yield and enantioselectivity. However, acylhydrazones derived from aliphatic aldehydes underwent allylation with low enantioselectivity (normally lower than 50% ee). Fortunately, when substrates bearing electron deficient (*N*-acyl groups) were used the enantioselectivities improved (**Scheme 1.32**). This work is considered to

be the first application of urea catalysis for highly enantioselective additions of organometallic reagents.



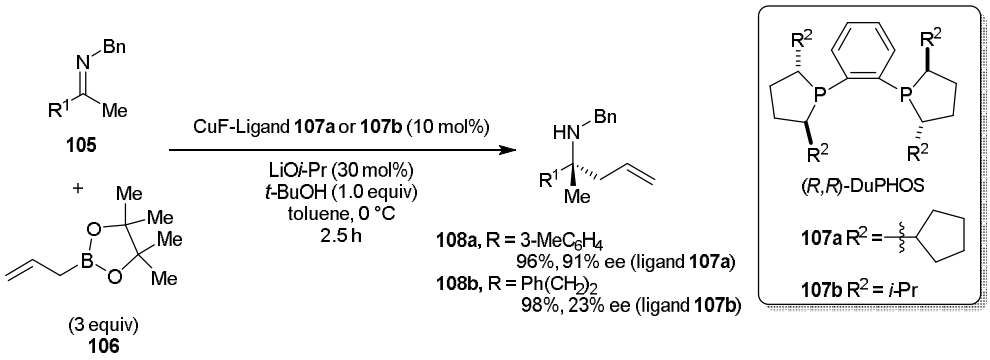
Scheme 1.32: Indium-sulfinamide urea-catalysed asymmetric allylation of hydrazones.

1.2.5 Allylation Using Allylborons

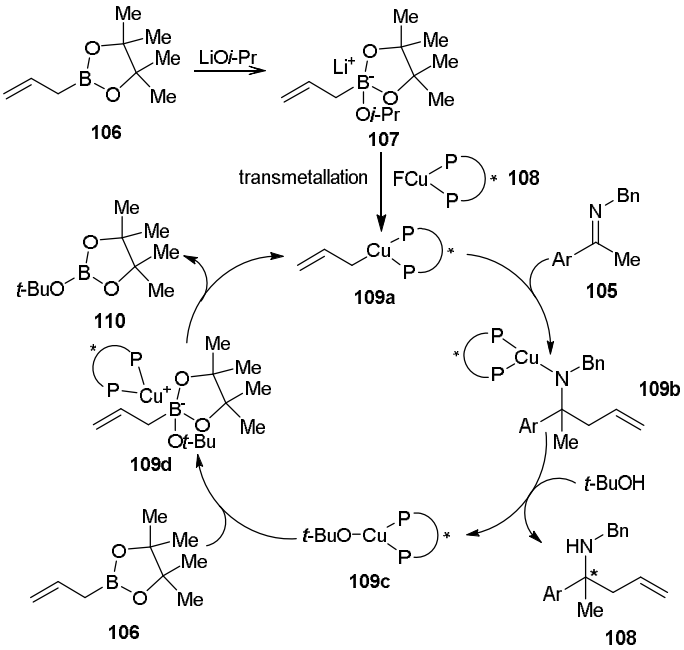
Organoboron reagents have been widely used in various new methodologies for carbon−carbon bond formation in organic synthesis both in the laboratory scale and industrial scale.[55,56] In comparison with other organometallic reagents such as organomagnesium, organolithium and organotin etc., organoboron reagents have been shown to be less toxic. These reagents have many other advantages;[57] e.g. (1) readily available by hydroboration and transmetallation, (2) stability in water and related solvents, (3) remarkably stable towards sensitive functional groups and (4) generates low or non-toxic byproducts. There are many examples for the use of organoborons as an allylating reagent in the allylations of imines as shown below.

The catalytic enantioselective allylation of ketimines was reported by Kanai and Shibasaki.[58] By using allylboronate esters, the optimum ligand, (*R*,*R*)-cyclopentyl-DuPhos **107**, and CuF combined with LiO*i*-Pr or LaO*i*-Pr co-catalysts it was possible to synthesise homoallylic amines featuring a quaternary stereocentre. The yields and enantioselectivities for arylketone substrates were high but aliphatic ketimines afforded unsatisfactory enantioselectivity (**Scheme 1.33**). The reaction mechanism proposed

involved the addition of LiO*i*-Pr, which improves the reaction rate by increasing the concentration of the active allylcopper nucleophile **109a** (**Scheme 1.34**).



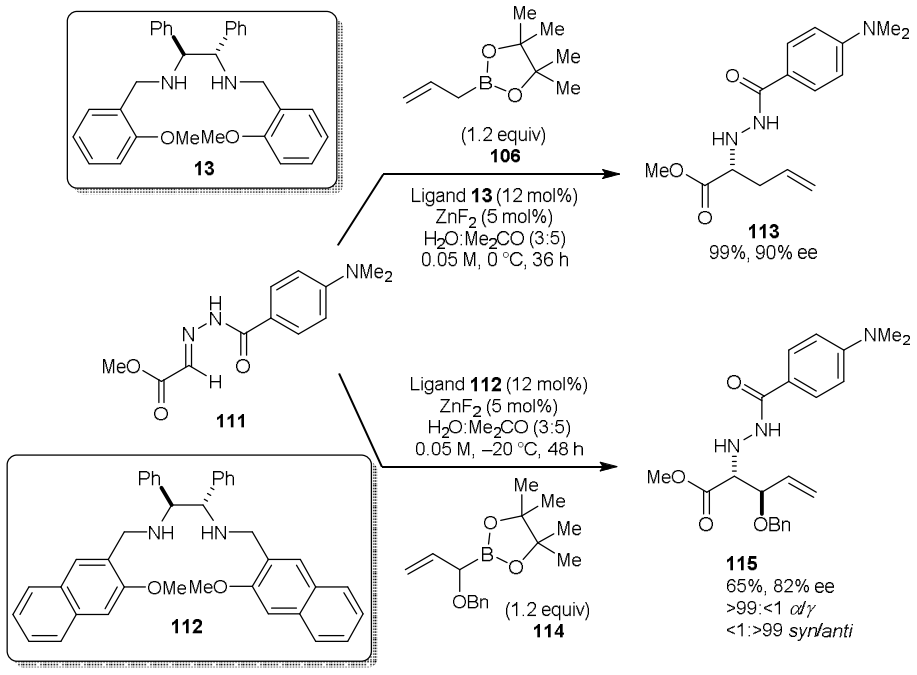
Scheme 1.33: Copper(I)-catalysed enantioselective allylation of benzyl ketoimines.



Scheme 1.34: Proposed mechanism for copper (I)-catalysed enantioselective allylation of benzyl ketoimines.

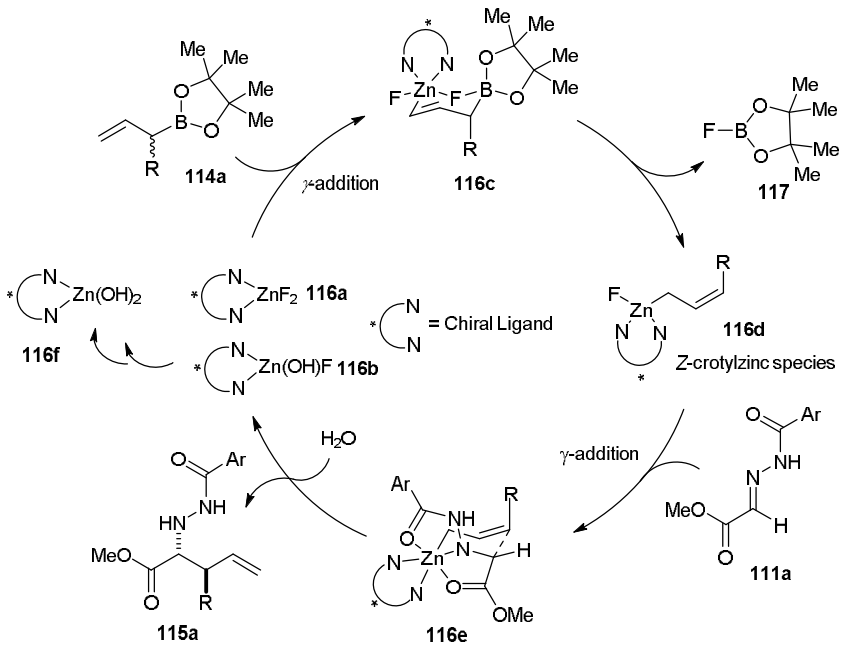
As mentioned in **Section 1.2.1**, the group of Kobayashi reported the catalytic asymmetric allylation of hydrazono esters with allyltrimethoxysilane (**12**).[26] However,

the disadvantages of that reaction are the requirement to employ an excess (3 equiv) of **12**, a relatively low reactivity, and a narrow substrate scope. To address these issues, having allylboronates as allylating agents instead of **12** was investigated. Using a similar catalytic system and acetone/ water as solvent it was found that the amount of allylating agent could be reduced from 3 equiv to 1.2 equiv and these optimal conditions gave products in high yields and enantioselectivities. Furthermore, when substituted allylboron reagents were used, *α*-addition products were obtained exclusively with high yields and stereoselectivities (**Scheme 1.35**).[59]

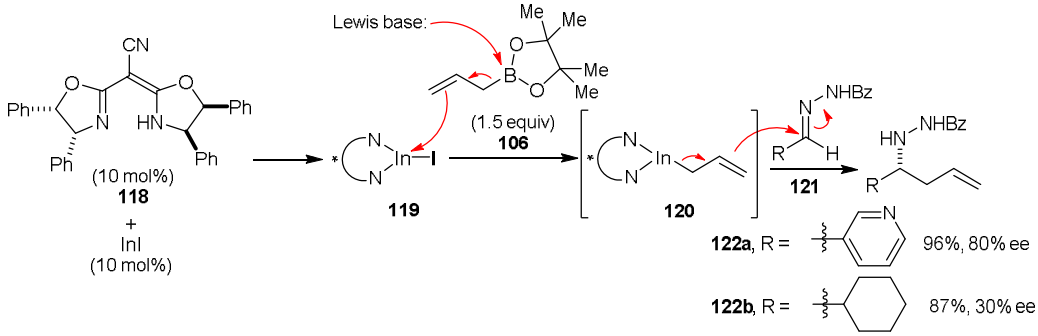


Scheme 1.35: Zinc-catalysed enantioselective allylation of acylhydrazono ester **111**.

A catalytic cycle of this reaction was proposed which explained the stereoselectivity of the obtained chiral amine adducts (**Scheme 1.36**). The mechanism begins with the formation of *γ*-substituted *Z*-allylzincate **116d**, which then reacts stereoselectively with the hydrazono ester **111a** *via* *γ*-addition giving the *anti*-configuration product **115a** after hydrolysis.



Scheme 1.36: Plausible mechanism of zinc-catalysed asymmetric allyllation of imine **111a**.

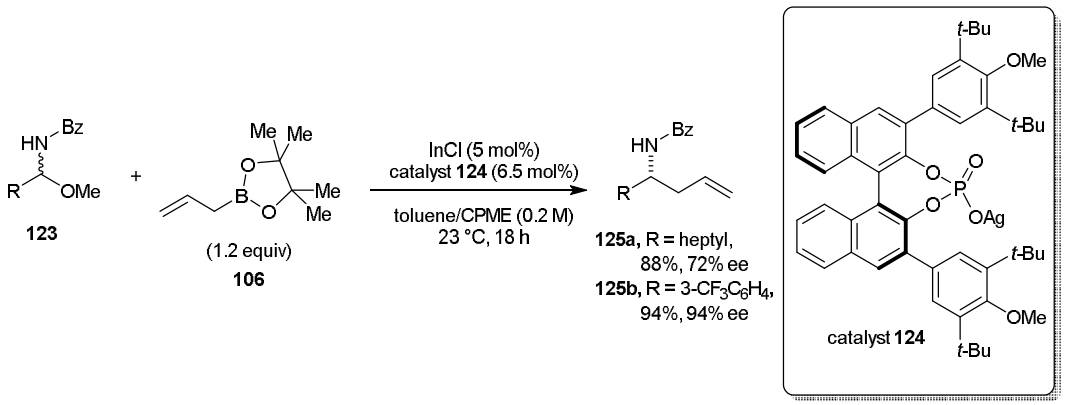


Scheme 1.37: Indium-catalysed enantioselective allylation of *N*-benzoyl hydrazones with the presence of the semicorrin ligand **118**.

In 2010, Kobayashi and co-workers[60] reported the indium-catalysed allylation of hydrazones with allylboronate esters, using the chiral semicorrin ligand **118** (**Scheme 1.37**). Unfortunately, low yields and poor enantioselectivities were obtained with aliphatic hydrazone substrates. The postulated mechanism suggested that the Lewis

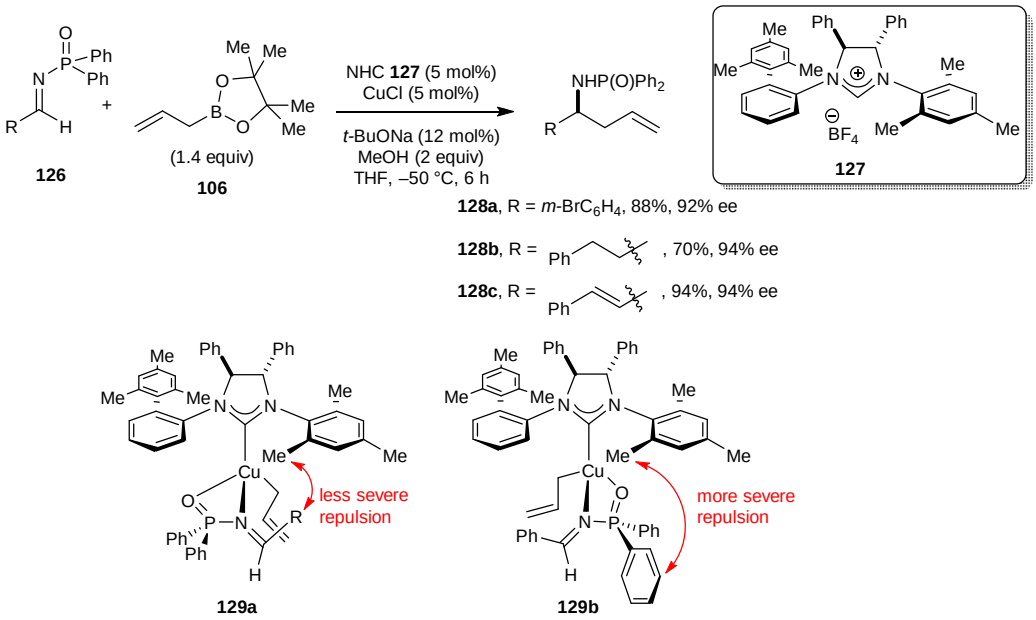
basic hydrazone activates the allylic boronate leading to transmetalation. The allylindium then adds to the imines to form the non-racemic products.

The first highly enantioselective Hosomi−Sakurai reactions with Csp^3 centres employing boronates instead of the classic silicon-based reagents were reported by Kobayashi and co-workers.[61] Under the optimal conditions, substituted aromatic, heteroaromatic and aliphatic aminals were allylated smoothly to provide the desired products with high asymmetric induction (**Scheme 1.38**). This transformation is thought to proceed *via* a Csp^2 centre by the elimination of methoxy group to generate a reactive imine. It is considered as the first main group metal-catalysed activation of allyl boronates for asymmetric C−C bond formation with Csp^3 centre starting materials.



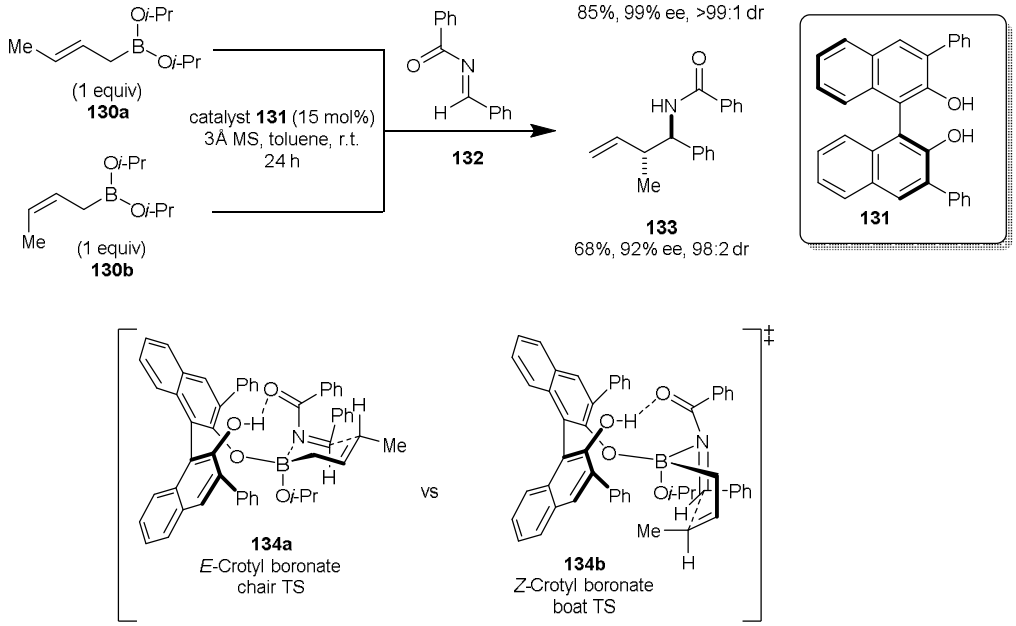
Scheme 1.38: A catalytic asymmetric borono variant of Hosomi−Sakurai reactions with *N*,*O*-aminals.

The enantioselective allylation of aldimines with (pinacolato)allylborons catalysed by NHC−Cu complexes was investigated by Hoveyda and co-workers.[62] It was showed that aryl-, heteroaryl-, alkyl-, and alkenyl-substituted *N*-phosphinoylimines underwent allylations efficiently to afford homoallylic amines in high yields and high enantioselectivities (**Scheme 1.39**). Furthermore, a mechanistic model was proposed that showed a preference for the reaction *via* **129a** versus the competing mode **129b**, due to subtle steric repulsions between the catalyst and the substrate.



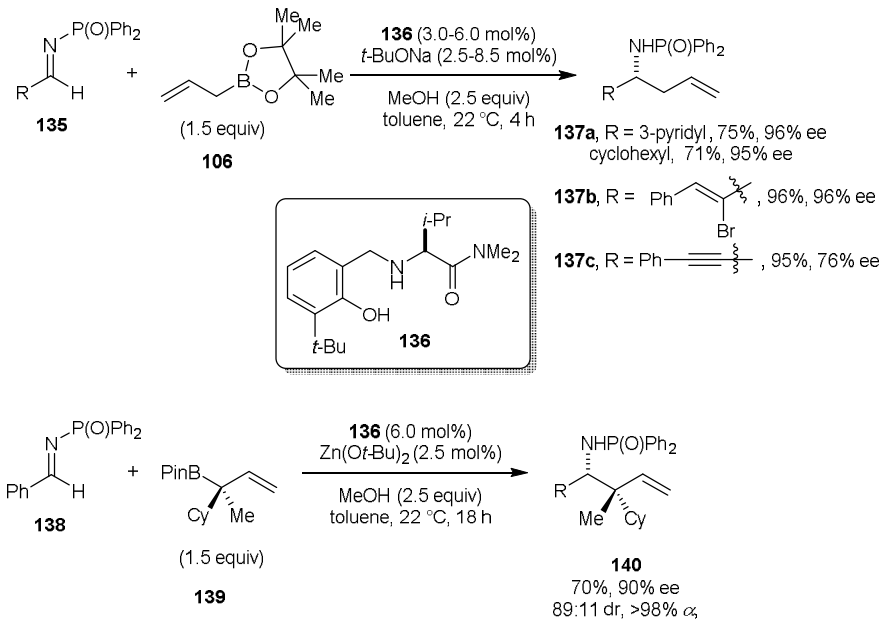
Scheme 1.39: NHC-Copper complex-catalysed enantioselective allylations of aldimines.

Regarding organocatalysis, in 2007 Schaus and co-workers[63] developed a highly enantioselective allylation of acyl imines catalysed by chiral binol-derived catalyst **131**. It was found that the reaction was highly selective for aryl as well as aliphatic acyl imines (**Scheme 1.40**). The reaction of crotyl boronate **130** afforded the corresponding *anti*-product in high diastereoselectivity. Mechanistic investigations strongly suggest that acyclic boronates are activated by chiral diols *via* exchange of one of the boronate alkoxy groups. This chiral diol again activates the acylimine *via* hydrogen bonding.



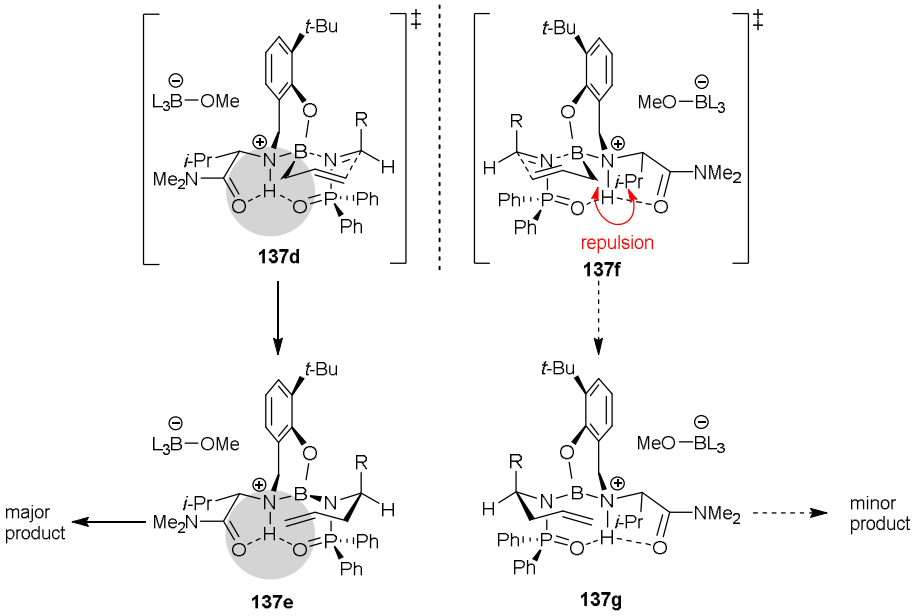
Scheme 1.40: Asymmetric allylboration of acyl imines catalysed by chiral diol **131**.

In 2013, Hoveyda and co-workers [64] discovered a set of small organic molecules that can catalyse the addition of allylboron reagents to imines and carbonyls (**Scheme 1.41**). Distinguishingly, this catalyst class has a "key" proton embedded within their structure. With the optimal condition in hand, aryl-, alkenyl-, alkynyl- and alkylimines were converted to homoallylic amides with high efficiency and enantioselectivities. Moreover, when α-substituted allylborons were used, homoallylamides with an additional tertiary or quaternary carbon stereogenic centre were obtained with high diastereo- and enantioselectivities with reversal of stereochemistry at the β-substituted carbon.



Scheme 1.41: Simple organic molecules as catalysts for enantioselective synthesis of amines.

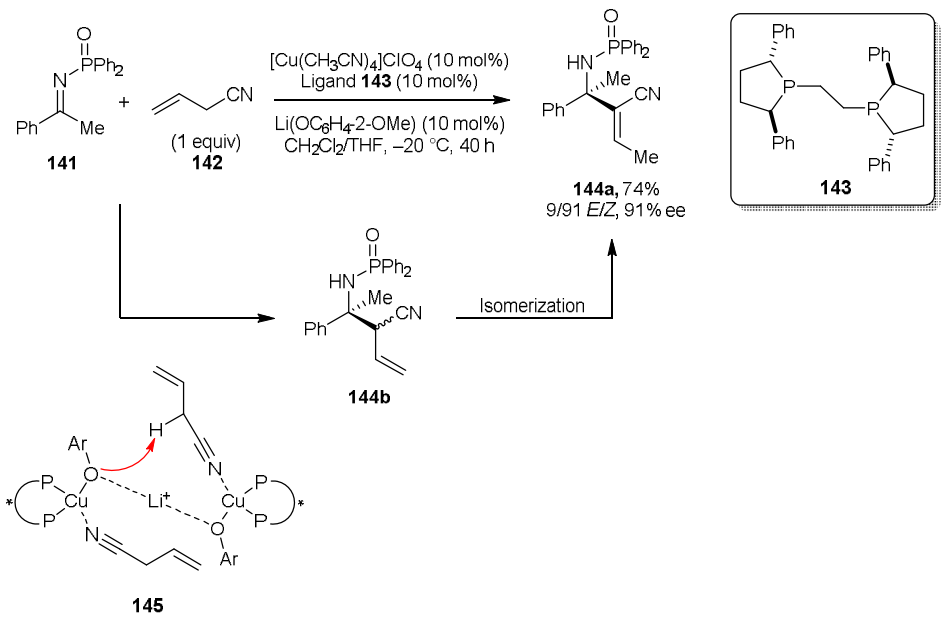
Stereochemical models accounted for the observed enantioselectivity, which was proposed as shown in **Scheme 1.42**. It involves hydrogen-bonding interactions, which bring the catalyst's amine and amide carbonyl and the phosphinoyl unit together. Thus the bond formation proceeds *via* the organised transition state **137d**, which minimises steric repulsion between the allyl and the *i*-Pr groups of the catalyst caused by the converging heteroatoms. This hypothesis is supported by computational studies together with X-ray crystallography analysis, which indicates a proton-bridge connecting the amine and carbonyl units.



Scheme 1.42: Proposed transition states of allylation of dpp-imines.

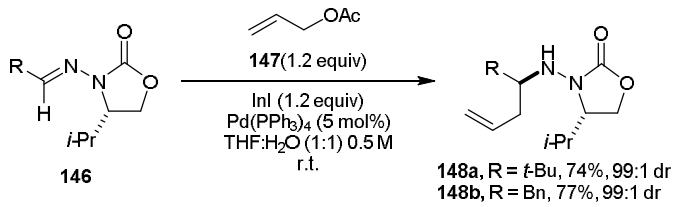
1.2.6 Allylation Using Other Allylating Reagents

Shibasaki and co-workers demonstrated a catalytic asymmetric addition of allylic cyanides to *N*-diphenylphosphinoyl ketimines using copper catalysis. Fortunately, the α,β-unsaturated products (with a stereogenic tetrasubstituted carbon), which formed from isomerisation of the obtained β,γ-unsaturated nitriles, were achieved in high yields and high enantioselectivities. The reaction mechanism proposed that the imine substrate is activated by coordination to soft Lewis acid (Cu) and then deprotonated by neighbouring aryloxide to generate a nitrile nucleophile. This active nucleophile subsequently adds to *N*-dpp ketimines to afford chiral homoallylic amine **144b** (**Scheme 1.43**).[65]

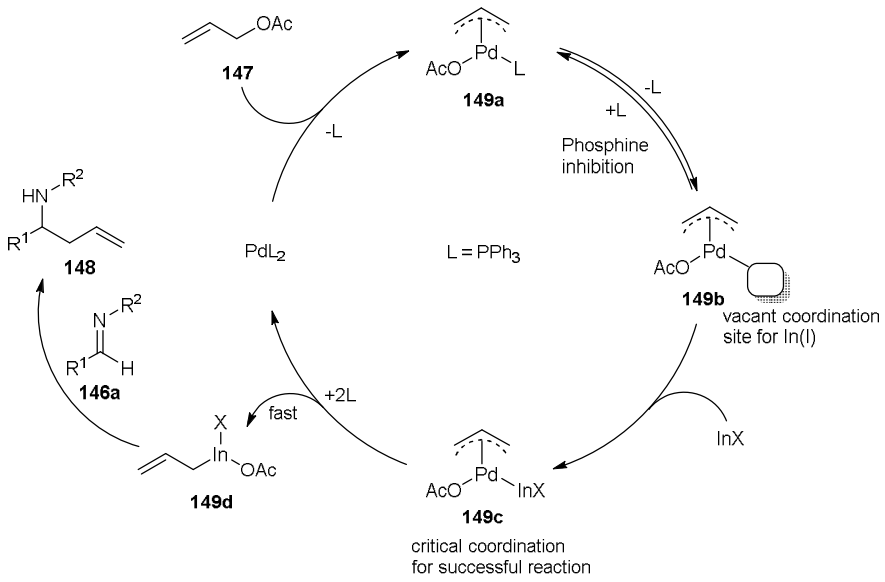


Scheme 1.43: Copper-catalysed enantioselective allylation of diphenylphosphinoyl imine **141**.

In 2014, a diastereoselective allylation of chiral hydrazones was developed by Cook and co-workers utilising an indium mediator and a palladium catalyst (**Scheme 1.44**).[66] This method used an allylindium reagent generated from allylic acetates through a reductive transmetalation process. The reaction was inhibited when the phosphine concentration was increased. From this result, the authors suggested that an intermediate **149c** (involving a Pd-In bond) is important for generating the nucleophilic allylindium species **149d** (**Scheme 1.45**).



Scheme 1.44: Palladium-catalysed allylation of chiral hydrazone **146**.



Scheme 1.45: Proposed mechanism of palladium-catalysed allylation of chiral hydrazones.

In conclusion, the enantioselective nucleophilic allylation to prochiral imines is widely studied. A range of transition metal catalysts was used to obtain chiral homoallylic amines. However, among the variety of allylating reagents utilised, organoboron reagents were less toxic and have many more advantages. Therefore, in the Lam group, we are keen to further investigate the rhodium-catalysed enantioselective allylation of allylboron reagents to imines. Not only is rhodium a new metal in this transformation but it also has many advantages as discussed in **Section 1.3**.

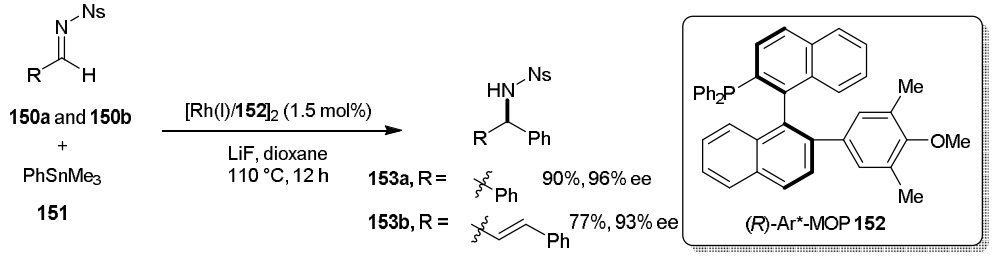
1.3 Rhodium-Catalysed Enantioselective Addition of Organoboron Reagents to Imines

Rhodium catalysis has been an important industrial catalyst for many years and has been utilised in many important reactions (Monsanto process, hydrogenation, hydroformylation etc.). Although this rare metal is extremely expensive, its catalytic properties are very unique and useful. According to the several literature reviews mentioned above, the allylation reactions catalysed by other cheaper elements such as Cu, Zn, Pd, Ag and In also produced chiral homoallylic amines successively; however,

the yields and enantioselectivities were not good in all cases. When stoichiometric promoters were used both yields and enantioselectivities of products were high. Unfortunately, however, there is still the problem of the quantity of chiral additive (normally, more than one equivalent of chiral promoter being required). Owing to some significant drawbacks of using other metals in asymmetric allylation of imines, extensively studied metals such as rhodium should be investigated in this reaction. Apart from the advantages of rhodium mentioned above, there are many studies which have demonstrated that rhodium complexes are very powerful catalysts in the asymmetric synthesis of chiral amines which will be detailed below.

1.3.1 Rhodium-Catalysed Arylation

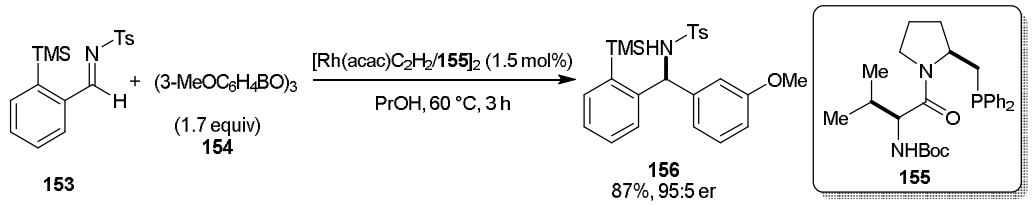
Rhodium-catalysed arylation has been investigated widely for nearly two decades. Therefore in this report only examples utilising imines as the electrophilic substrate will be covered. In 2000, Hayashi and Ishigedani reported a new chiral catalyst system for the asymmetric addition of arylmetal reagents to imines.[67] The result demonstrated that some rhodium complexes coordinated with chiral monodentate phosphine ligands (MOP's) catalysed the addition of arylstannanes to *N*-alkylidenesulfonamides to give sulfonamide of diarylmethylamines with high enantioselectivities. Pleasingly, this present catalytic asymmetric arylation could also be applied to sulfonamide of an α,β-unsaturated aldehyde, giving 1,2-addition allylic amine adduct **153b** (**Scheme 1.46**).



Scheme 1.46: Rhodium-catalysed arylation of aldimines with arylstannanes.

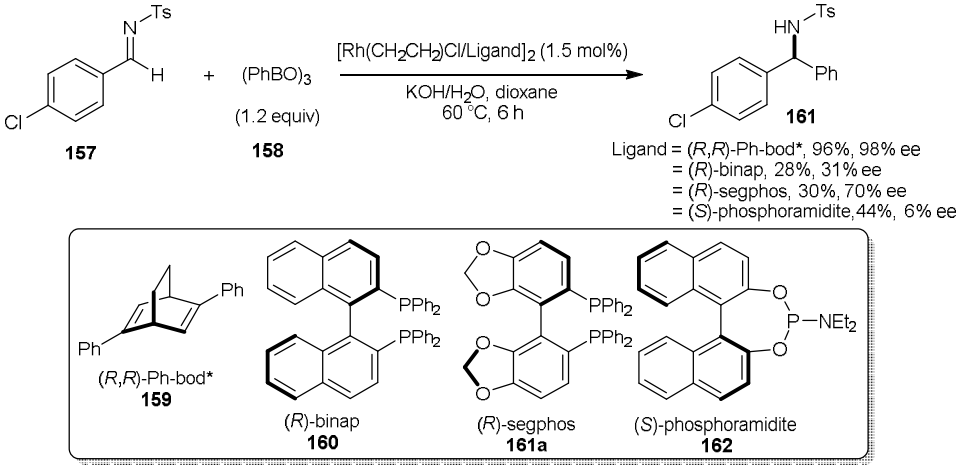
Tomioka and co-workers developed a catalytic asymmetric arylation of sterically tuned imines with arylboroxines (**Scheme 1.47**).[68] Using a *N*-Boc-*L*-valine-connected

amidomonophosphine rhodium(I) catalyst, chiral biarylmethylamides were obtained in high yields and selectivities. Moreover, the TMS group used for the steric tuning of the imine was easily converted to other functionalities.



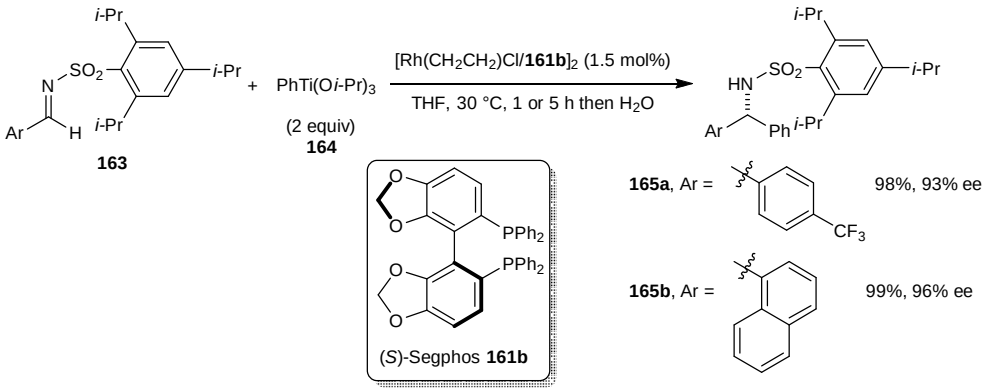
Scheme 1.47: Rhodium-catalysed arylation of imine **153** with arylboroxine **154**.

Continuing on their previous work[67], Hayashi and co-workers investigated the preparation of new chiral diene ligands and their application towards catalytic asymmetric reactions.[69] The result showed that the new C2-symmetric bicyclo[2.2.2]octadienes (bod*) had a clear superiority over chiral phosphorus ligands in both catalytic activity and enantioselectivity in the rhodium-catalysed arylation of *N*-tosylarylimines (**Scheme 1.48**). This is the first example of a rhodium-catalysed arylation utilising a C2-symmetric diene ligand, Ph-bod* **159**.



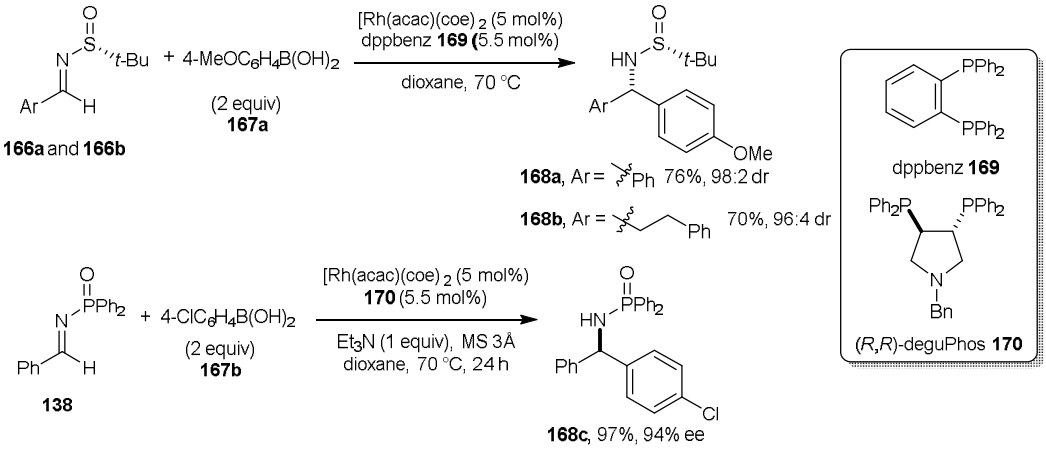
Scheme 1.48: Rhodium-catalysed arylation of imine **157**.

Later Hayashi and co-workers reported an additional scope of the rhodium-catalysed asymmetric arylation (**Scheme 1.49**).[70] It was shown that the reaction of sulfonylimines with aryltitanium reagents proceeded with high enantioselectivity under mild conditions to give diarylmethyl amines with up to 96% ee. By introducing *iso*propyl groups onto the phenyl ring of the arene sulfonamide moiety much higher enantioselectivities were achieved (86-96% ee).



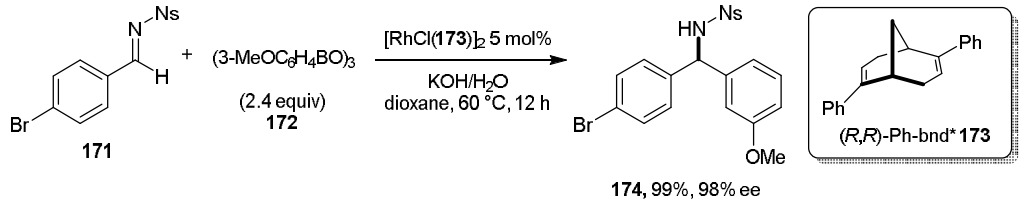
Scheme 1.49: Rhodium-catalysed arylation of imines with aryltitanium reagent **164**.

Ellmann and co-workers reported the diastereoselective rhodium-catalysed addition of arylboronic acids to both aromatic and aliphatic *N*-*tert*-butanesulfinylimines using 1,2-*bis*(diphenylphosphino)benzene ligand **169**. Furthermore, with the use of (*R*,*R*)-deguPhos ligand **170**, *N*-diphenylphosphinoyl benzaldimine **138** was arylated with high yield and enantioselectivity (**Scheme 1.50**).[71] Importantly, the authors believed that both *N*-*tert*-butanesulfinyl group and the *N*-diphenylphosphinoyl group could be cleaved under mildly acidic conditions that tolerate even sensitive functionality.



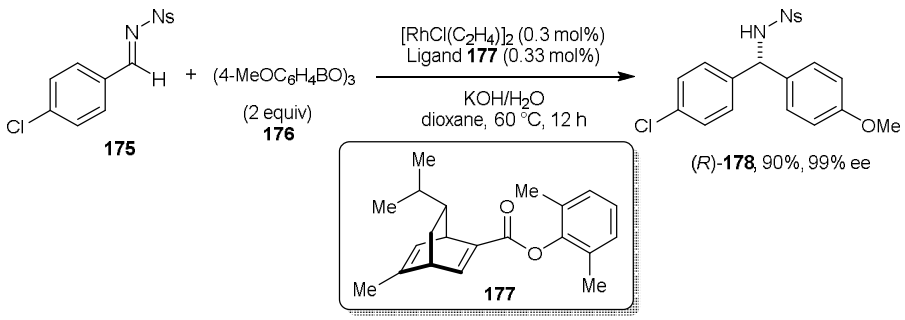
Scheme 1.50: Rhodium-catalysed arylation of *N-tert*-butanesulfinylimines and *N*-diphenylphosphinoyl imines.

In 2005, Hayashi and co-workers reported the use of a new C2-symmetric chiral diene in the rhodium-catalysed asymmetric arylation of *N*-4-nitrobenzenesulfonylimines. (**Scheme 1.51**).[72] With the use of 2,6-diphenylbicyclo-[3.3.1]nona-2,6-diene **173**, chiral biarylmethylamines were obtained in excellent yields and selectivities.

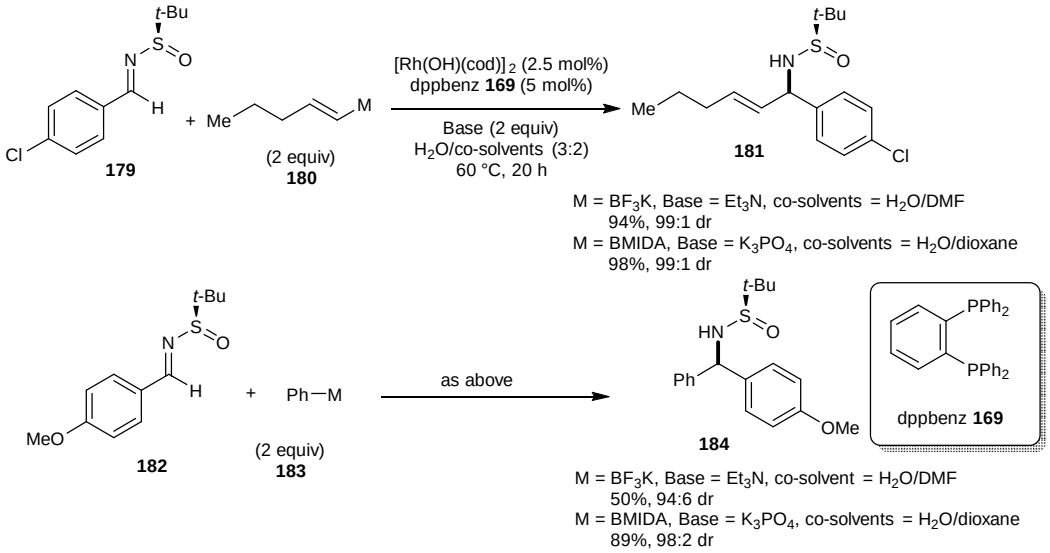


Scheme 1.51: Rhodium-catalysed arylation of imine **171** using C2-symmetric chiral diene **173.**

Four years later, the same research group investigated the rhodium-catalysed asymmetric arylation of imines using electronically and sterically-modified chiral diene ligands. [73] Fortunately, the corresponding diarylmethylamines were synthesised in high yield and high enantioselectivity using only 0.3 mol% of rhodium catalyst (**Scheme 1.52**). The results clearly demonstrated that arylation of imines can be successful employing a very low amount of catalyst.



Scheme 1.52: Rhodium-catalysed arylation of imine **175** using a very low catalyst loading.

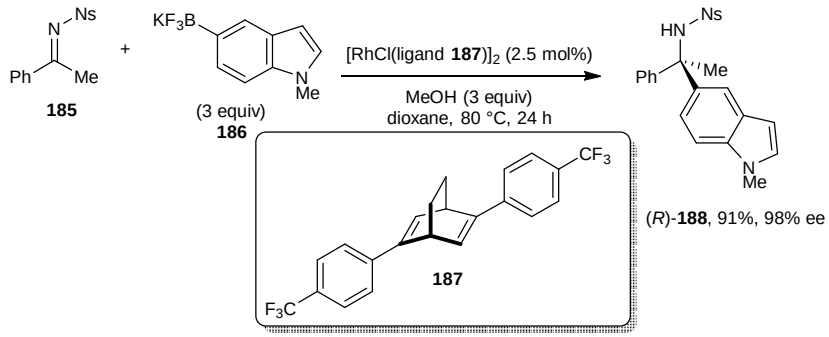


Scheme 1.53: Rhodium(I)-catalysed alkenylation and arylation of *N-tert*-butanesulfinyl aromatic and aliphatic imines.

Brak and Ellmann studied the rhodium(I)-catalysed addition of alkenyl and aryl boronates to chiral *N-tert*-butanesulfinyl aromatic and aliphatic imines (**Scheme 1.53**). The reaction proceeded with high yields and very high diastereoselectivity. In comparison with using trifluoroborate reagents, MIDA boronates (slow release boronic acids) gave higher yields and selectivities in the addition to aromatic imines. This new method represents a versatility of the rhodium(I)-catalysed nucleophilic addition of

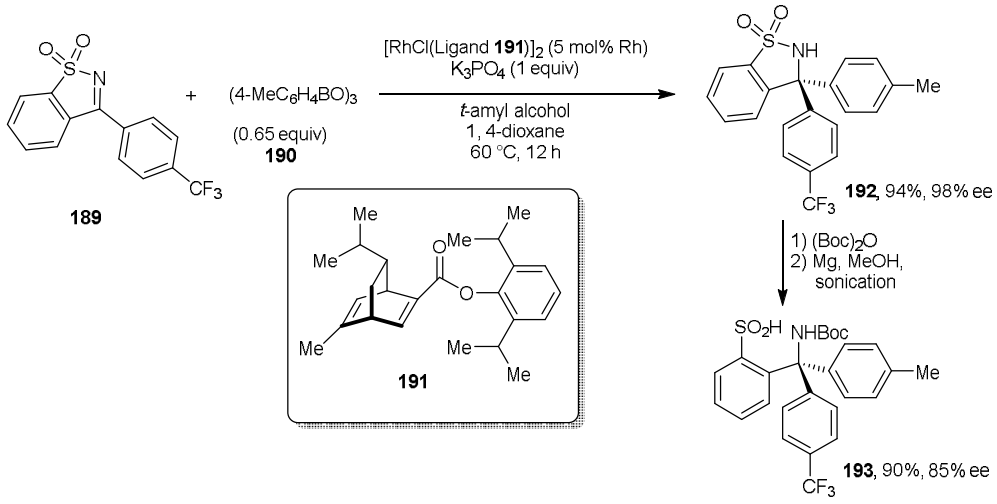
boron reagents to electrophiles which could be used for the synthesis of chiral α-branched amines.[74]

In 2011, the rhodium-catalysed asymmetric addition of potassium organotrifluoroborates to both *N*-tosyl and *N*-nosyl ketimines was further developed by Hayashi and co-workers.[75] To solve the problem of the requirement of tetraarylborates to effectively promote the reaction in previous works,[68,69,72,73] the readily available potassium organotrifluoroborates were employed as the nucleophile. High enantioselectivity was achieved by using a chiral diene ligand **187** (**Scheme 1.54**). The nosyl group of the chiral products could be easily removed without erosion of enantiopurity.



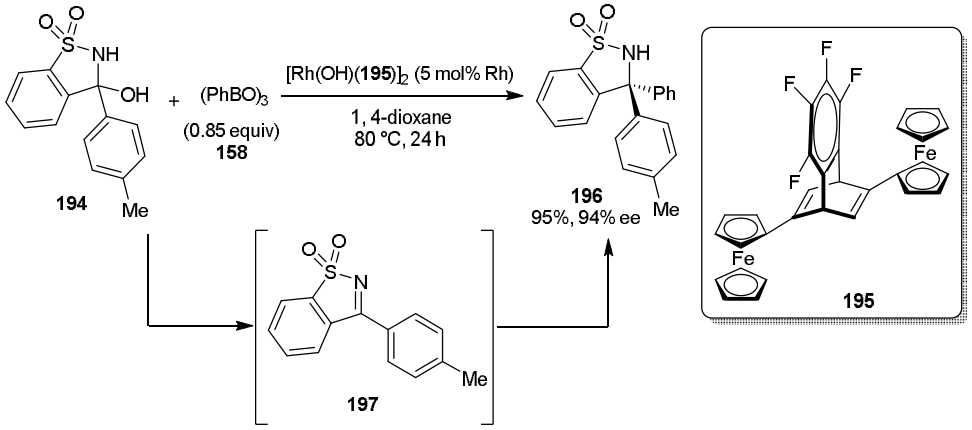
Scheme 1.54: Rhodium-catalysed arylation of ketimine **185**.

Furthermore, cyclic imines such as cyclic *N*-sulfonyl ketimines are also a very good source of prochiral substrates for the rhodium-catalysed asymmetric arylation with arylboroxines.[76] Utilising chiral diene ligand **191,** the triarylsubstituted stereogenic carbon centre of the resultant benzosultam **192** was produced with high yield and high enantioselectivity. Importantly, the chiral benzosultam **192** was easily transformed into the chiral (triaryl)-methylamine **193** by breaking the cyclic structure (**Scheme 1.55**).



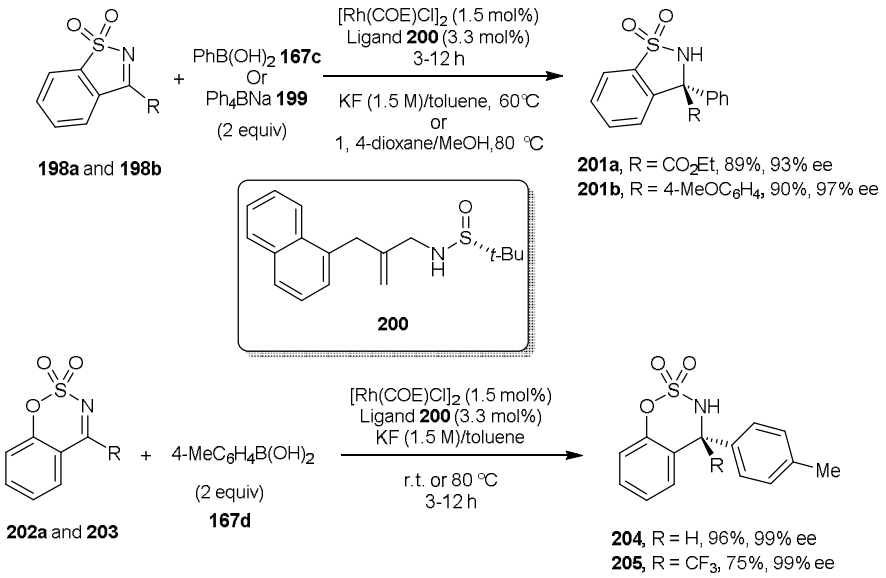
Scheme 1.55: Rhodium-catalysed asymmetric arylation of the cyclic imine **189**.

Concurrently, Hayashi reported the rhodium-diene complex catalysed asymmetric arylation of cyclic *N*-carbonyl ketimines resulting in isoindolin-1-ones bearing a triaryl-substituted stereogenic carbon centre (**Scheme 1.56**). The cyclic ketimines were generated *in situ* by the dehydration of hemiaminols with arylboroxines. Arylboroxine **158** was used with a dual propose; as a dehydrating reagent to generate ketimine **197**, and as an arylating reagent.[77]



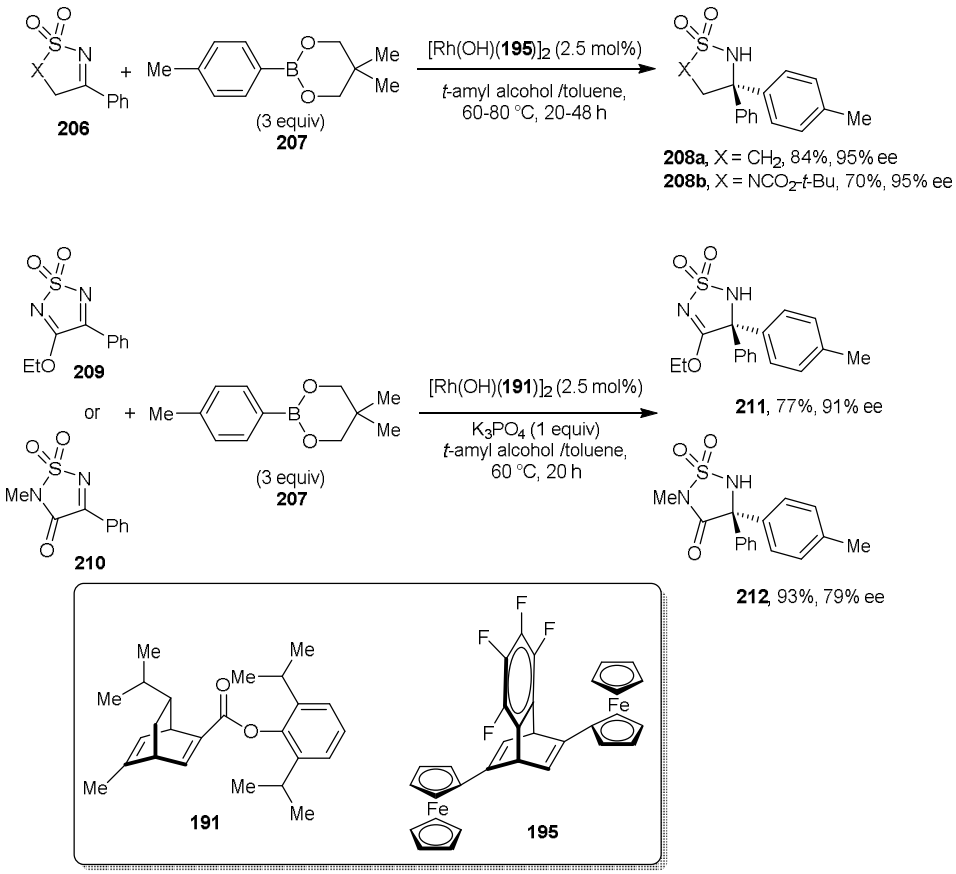
Scheme 1.56: Rhodium-catalysed arylation of 3-aryl-3-hydroxyisoindolin-1-ones.

Two weeks later the Xu group published the rhodium-catalysed asymmetric arylations of cyclic ketimines using simple sulphonamide-based olefin ligands. Both 5- and 6-membered *N*-sulfonyl ketimines containing ester, CF_3 or aryl substitutents were successfully arylated to generate benzosultams and benzosulfamidates. This is the first example of the use of a sulphur-olefin ligand **201** in asymmetric nucleophilic addition of imine substrates (**Scheme 1.57**).[78]



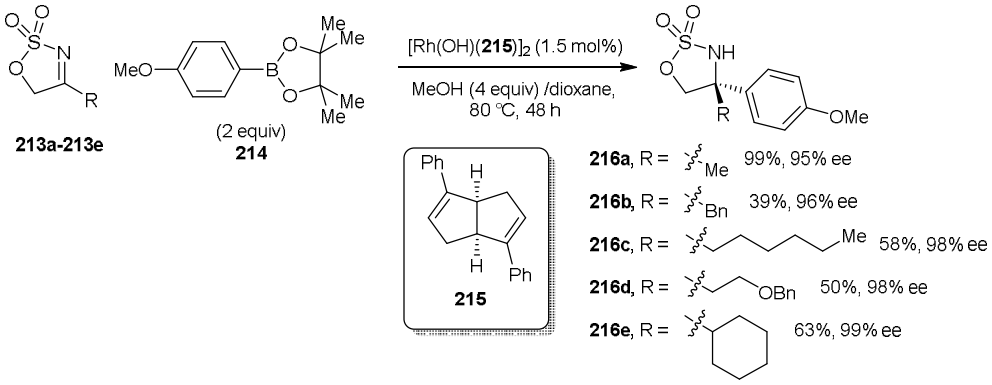
Scheme 1.57: Rhodium-catalysed arylation of cyclic imines using sulfonamide-based branched olefin ligand.

The scope of cyclic substrates for the rhodium-catalysed arylation was expanded from *N*,*N*- or *N*,*O*-5-membered ring ketimines. The results showed that the asymmetric arylation proceeded smoothly in the presence of a rhodium catalyst coordinated with chiral diene ligands to give high yields and stereoselectivities of sulfamidates and sulfamides (**Scheme 1.58**).[79]



Scheme 1.58: Rhodium-catalysed arylation of cyclic imines.

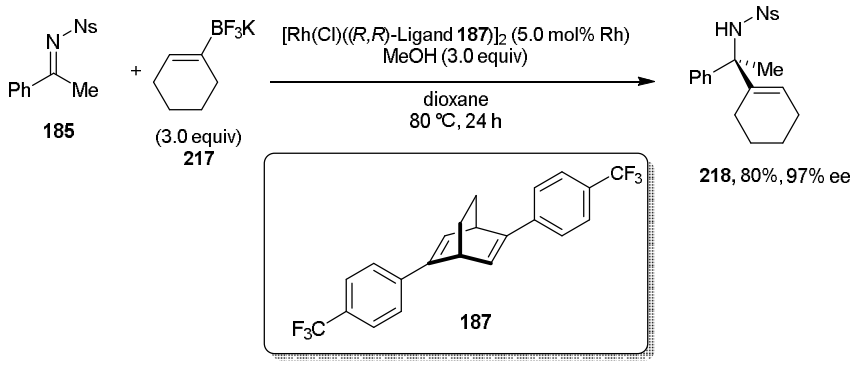
Recently, Lin and co-workers developed the enantioselective rhodium-catalysed 1,2-addition of arylboronates to cyclic *N*-sulfamidate alkylketimines.[80] Despite low yields, high enantioselectivities and broad functional group tolerance were observed for this reaction. Furthermore, the resulting sulfamidates could easily be reduced, providing a convenient approach to access chiral *β*-alkyl-*β*-aryl amino alcohols (**Scheme 1.59**).



Scheme 1.59: Rhodium-catalysed arylation of cyclic imines using ligand **215**.

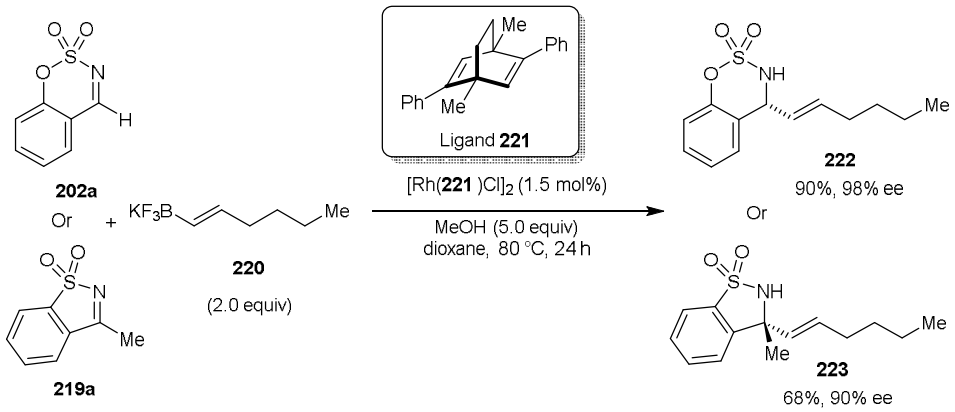
1.3.2 Rhodium-Catalysed Alkenylation

Following the report by Brak and Ellmann the rhodium-catalysed asymmetric alkenylation of chiral auxiliary imine substrates,[74] there has been no further discription of this reaction employing chiral catalysts to control stereoselectivity. However, in 2011, Hayashi and co-workers demonstrated a rhodium-catalysed asymmetric addition of potassium organotrifluoroborates to both *N*-tosyl and *N*-nosyl ketimines. In terms of arylation high enantioselectivity was achieved by using a chiral diene ligand **187** (**Scheme 1.54**). Importantly, one example of an alkenylation reaction was revealed with high yield and enantioselectivity (**Scheme 1.60**).[75]



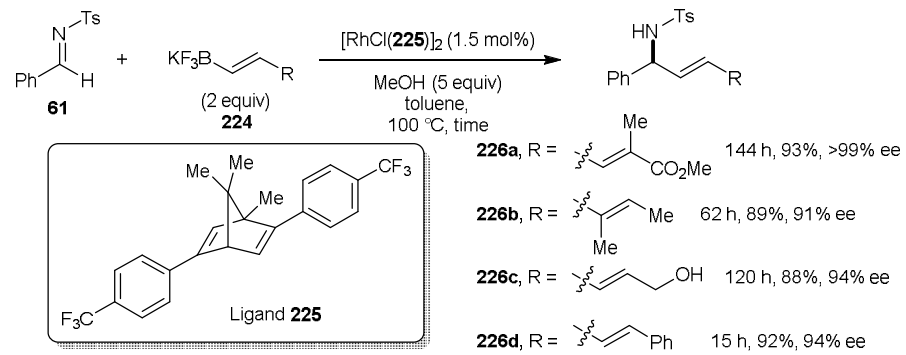
Scheme 1.60: Rhodium-catalysed asymmetric alkenylation and arylation of a *N*-nosylate ketamine **185**.

Enantioselective alkenylation of imines using potassium alkenyltrifluoroborates was investigated by Lam and co-workers in 2012.[81] With the use of rhodium-chiral diene catalysts, both acyclic and cyclic imine substrates were alkenylated and it was found that acyclic imines gave low yields and enantioselectivities. Fortunately, high yields and excellent enatioselectivities were observed when cyclic imines were employed (**Scheme 1.61**). Moreover, it was reasonalised that the cyclic structure of these imines, in which the C=N bond is constrained in the *Z* geometry, is crucial for the success of the reactions.

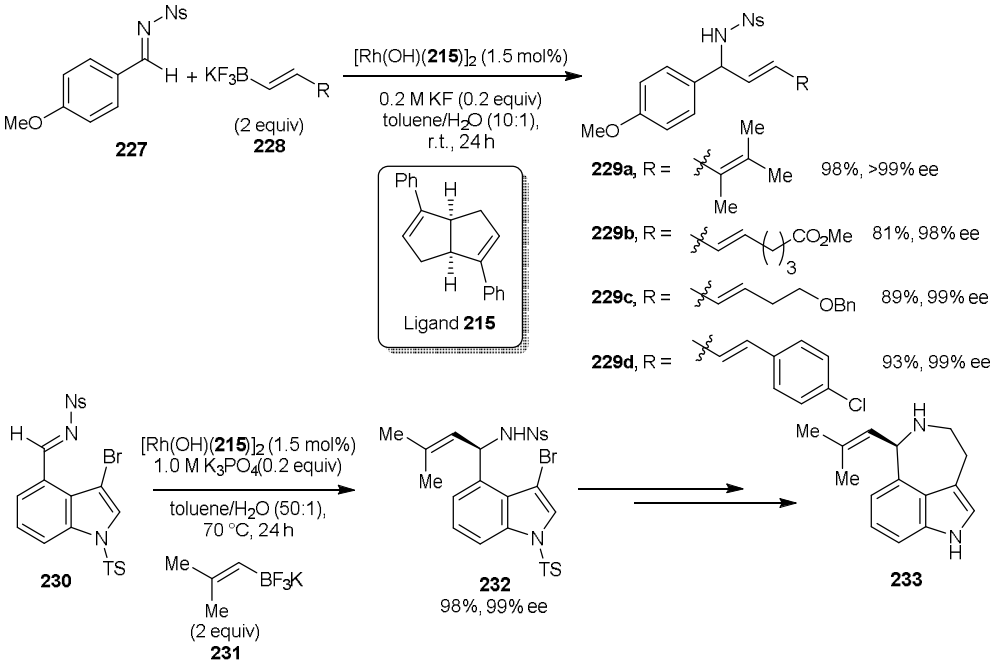


Scheme 1.61: Rhodium-catalysed asymmetric alkenylation of 5- and 6- membered cyclic imines.

A year later, Wu and co-workers investigated a rhodium-catalysed enantioselective addition of various potassium alkenyltrifluoroborates to acyclic aryl aldimines in the hope that the problem of using acyclic imines will be resolved. This is the first preparation of chiral allylic *N*-tosyl amines *via* the asymmetric 1,2-addition of potassium alkenyltrifluoroborates to *N*-tosyl arylaldimines. Generally, the enantioselective alkenylation reaction proceeded smoothly in a highly enantioselective manner to provide optically active allylic *N*-tosyl amines in good yields. The reaction was tolerant of unprotected alcohol and ester functionality in the nucleophile as well as various substituted aryl and heteroaryl aldimines (**Scheme 1.62**).[82]



Scheme 1.62: Rhodium-catalysed asymmetric alkenylation of acyclic imine **61**.



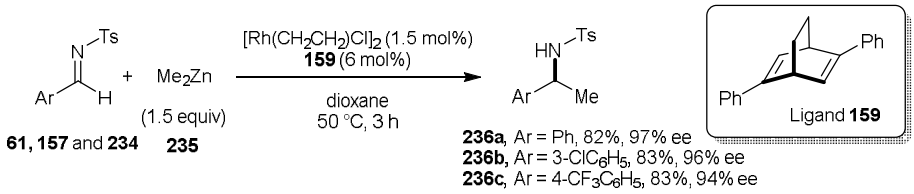
Scheme 1.63: Rhodium-catalysed asymmetric alkenylation of acyclic imine using ligand **215**.

Recently, an enantioselective rhodium-catalysed addition of potassium alkenyltrifluoroborates to *N*-nosylaldimines was reported by Lin and co-workers.[83] The reaction displayed a broad scope with respect to both imine substrates and alkenylborate partners (**Scheme 1.63**). This provided a simple, reliable, and scalable method for the

modular synthesis of chiral α-branched allylic amines. To demonstrate the utility of this method the concise formal synthesis of (−)-aurantioclavine was achieved (**233**).

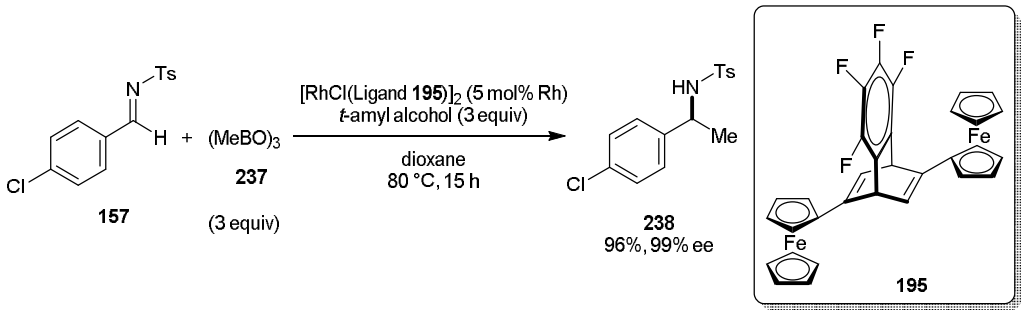
1.3.3 Rhodium-Catalysed Methylation

Hayashi and co-workers demonstrated the first example of an asymmetric rhodium-catalysed methyl-transfer reaction of *N*-tosylimines with dimethylzinc.[84] The methylation reaction proceeded with reasonable yield and high enantioselectivity in the presence of a chiral diene-rhodium catalyst (**Scheme 1.64**). The proposed mechanism was that the reaction of $[Rh(diene)Cl]_2$ with dimethylzinc generates a methylrhodium species, which then adds to the C=N bond to form an aminorhodium species. This aminorhodium species undergoes the σ-bond metathesis with Me_2Zn to regenerate the methylrhodium species and to produce the methylated product as a zinc amide.



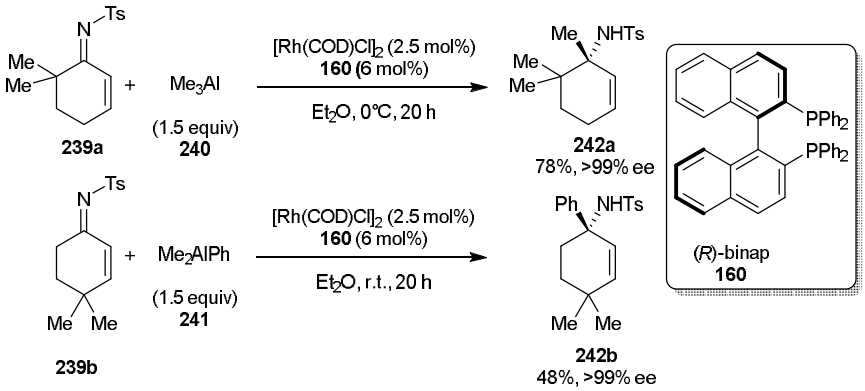
Scheme 1.64: Rhodium-catalysed methylation of acyclic imines.

Six years later, the same research group reported the rhodium-catalysed asymmetric methylation of *N*-sulfonylarylimines using trimethylboroxine **237** as a methylating agent.[85] The result showed that a hydroxorhodium complex coordinated with the chiral diene ligand **195** had a high catalytic activity, and chiral 1-aryl-1-ethylamines were achieved with high yields and enantioselectivities (**Scheme 1.65**).



Scheme 1.65: Rhodium-catalysed asymmetric methylation of the *N*-tosylate imine **157**.

The first enantioselective rhodium-catalysed 1,2-addition of methyl- and arylaluminum reagents to cyclic *α,β*-unsaturated *N*-tosyl ketimines was developed by von Zezschwitz and co-workers (**Scheme 1.66**).[86] Depending on the solvent and substituted groups on the ring of the imines, the reaction occurred in either 1,2- or 1,4-manner. In terms of 1,4-addition, 3-substituted cycloalkyl amines were obtained in modest to high yields and excellent enantioselectivities after subsequent reduction of addition products.



Scheme 1.66: Rhodium-catalysed asymmetric methylation of cyclic imines.

In summary, a number of rhodium-catalysed enantioselective additions of nucleophiles to prochiral imines have been developed. With the use of organoboron reagents, chiral amines are generated with high yields and high levels of selectivities. Although this research area is widely studied by many research groups it is still challenging to find a new mode of catalysis for rhodium. The most recent contribution to the field from the

Lam group: the enantioselective addition of allylboron reagents to imines under rhodium catalyst, is presented in **Section 1.5**.

1.4 Aims and Approach

For decades, numerous examples of using rhodium-catalysts in asymmetric synthesis have been reported.[87,88] Furthermore, plenty of work mentioned in the previous sections outlines the advantages of rhodium and organoboron reagents in generating enantioenriched chiral amines. However, to date, the field of rhodium-catalysed enantioselective nucleophilic addition to imines has been dominated by the addition of arylboron reagents, although there are some reports of additions of alkenylboron and methylboron reagents. Regardless the crucial importance of nucleophilic allylations in synthesis,[8a,89] the rhodium(I)-catalysed enantioselective additions of allylboron reagents to electrophiles have not been described before.

To the best of our knowledge, enantioselective rhodium-catalysed nucleophilic allylations are limited to additions of allylstannanes to aldehydes (where a chiral rhodium(III) complex functions as a Lewis acid), and cyclisations of allylrhodium species generated by additions to allenes.[90] Also there are a number of examples of the rhodium-catalysed isomerisation of alkenylboron reagents into allylboron reagents followed by *in situ* racemic allylation of aldehydes,[91] and the rhodium-catalysed redox allylation of ketones with allyl acetate and *bis*(pinacolato)diboron.[92]

This chapter will focus on using rhodium as an asymmetric catalyst to allylate both acyclic and cyclic imines and using allylboron as an allylating reagents. Hopefully, the homoallylic chiral amines will be achieved in high yield and high enantioselectivity. Also, the applications of this chemistry will be conducted to demonstrate the utility of this new area of rhodium catalysis.

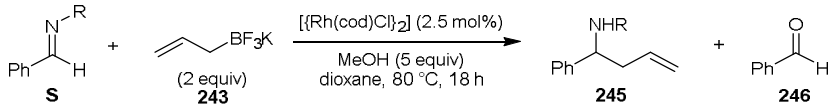
1.5 Results and Discussions

Rhodium catalysed enantioselective allylation to imine is a new concept in asymmetric synthesis using rhodium catalysts. Therefore, in order to achieve our goal, several acyclic and cyclic imine starting materials; allyltrifluoroborates in combination with chiral ligands were investigated in **Section 1.5.1**. The reaction mechanism will be discussed in **Section 1.5.2**, followed by the manipulations of allylation products which will be demonstrated in **Section 1.5.3.**

1.5.1 The rhodium-Catalysed Enantioselective Allylation of Cyclic Imines

In order to attempt to realise the goal of developing a rhodium-catalysed asymmetric allylation of imine, a range of imine substrate were screened to analyse whether any allylation reaction would occur with a rhodium catalyst. The first attempts were focussed on the allylation of various benzaldehyde-derived imines using 2 equivalents of potassium allyltrifluoroborate (**243**)[93] in the presence of 2.5 mol% of [{Rh(cod)Cl}$_2$] and 5 equivalents of MeOH in dioxane at 80 ºC (**Table 1.1**). Unfortunately, satisfactory results were not obtained, with *N*-phenyl and *N*-diphenylphosphinoyl imines **96** and **138**, more than 95% of starting material was recovered (**Table 1.1**, entries 1 and 2), whereas with dimethylsulfamyl imine **244** trace quantities of the allylation product were observed (**Table 1.1**, entry 3). With reactive *N*-sulfonylimines **61** and **150a**, more than 25% of homoallylic sulfonamides were obtained, but significant quantities of starting cyclic imine remained, along with benzaldehyde (**246**) resulting from imine hydrolysis especially from the more reactive *N*-Ns imine the benzaldehyde (**246**) was observed up to 30% (**Table 1.1**, entries 4 and 5).

Table 1.1: Rhodium-catalysed allylation of benzaldehyde-derivative imines



Entry	R	S (%)[b]	**245** (%)[b]	**246** (%)[b]
1	Ph (**96**)	>95	<5	<5
2	$P(O)Ph_2$ (**138**)	>95	<5	<5
3	SO_2NMe_2 (**244**)	85	5	10
4	Ts (**61**)	60	25	15
5	Ns (**150a**)	42	28	30

[a] Reactions were conducted by Hamish B. Hepburn using 0.10 mmol of **S**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures.

In accordance with a recent discovery by Lam and co-workers,[81] cyclic imines (which has a constrained geometry) were found to be highly effective substrates for enantioselective rhodium-catalysed alkenylations, the allylation of benzoxathiazine-2,2-dioxide **202a** was investigated (**Table 1.2**) using the same reaction conditions employed in **Table 1.1**. The results showed that the imine was consumed completely after 3 h to afford a desired product in 87% yield upon isolation (**Table 1.2**, entry 1). Several chiral ligands (**Figure 1.3**) were examined and it was found that the use of (*R*)-binap **160** was totally ineffective showing only less than 5% conversion (**Table 1.2**, entry 2). Chiral diene **247**,[73] however, provided a superior result with 60 % conversion and 67 % ee (**Table 1.2**, entry 3). In terms of the other five chiral dienes, fortunately, most of them produced reasonable yields and selectivities (**Table 1.2**, entries 4-8). Especially the use of 2.5 mol % of [{Rh(**221**)Cl}$_2$],[81,94] the percent conversion was greater than 95% and homoallylic amine **251a** was obtained with excellent enantioselectivity (**Table 1.2**, entry 8). These results from both **Tables 1.1** and **1.2** clearly demonstrated that both the cyclic imine and diene ligand **221** was required to facilitate an efficient allylation reaction. To highlight the importance of potassium allyltrifluoroborate (**243**) for this

reaction, allylboronic acid pinacol ester (**106**) (with the addition of aqueous 0.5 equivalents of K_3PO_4), was used instead. It showed that this allylboronic acid pinacol ester (**106**) had no effect on the reaction conversion but adversely affected the enantioselectivitiy. The reasons for this diminished enantioselectivity are not clear but a non-rhodium-catalysed alternative pathway is most likely to be the cause of such a loss of stereoselectivity.

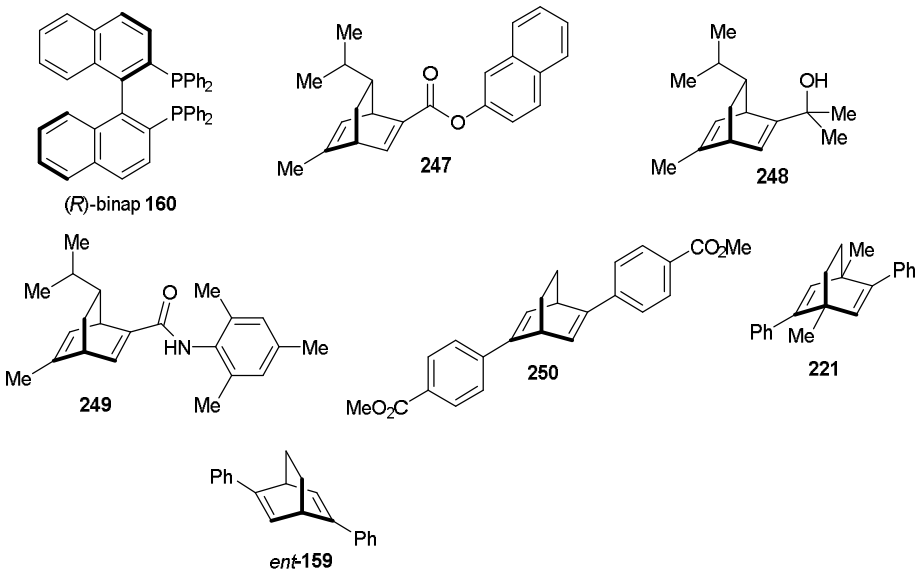
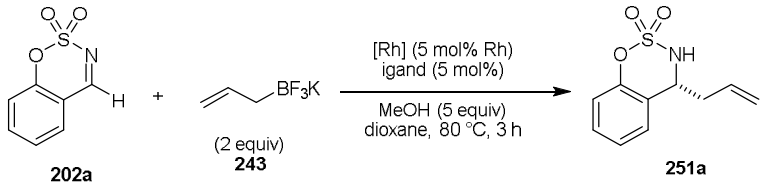


Figure 1.3: Chiral ligands for screening.

Table 1.2: Rhodium-catalysed allylation of imine **202a**.[a]



Entry	[Rh] (2.5 mol%)	Ligand (5 mol%)	Conv (%)[b]	ee (%)[c]
1	[{Rh(cod)Cl}$_2$]	None	>95[d]	-
2	[{Rh(C_2H_4)Cl}$_2$]	**160**	<5	-
3	[{Rh(C_2H_4)Cl}$_2$]	**247**	60	67
4	[{Rh(C_2H_4)Cl}$_2$]	**248**	85	50
5	[{Rh(C_2H_4)Cl}$_2$]	**249**	35	55
6	[{Rh(C_2H_4)Cl}$_2$]	*ent*-**159**	95	−82
7	[{Rh(C_2H_4)Cl}$_2$]	**250**	89	87
8	[{Rh(**221**)Cl}$_2$]	None	>95	93
9[e]	[{Rh(**221**)Cl}$_2$]	None	>95	28

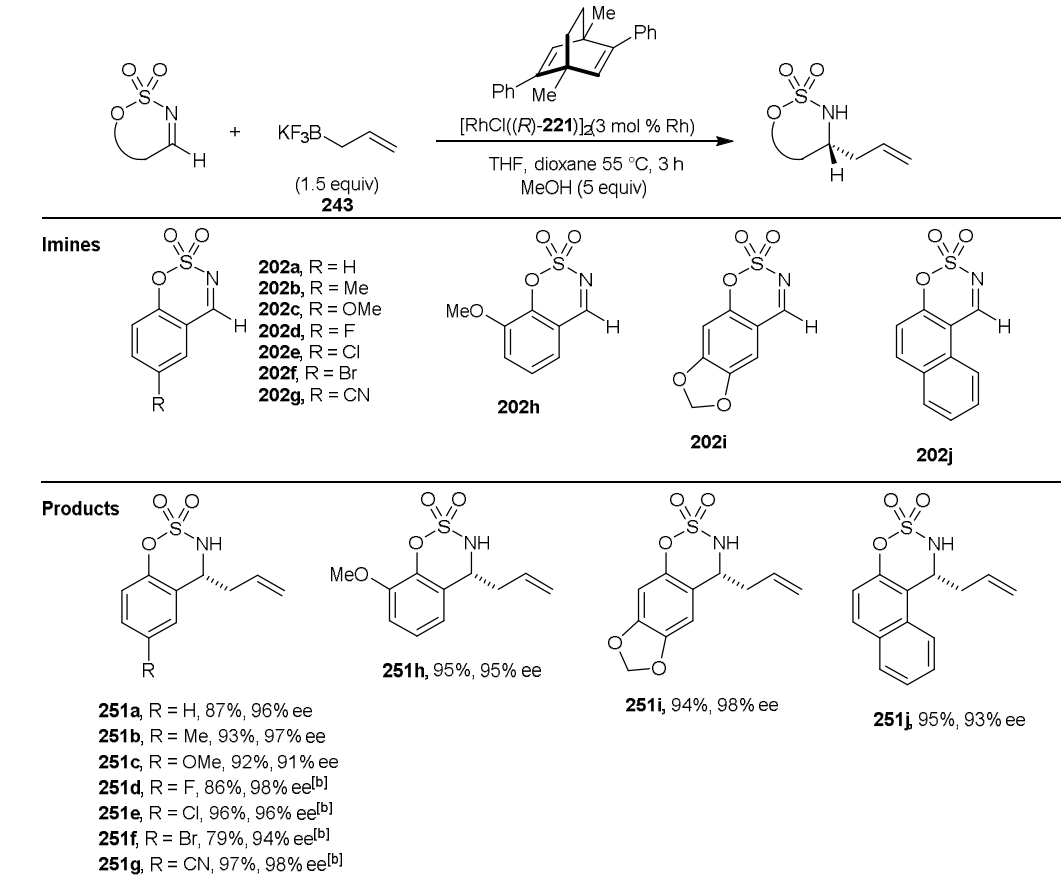
[a] Reactions were conducted by Hamish B. Hepburn using 0.10 mmol of **202a**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Determined by HPLC analysis on a chiral stationary phase. [d] *rac*-**251a** isolated in 87 % yield. [e] AllylBPin **106** with K_3PO_4 was used instead of allylBF$_3$K **243**.

With an effective ligand identified, the scope of this process was investigated under slightly modified reaction conditions. Both 5 and 6-membered cyclic imines, namely benzoxathiazine 2,2-dioxides, 1,2,6-thiadiazine 1,1-dioxides, 1,2,5-thiadiazolidine 1,1-dioxides, cyclic sulfamidates and cyclic *N*-sulfonylketimines, underwent enantioselective allylation as shown in the following sections.

Firstly, for the use of 1.5 mol % of [{Rh(**221**)Cl}$_2$] and MeOH (5 equivalents) in a THF/dioxane mixture at 55 °C, a wide range of 6-membered ring *N*,*O*-aldimines underwent allylation in generally good yields (79-97%) and good enantioselectivities (91-98%). Although, in some cases such as halogen- or cyano-substituted

benzoxathiazine-2,2-dioxides, longer reaction times and the use of *i*-PrOH (13 equivalents) in toluene/dioxane rather than MeOH in THF/dioxane were required for the yields and enantioselectivities to be high (**Table 1.3**).

Table 1.3: Enantioselective rhodium-catalysed allylation of 6-membered ring *N*,*O*-aldimines.[a]

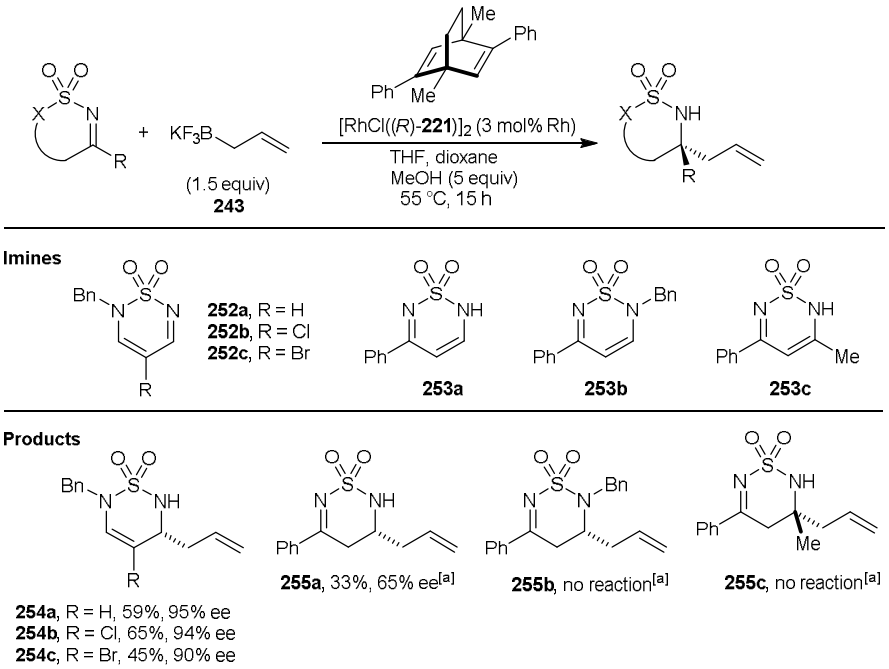


[a] Reactions were conducted by Dr Yunfei Luo and Hamish B. Hepburn. [b] Using *i*-PrOH (13 equiv) in toluene/dioxane for a reaction time of 18 h.

N,*N*-Cyclic aldimines such as 1,2,6-thiadiazine-1,1-dioxides **252a**-**252c**, also underwent allylation. Although the stereoselectivities were high (90-95%) in all cases studied, the yields were disappointingly modest (45-69%). Moreover, chiral adduct **254a** was not bench-stable and exhibited signs of decomposition after *ca*. 2 h. The allylation of

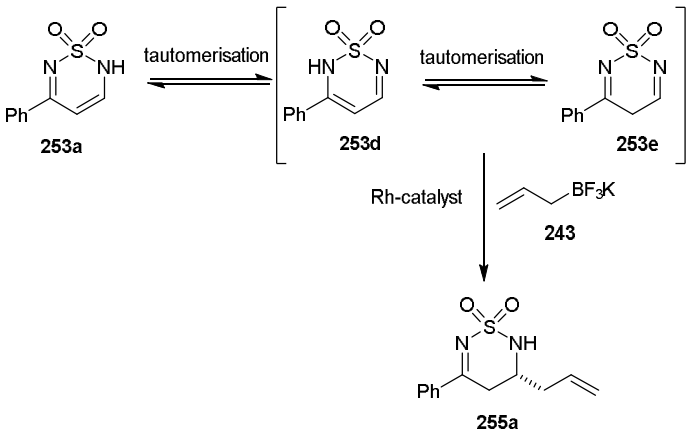
ketimine **253c** was also carried out, which did not undergo allylation to generate **255c** due to the steric hindrance of the methyl group (**Table 1.4**).

Table 1.4: Enantioselective rhodium-catalysed allylation of 6-membered ring *N*,*N*-imines.



[a] the reaction was set at 0.1 mmol scale and run for 24 h.

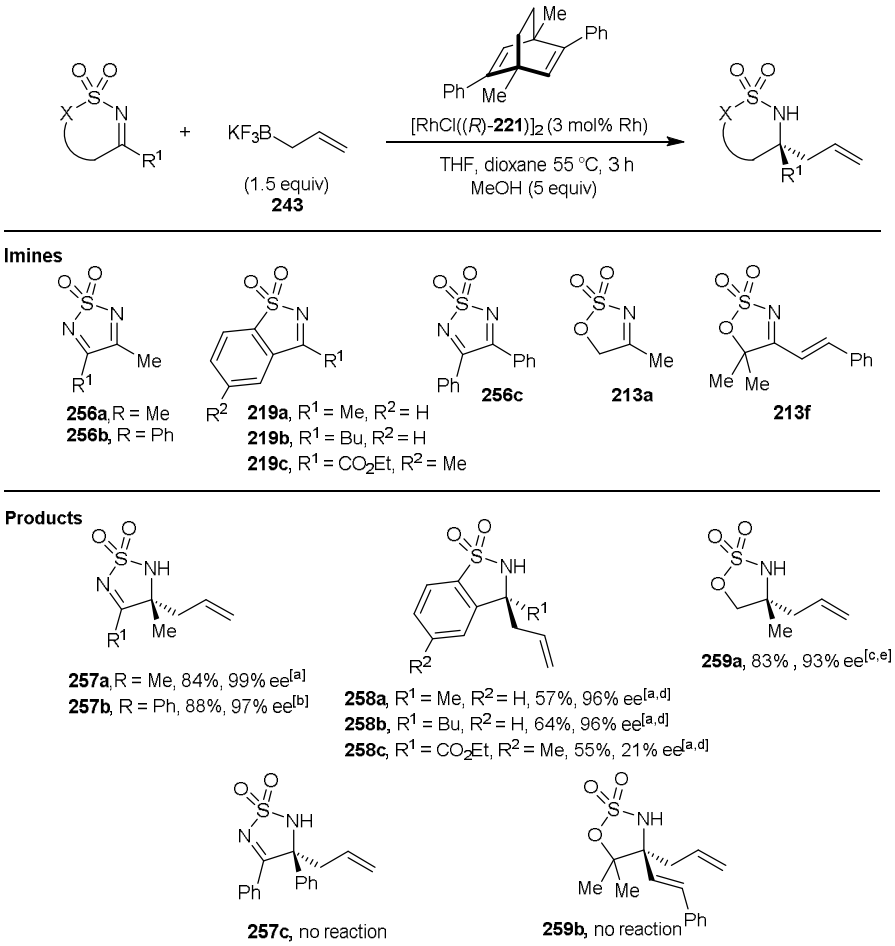
Surprisingly, 1,2,6-thiadiazine-1,1-dioxide **253a** can be allylated and the allylation occurred at the *β*-position of this *α*,*β*-unsaturated imine. The yield was low (33%) and enantioselectivity was modest (65% ee). The reason why the nucleophile attacked at this position is unclear, but it could be because compound **253a** can isomerise to aldimines **253d** and **253e** which can possibly undergo nucleophilic allylation to form the product **255a** (**Scheme 1.67**). This hypothesis was supported by the allylation of benzyl protected imine **253b** by using the standard reaction conditions. Unsurprisingly, as this substrate is unable to generate aldimine isomers, no allylated product **255b** was observed (**Scheme 1.67**).



Scheme 1.67: Rhodium-catalysed allylation of an imine **253a**.

Not only 6-membered ring cyclic ketimine **253c** but 5-membered ring cyclic ketimines such as 1,2,5-thiadiazolidine-1,1-dioxides (**256a-256c**), cyclic *N*-sulfonylketimines (**219a-219c**) and a cyclic sulfamidate imines (**213a** and **213f**) were also investigated (**Table 1.5**). Most of *N*,*N*- and *N*,*O*-5-membered ring cyclic ketimines underwent allylation to give homoallylic amines with high yields and enantioselectivities. However, bulky ketimines **256c** and **213f** did not convert to products **257c** and **259b** under the same conditions. All cyclic *N*-sulfonylketimines (**219a**-**219c**) were effective substrates. Methyl- and butyl-substituted ketimines underwent allylation with potassium allyltrifluoroborate (**243**) to give benzosultams **258a** and **258b**, respectively, with moderate yields (57% and 64%) and with high enantioselectivities (96% ee). It was clear that the allylations of sulfonylketimine **219c** containing electron-withdrawing substituent (such as ethyl ester) proceeded with lower enantioselectivities (21% ee).

Table 1.5: Enantioselective rhodium-catalysed allylation of 5-membered ring imines.

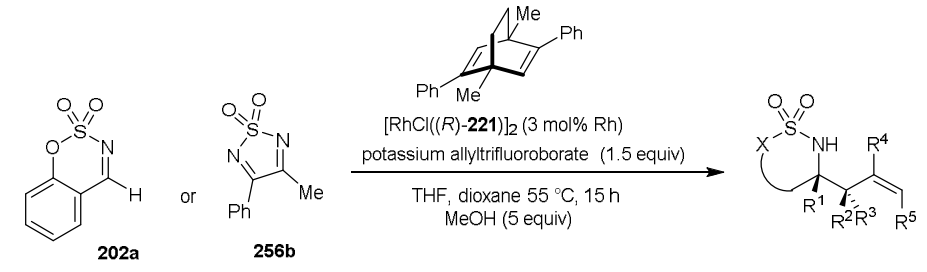


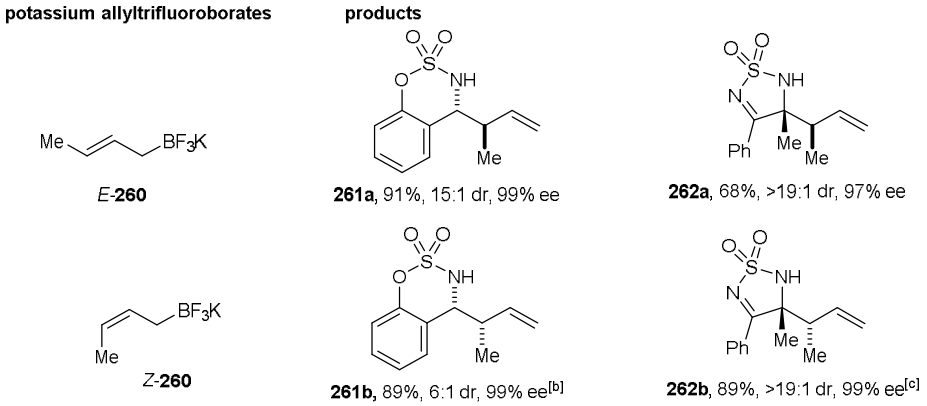
[a] Reactions were conducted by Hamish B. Hepburn. [b] With reaction time of 12 h. [c] Reaction was conducted by Dr Yunfei Luo using dioxane in place of THF. [d] Using [RhCl((*ent*-**221**)]$_2$ in place of [RhCl((*R*)-**221**)]$_2$ with reaction time of 15 h.

As previously discussed in **Table 1.3**, benzoxathiazine 2,2-dioxides containing electron-withdrawing substituents on the benzene ring were allylated with higher enantioselectivities when *i*-PrOH in toluene/1,4-dioxane was used instead of MeOH in THF/1,4-dioxane. However, application of this modified condition to the synthesis of product **258c** did not improve the enantioselectivity.

The allylation of cyclic imines **202a** and **256b** with *E*-and *Z*-crotyltrifluoroborates were also studied (**Table 1.6**). Under the standard reaction conditions, the results showed that a new carbon-carbon bond formation took place at the more substituted *γ* carbon atom of the allyltrifluoroborates. *E*-Crotyltrifluoroborate **260** underwent highly diastereoselective allylations to **202a** and **256b** to afford *anti* products **261a** and **262a**, respectively, with reasonable yields. Importantly, *Z*-crotyltrifluoroborate (**260**) resulted in the corresponding *syn* products **261b** and **262b** with high yields and enantioselectivities. Unfortunately, the diastereomeric ratio in the case of **261b** was reduced to 6:1.

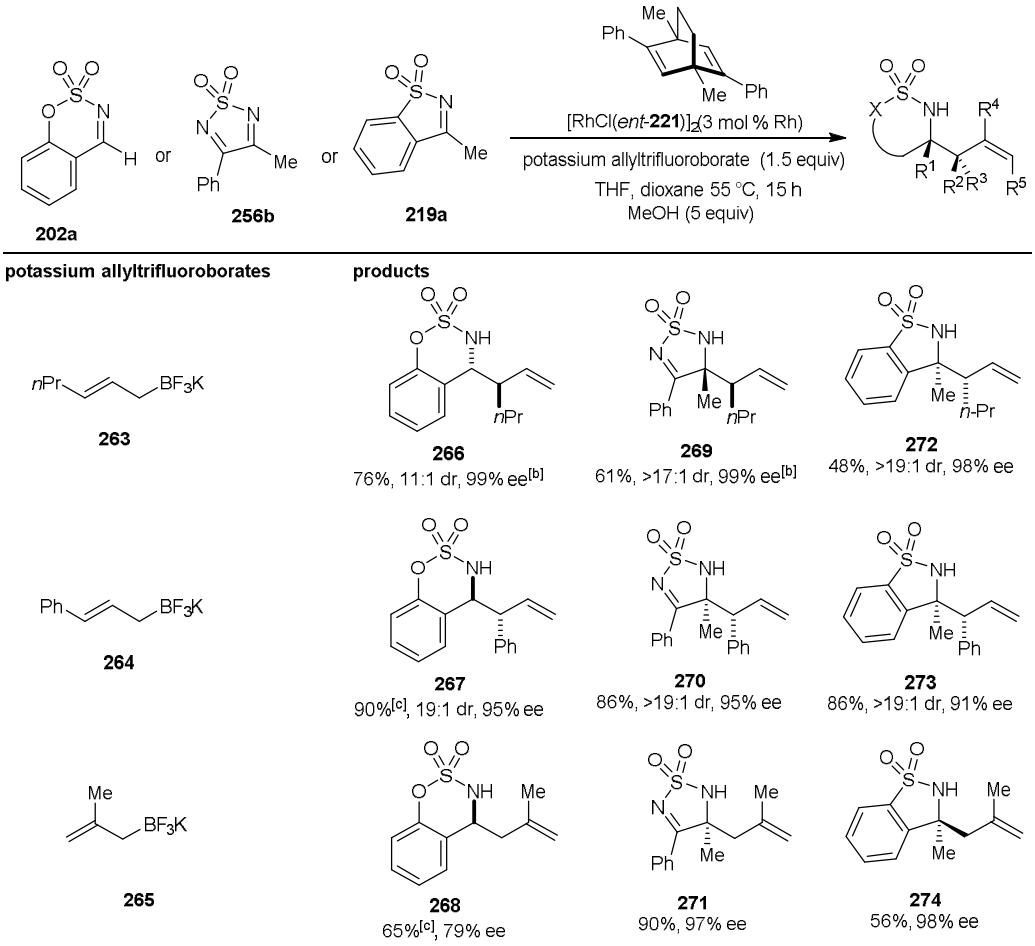
Table 1.6: Allylation of cyclic imines with various *E*- and *Z*-crotylltrifluoroborates.[a]





[a] Reactions were conducted by Hamish B. Hepburn. [b] Yield of an isolated inseparable mixture of diastereomers. [c] Reaction time of 12 h.

Table 1.7: Reaction of imines with the monosubstituted allyltrifluoroborates.[a]

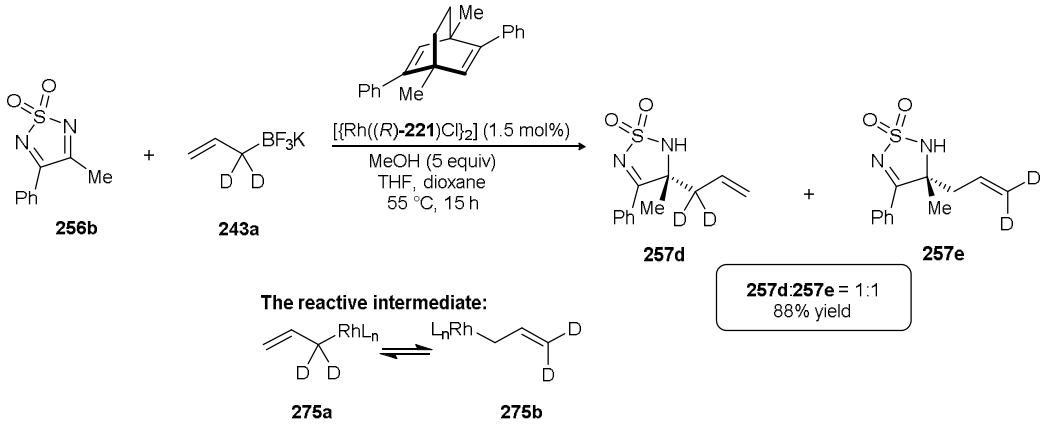


[a] Reactions were conducted by Hamish B. Hepburn. [b] Using [RhCl((*R*)-**221**)]$_2$ in place of [RhCl(*ent*-**221**)]$_2$. [c] Reaction conducted using *i*-PrOH (5 equiv) in toluene-1,4-dioxane instead of MeOH in THF-1,4-dioxane

Similar to *E*-crotyltrifluoroborates, *γ*-*n*-propyl-substituted allyltrifluoroborate (**263**) and *γ*-phenyl-substituted allyltrifluoroborate (**264**) generally afforded products with high yields, diastereo- and enantioselectivities except with products **269** and **272** that gave moderate yields (61% and 48% respectively). Exploiting the results mentioned in the previous section, the use of *i*-PrOH (5 equiv) in toluene/1,4-dioxane provided higher enantioselectivities compared with the standard reaction conditions of MeOH (5 equiv) in THF/1,4-dioxane, products **267-268** were synthesised with high yields and high

enantioselectivities. *β*-Methyl-substituted allyltrifluoroborate (**265**) reacted with both aldimines **202a** and ketimine **256b** as well as ketimine **219a** to give products with high enantioselectivities, the yield were lower in the reaction with aldimines **202a** and ketimine **219a** (65% and 56%), although product **268** was generated *via* the use of *i*-PrOH in toluene/1,4-dioxane (**Table 1.7**).

In order to gain some insight into the mechanism of these processes, ketimine **256b** was allylated by dideuterated potassium allyltrifluoroborate **243a** (**Scheme 1.68**).[95] It was found that products **257d** and **257e** (1:1 mixture) were obtained in 88% yield. This result suggests that allylation proceeds *via* an allylrhodium(I) species which undergoes rapid interconversion between the two σ-allyl haptomers **275a** and **275b**.[96]. If the rhodium did not form an allyrhodium species and the reaction proceed *via* another mechanism, then only product **257e** would be formed.[8a,89]

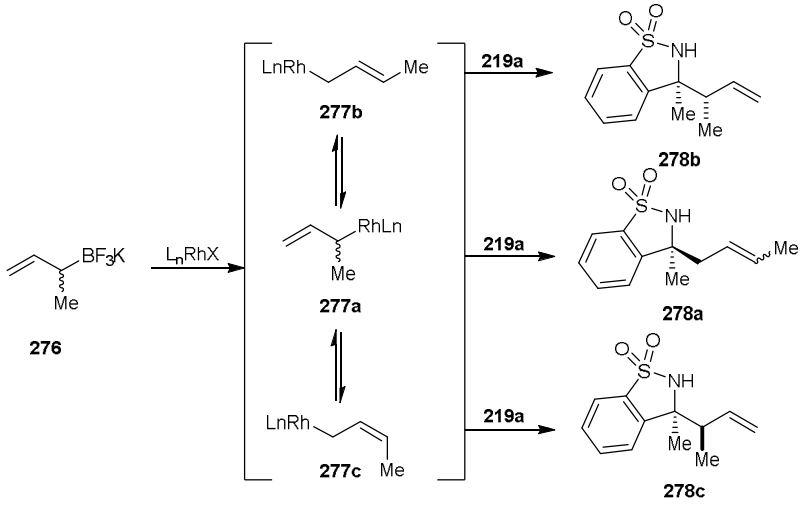


[a] Reaction was conducted by Dr Yunfei Luo.

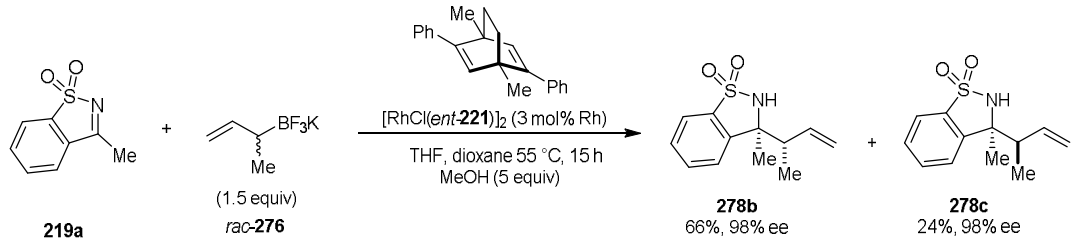
Scheme 1.68: Deuterium-labelling experiment.[a]

Previously, all of the allylboron reagents that had been studied featured the boron atom connected to a primary carbon atom. In all cases it was clear that C−C bond formation occurred exclusively at the *γ*-carbon of the allyltrifluoroborates. It was important, therefore, to examine the reactions using racemic *α*-methyl-substituted allyltrifluoroborate (**276**), where the boron is bonded to a secondary carbon atom.

Through deuterium experiments, it was speculated that these allylations proceed *via* the intermediacy of allylrhodium species. In agreement with this hypothesis, transmetalation of *rac*-**276** with the chiral rhodium complex could therefore, in principle, lead to several interconverting isomeric allylrhodium species (**277a**-**277c**). Reactions of these reactive species with imine **219a** would provide three different products (**Scheme 1.69**). However, it was unclear whether the γ-selectivity observed previously would be maintained using *rac*-**276**.



Scheme 1.69: Possible outcomes of reactions using α-methyl-substituted allyltrifluoroborate (**276**).



[a] The reaction was conducted by Hamish B. Hepburn.

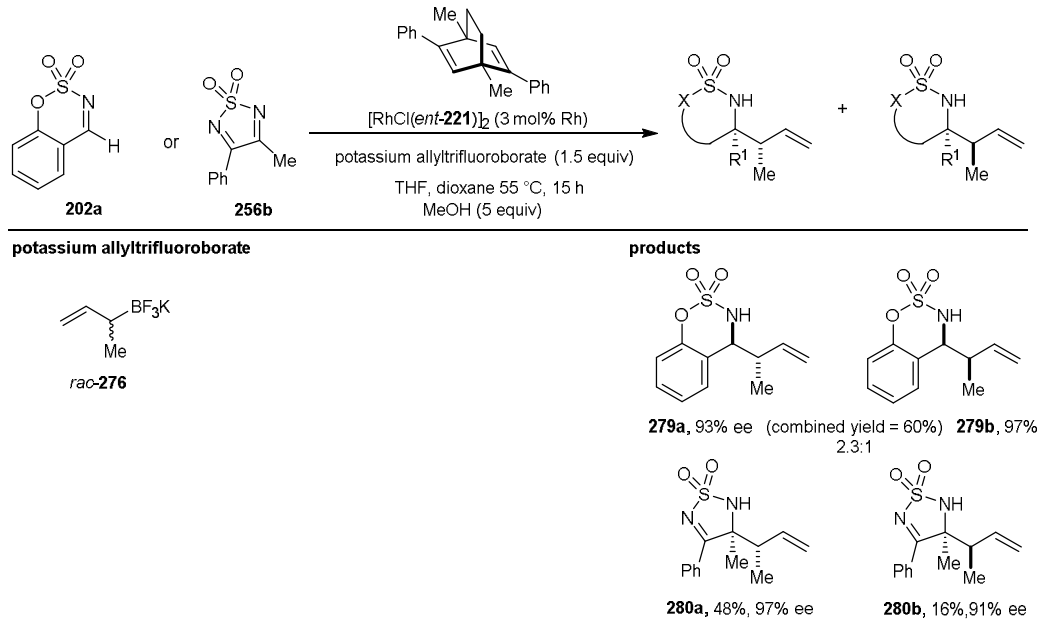
Scheme 1.70: Reaction of imine **219a** with the α-methyl-substituted allyltrifluoroborate (**276**).[a]

After the reaction was conducted using imine **219a** and *rac*-**276** under standard reaction conditions, it was found that diastereomeric products **278b** and **278c** were obtained with excellent enantioselectivities. Surprisingly, C−C bond formation only occurred at the α-carbon of *rac*-**276** and other isomeric products such as **278a** where C−C bond was formed at γ-carbon of *rac*-**276** were not observed (**Scheme 1.70**).

The above result not only provided further evidence that these allylations proceeded *via* allylrhodium intermediates, but also indicated that the contributions of these three allylrhodium species to the allylation of imine are different. Clearly, the greatest contribution is by *E*-crotylrhodium species **277b**, followed by *Z*-**277c**, while the contribution of **277a** is negligible. If there is a rapid interconversion between the different allylrhodium species compared with the imine allylation rates, the product ratio will only depend upon the relative rates of allylation from *E*-**277b**, **277a**, and *Z*-**277c**, and not upon their equilibrium distribution (Curtin–Hammett-type kinetics).[97] However, the allylations of imine **202a** using *E*- and *Z*-crotyltrifluoroborates (**260**) brought about the high degrees of stereochemical transfer (see **Table 1.6**). This result suggests that the isomerisation between *E*-**277b** and *Z*-**277c** is slow compared with the rate of imine allylation. Therefore, regarding the allylation of imine **219a** with *rac*-**276** in similar scenario it is likely that the ratio of **278b** and **278c** obtained relies significantly on the ratio of *E*-**277b** and *Z*-**277c** formed in the initial transmetallation.

In addition to providing further evidence that the ratio of allyation products from imine **219a** is dependent on the ratio of allylrhodium species, allylations of imines **202a** and **256b** with *rac*-**276** were investigated. It was found that similar outcomes were observed, in the case of imine **202a**, two diastereomers *ent*-**279a** and *ent*-**279b** were obtained as an inseparable 2.3:1 mixture with 60% combined yield, and with 93% ee and 97% ee, respectively. With imine **256b**, the two separable products **280a** and **280b** were isolated with 48% and 16% yields, and with 97% ee and 91% ee, respectively (**Table 1.8**).

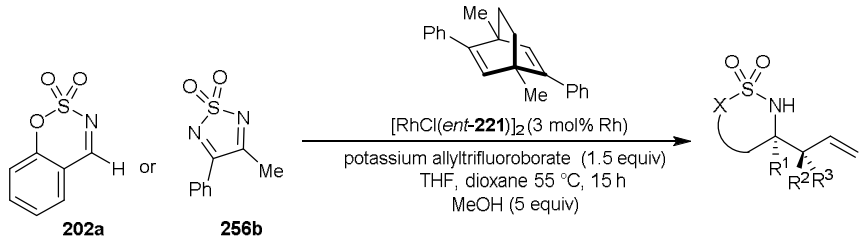
Table 1.8: Reaction of cyclic imines with the α-methyl-substituted allyltrifluoroborate **276**.[a]

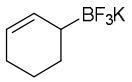
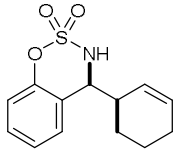
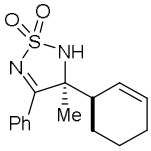
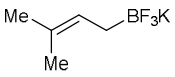
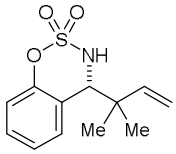
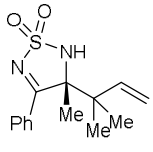
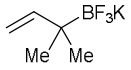
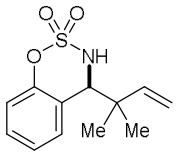
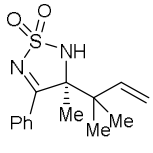


[a] Reactions were conducted by Hamish B. Hepburn.

To show an example of a disubstituted allyltrifluoroborate containing substituent at both the α- and γ-carbons, allylation with cyclohexenyltrifluoroborate **281** was studied. The result showed that the reaction between this reagent and aldimine **202a** provided a product **284** with only 36% yield, though with good diastereo- and enantioselectivity. Moreover, with ketamine **256b** the allylation was unsuccessful, and provided a complex mixture of unidentified products (note it was known that substrate **256b** is unstable under the reaction conditions, and if rhodium-catalysed allylation does not occur, it was found that no starting material or product was present in the resultant reaction mixture). In terms of γ,γ-dimethyl-substituted allyltrifluoroborate **282**, the allylation with both imines **202a** and **256b** delivered reverse prenylation products with high yields and excellent selectivities. Similarly, allylation of α,α-dimethyl-substituted allyltrifluoroborate (**283**) with imines **202a** and **256b**, resulted in reverse prenylation products **286b** and **287b** with reasonable yields and with high enantioselectivities, where the C−C bond formed exclusively at the α-carbon (**Table 1.9**).

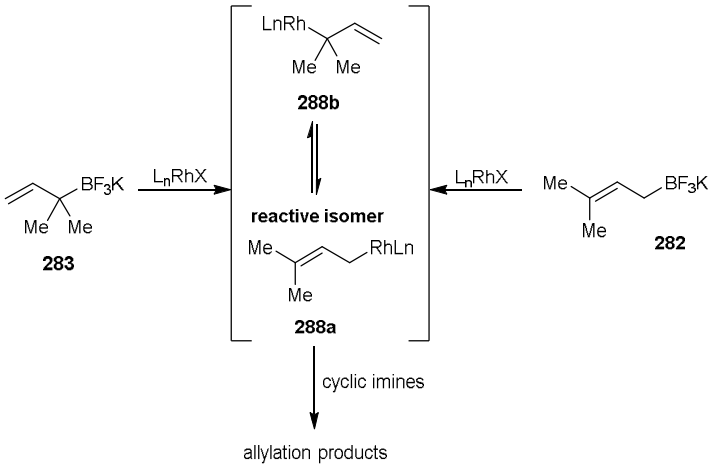
Table 1.9: Reaction of imines with the disubstituted allyltrifluroborates[a]



potassium allyltrifluoroborates	products	
 **281**	 **284**, 36%, 10:1 dr, 93% ee	 **285**, <5%
 **282**	 **286a**, 91%, 97% ee[b]	 **287a**, 75%, 95% ee[b]
 **283**	 **286b**, 71%, 90% ee[c]	 **287b**, 87%, 91% ee

[a] Reactions were conducted by Hamish B. Hepburn. [b] Using [RhCl((*R*)-**221**)]$_2$ in place of [RhCl(*ent*-**221**)]$_2$. [c] Reaction conducted using *i*-PrOH (5 equiv) in toluene/1,4-dioxane instead of MeOH in THF-1,4-dioxane.

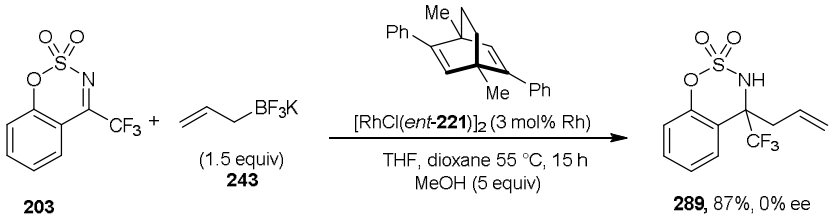
According to the interesting result mentioned above, for both allyltrifluoroborates **283** (α-selectivity) and **282** (γ-selectivity) the reverse prenylation products were isolated. This result suggests that allylation proceeds *via* the reactive allylrhodium species **288a** rather than the isomeric species **288b** (**Scheme 1.71**).



Scheme 1.71: Allylrhodium species from allyltrifluoroborates **282** and **283**.

Other Reactive Substrates

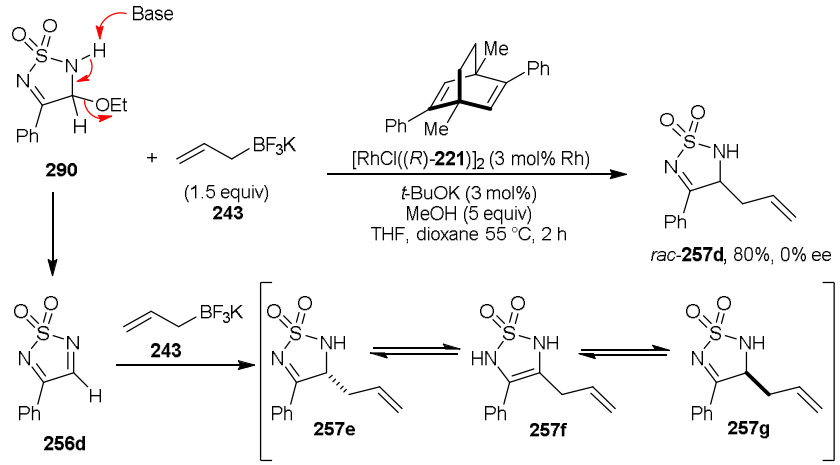
In addition to the imine substrates described in the previous sections, ketimine **203** containing a trifluoromethyl group was also investigated. This imine underwent allylation with allyltrifluoroborate (**243**) in 85% yield, but unfortunately the product **289** was obtained as a racemate (**Scheme 1.72**).



Scheme 1.72: Allylation of imine **203**.

Under the standard reaction conditions imine **290** did not react with allyltrifluoroborate (**243**). However, when substoichiometric amount of *t*-BuOK base was added imine **290** underwent full conversion to provide homoallylic amine **257d** with 80% yield (**Scheme 1.73**). Again, disappointingly, it was obtained as a racemate. Presumably under strong basic conditions imine **256d** is generated *in situ* by de-ethoxylation of pro-diimine **290**. Then, the resulting imine **256d** is allylated by allyltrifluoroborate (**243**)

to afford **257e**, which can easily undergo tautomerisation to provide racemic compound **257d**.



Scheme 1.73: Rhodium-catalysed allylation of an imine **290**.

Other Unreactive Substrates

Although most substrates underwent allylation very well, some of these compounds such as acyclic imines and cyclic enamides shown in **Figure 1.4** were unreactive under standard allylation conditions.

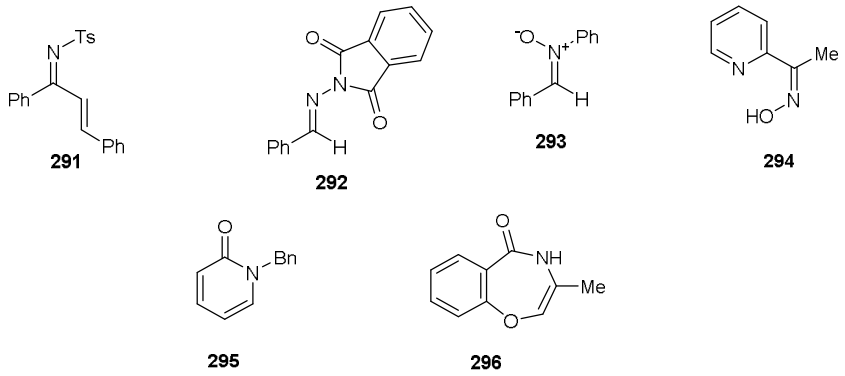
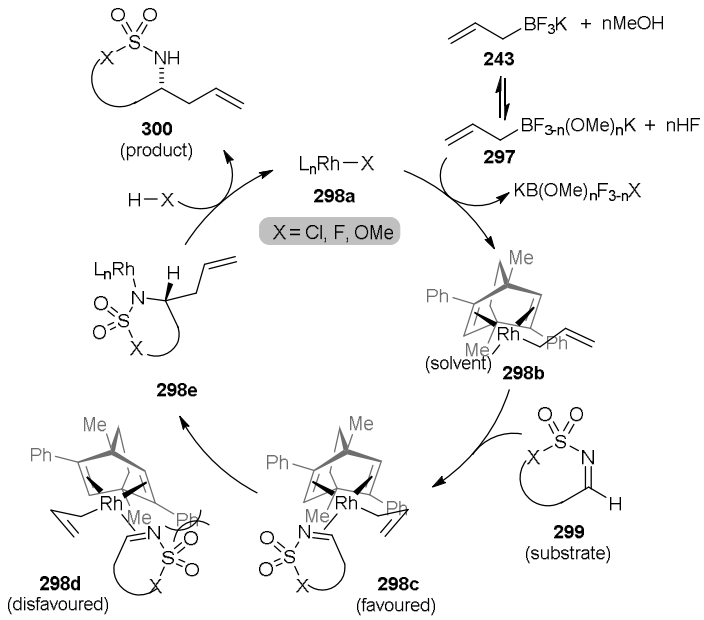


Figure 1.4: Unreactive substrates.

1.5.2 Mechanistic Discussion

Owing to the fact that *E*- and *Z*-crotyltrifluoroborates (**260**) provided *anti*- and *syn*-allylation products (**261a** and **261b** respectively), with good to high diastereoselectivities (**Table 1.6**), it is likely that the reaction proceeds *via* 6-membered cyclic transition states. The corresponding allylrhodium(I) intermediates have appreciable configurational stability during their lifetime in the reaction mixture despite the possibility of rapid interconversion between the two σ-allyl isomers, a process which could erode *E*/*Z* stereochemistry.[96,98] On the basis of these features, a plausible catalytic cycle of the allylation reaction has been proposed (**Scheme 1.74**). Presumably, in the presence of MeOH, potassium allyltrifluoroborate (**243**) can undergo reversible methanolysis to generate an ate-complex **297**, which transmetallates with the rhodium complex **298a** to form the allylrhodium species **298b**. This species can then coordinate with imine **299** in a manner that gives less steric hindrance to afford complex **298c**. Allylation of the bound imine in **298c** through a cyclic chair-like transition state would give **298e**, which is then protonated with HX to release the product **300** and regenerate **298a**.

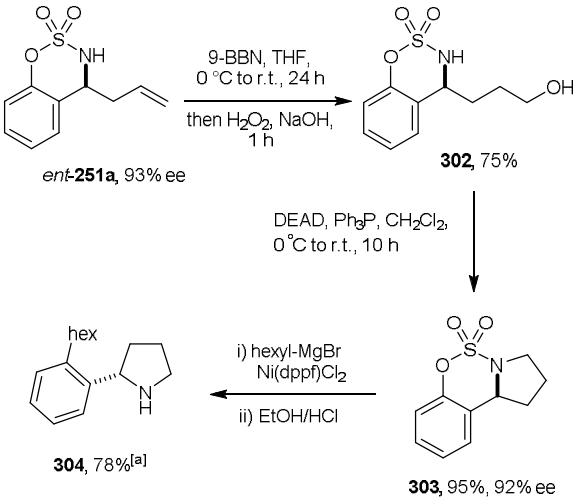


Scheme 1.74: Possible catalytic cycle.

1.5.3 Derivatisation of the Resultant Enantioenriched Homoallylic Amines

To demonstrate the utility of this methodology, representative transformations of allyation products were conducted as shown below. For example, removal of the sulfonyl group of compound **251a** was readily accomplished over two steps. Firstly, the treatment of cyclic compound **251a** with $LiAlH_4$ generated the amine adduct. This was followed by the *in situ* protection of the resultant amine with Boc_2O to provide Boc-protected amine **301** in 85% overall yield with retained stereochemistry (**Scheme 1.75**).

Scheme 1.75: Removal of the sulfonyl group of homoallylic amine **251a**.

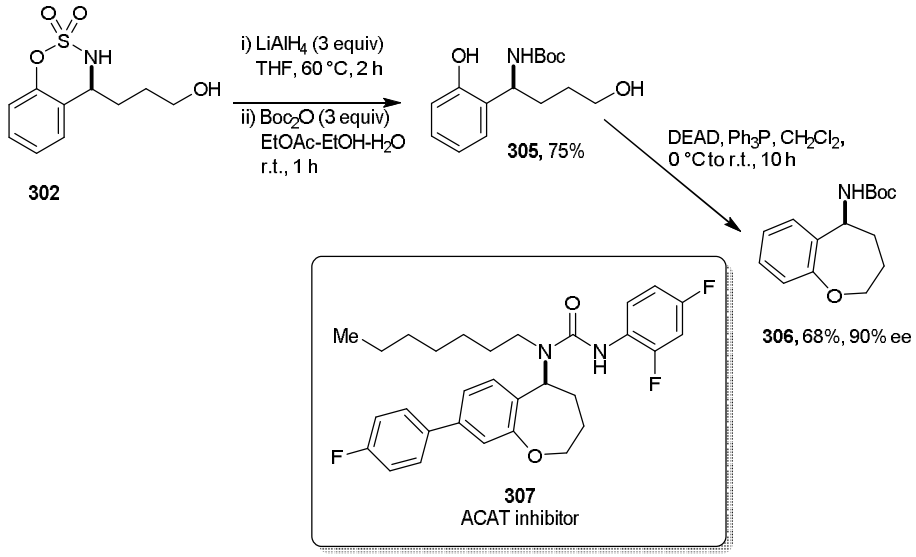


[a] Reaction was conducted my Hamish B. Hepburn.

Scheme 1.76: Conversion of *ent*-**251a** into amine **304**.

The hydroboration of the alkene of *ent*-**251a** (prepared in the same way as compound **251a** but using chiral diene *ent*-**221**) using 9-BBN provided primary alcohol **302** with reasonable yield. Further transformations provided tricyclic sulfamate **303** *via* a Mitsunobu cyclisation (**Scheme 1.76**). The resulting tricyclic sulfamate **303** then underwent a nickel-catalysed Kumada coupling with hexylmagnesium bromide, using the sulfamide moiety as a pseudo-halide to provide chiral 2-substituted pyrroldine **304** with 78% yield.

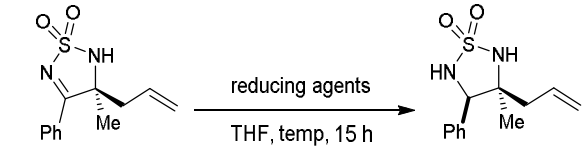
Alternatively, treatment of **302** with $LiAlH_4$ to remove the sulfonyl group followed by Boc protection provided carbamate **305** in 75% yield. This compound was successfully converted into the tetrahydrobenzoxepine **306** by a Mitsunobu cyclisation. Interestingly, amino-substituted tetrahydrobenzoxepines have been found to exhibit interesting biological activities. A study by Fescal and co-workers,[99] for example, showed that compound **307** is a strong ACAT (acyl coenzyme A, cholesterol *O*-acyltransferase) inhibitor (**Scheme 1.77**).



Scheme 1.77: Conversion of **302** into amino-substituted tetrahydrobenzoxepine **306**.

A diastereoselective reduction of imine *ent*-**257b** (prepared as the same way as compound **257b** but using chiral diene *ent*-**221** instead of (*R*)-**221**) was investigated. A range of different reducing agents was screened to enable good diastereomeric ratios to be achieved (**Table 1.10**). Pleasingly, with the use of DIBAL-H at –20 °C, chiral adduct **308** was obtained in 90% yield as a single observable diastereomer with no erosion of enantioselectivity (entry 8).

Table 1.10: Diastereoselective reduction of imine *ent*-**257b**[a]



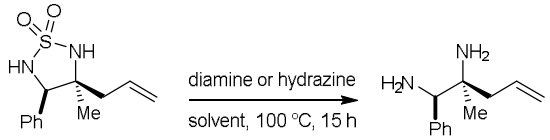
ent-**257b**, 97% ee **308**

Entry	Reducing agent	Solvent	Temp. (°C)	Time (h)	Conv (%)	dr
1	$NaBH_4$	THF	0	15	100	3:1
2	$LiAlH_4$	THF	0	15	100	6:1
3	$LiBHEt_3$	THF	0	15	100	2:1
4	DIBAL-H	THF	0	15	100	15:1
5	DIBAL-H	THF	–5 to r.t.	15	100	18:1
6	DIBAL-H	THF	–78 to r.t.	15	30	-
7	DIBAL-H	THF	–20 to r.t.	15	100	36:1
8[b]	DIBAL-H	THF	–20 to r.t.	15	100(90)	36:1

[a] Reactions were conducted using 0.05 mmol of *ent*-**257b** and 0.2 mmol of reducing agent which % conversions were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b] Reaction was conducted using 0.8 mmol of *ent*-**257b** to give product **308** in 90% isolated yield.

Finally, the removal of the sulfonyl group of compound **308** by heating in hydrazine solution was unsuccessful. Fortunately, when ethylenediamine (10 equiv) in 1,4-dioxane was used, 1,2-diamine **309** was achieved with 88% yield (**Table 1.11**, entry 3).

Table 1.11: Removal of sulfonyl group of compound **308**.[a]



308
>19:1 dr, 97% ee

309

Entry	Reducing agent	Solvent	Temp. (°C)	Time (h)	Conv (%)
1	$NH_2NH_2.H_2O$	-	100	15	100[b]
2	$NH_2CH_2CH_2NH_2$	1,4-dioxane	100	15	100
3[c]	$NH_2CH_2CH_2NH_2$	1,4-dioxane	100	15	100(88)

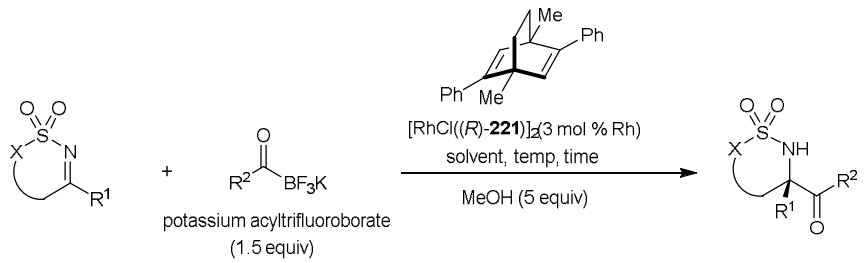
[a] Reactions were conducted using 0.1 mmol of **308** and 1 mmol of reducing agent, % conversions were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b] ^{1}H NMR result of crude mixture was very messy. [c] Reaction was conducted using 0.4 mmol of **308** to give product **309** in 88% isolated yield.

1.6 Conclusion and Future Studies

In summary, rhodium-catalysed enantioselective allylation of imines has been studied and developed.[100] Acyclic imines where imine-enamine tautomerisation takes place provide products in poor yields. In contrast, cyclic imines where the C=N bond is constrained in the *Z* geometry, allow the reactions to proceed in generally good yields and high levels of diastereo- and enantioselectivities using chiral diene ligand. *E*- and *Z*-allyltrifluoroborates generate exclusively different stereoisomers possibly because the use of the chiral allylrhodium(I) intermediates have appreciable *E*/*Z* configurational stability during the time scale of allylation. Moreover C–C bond formation preferably

occurs at the more highly substituted end of the allyl fragment of the trifluoroborate, regardless of the position of the boron atom. To the best of our knowledge, these reactions represent the first rhodium-catalysed enantioselective nucleophilic allylations of π electrophiles with allylboron reagents. The utility of the allylation products was demonstrated by several transformations.

In the future, the scope of nucleophilic boron reagents will be expanded in order to obtain complex and useful chiral products which are difficult to synthesise and also to understand more about the role of this rhodium catalyst in synthesis. For example, using potassium acyltrifluoroborate as nucleophilic reagents would result in chiral aminoacyl compounds (**Scheme 1.78**).



Scheme 1.78: Rhodium-catalysed acylation of cyclicimines.

2. Enantioselective Nickel-Catalysed Michael Additions of 2-Acetylazaarenes to Nitroalkenes

2.1 Introduction to Azaarenes

Azzaarenes; nitrogen-containing aromatic heterocycles, are ubiquitous structures in many chiral molecules.[101] These important chemical units can be featured in naturally occurring compounds[102] with biological properties such as Fuzanin D (**310**), Pateamine A (**311**) and Terezine A (**312**), drugs[103] such as Viagra (**313**), Telaprevir (**314**) and Topotecan (**315**) or even pesticides[104] such as Benzthiazuron (**316**) and nicotine (**317**) (**Figure 2.1**). Due to the exceptionally high significance of azaarenes, worldwide efforts have been made by many researchers to design and develop strategies for their synthesis.

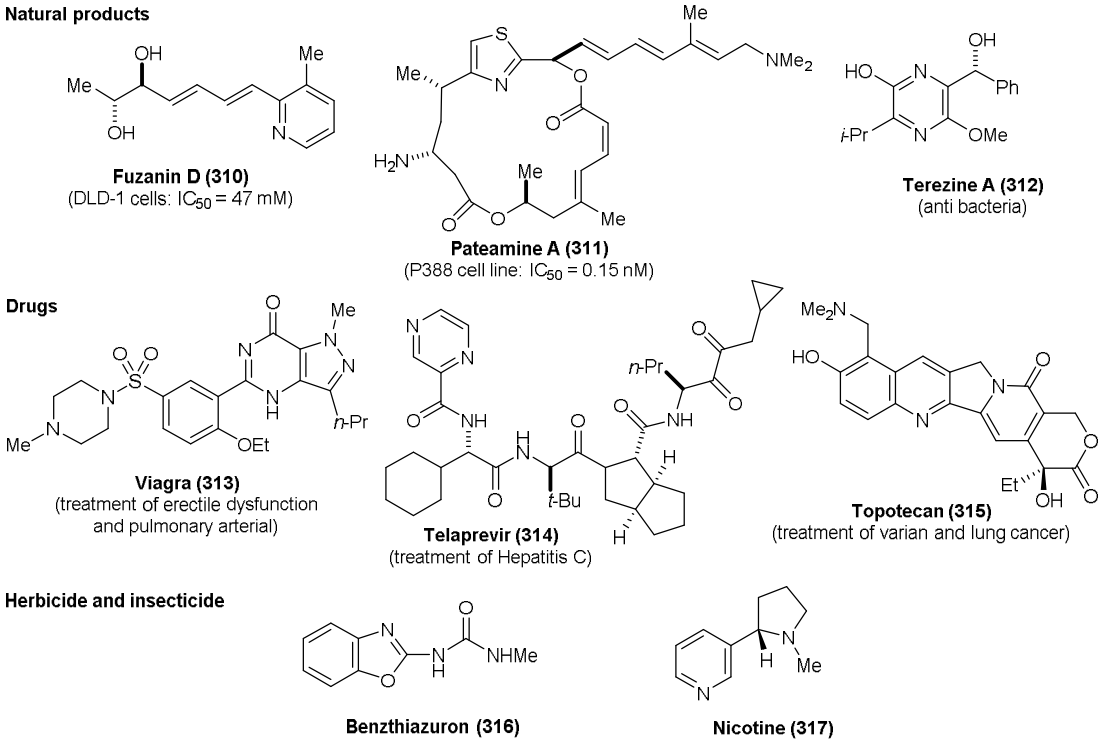
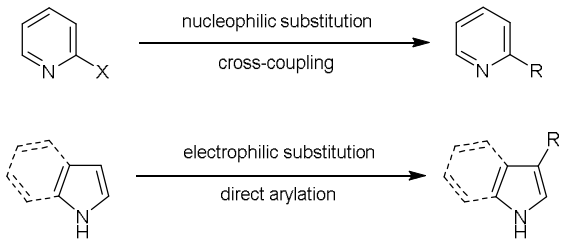


Figure 2.1: Biologically active compounds containing azaarenes.

There are many well established approaches for the synthesis of functionalised azaarenes such as transition metal-catalysed cross-coupling reactions,[105] Friedel−Crafts alkylations[106] and C−H functionalisation,[107] which are robust and often high yielding. However, most of them frequently lead to achiral or racemic products (**Scheme 2.1**). Therefore, the catalytic asymmetric functionalisation of azaarenes to generate optically active compounds is significantly challenging in organic synthesis and of great importance.



Scheme 2.1: Non-asymmetric functionalisation of azaarenes.

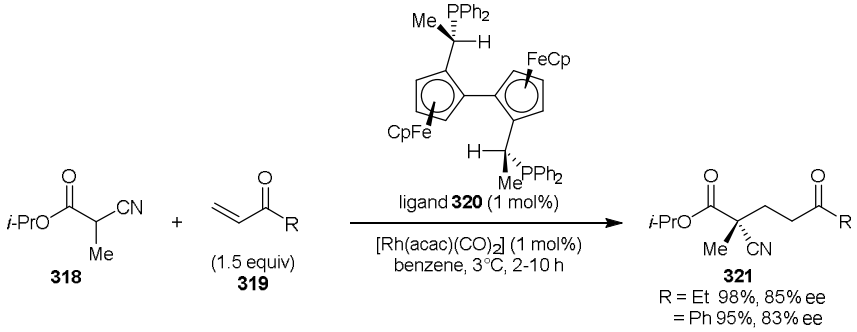
In this regard, a huge number of organic compounds have been studied in terms of biological activities especially those containing chiral carbon stereocentres. However, to the best of our knowledge, chiral molecules containing both azaarenes and all-carbon quaternary stereocentres are rarely synthesised or explored. Signifying its importance; more than 12% of the top 200 prescription drugs sold in the US in 2011 comprised of pharmaceutically active molecules containing a quaternary stereocentre.[108] This suggests that molecules bearing quaternary carbons may be useful in terms of medicinal properties and synthesising them in a controlled manner is a significant challenge. Thus, in the next **Section 2.2**, the synthesis of chiral compounds containing all-carbon quaternary stereogenic centre is discussed.

2.2 Chiral All-Carbon Quaternary Stereocentre Synthesis by Michael Reaction

For several decades, impressive progress have been made in the field of enantioselective synthesis of all-carbon quaternary stereocentres.[109] According to comprehensive reviews

by Overman[110] and others[111] there are many categories of these transformations; cycloaddition reactions, polyene cyclisations, metal-catalysed insertions, reaction of carbon nucleophiles, reaction of carbon electrophiles and desymmetrisation etc. However, it is too broad to cover all of these approaches here. In this section, only some important examples of all-carbon quaternary stereocentre syntheses by Michael reactions will be discussed.

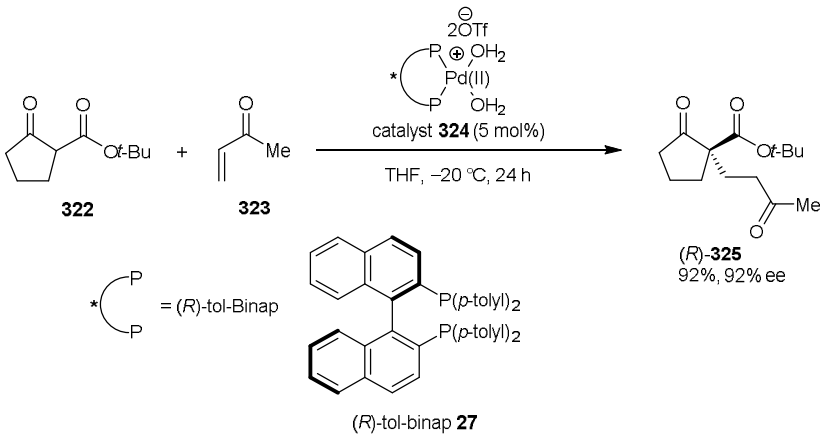
The Michael addition is one of the most important carbon-carbon bond-forming reactions in organic synthesis.[112] Historically, the pioneering study of the transition metal-catalysed Michael reaction to generate chiral quaternary carbons was studied by Ito and co-workers in 1992.[113] Utilising a catalytic complex generated *in situ* from *trans*-chelating chiral diphosphine ligand **320** and [$RhH(CO)(PPh_3)_3$], vinyl ketones and acroleins reacted with α-cyanoesters to obtain chiral products containing all-carbon quaternary stereocentres in high yields and enantioselectivities (**Scheme 2.2**).



Scheme 2.2: Rhodium-catalysed enantioselective Michael addition of α-cyanocarboxylate **318** to vinyl ketones.

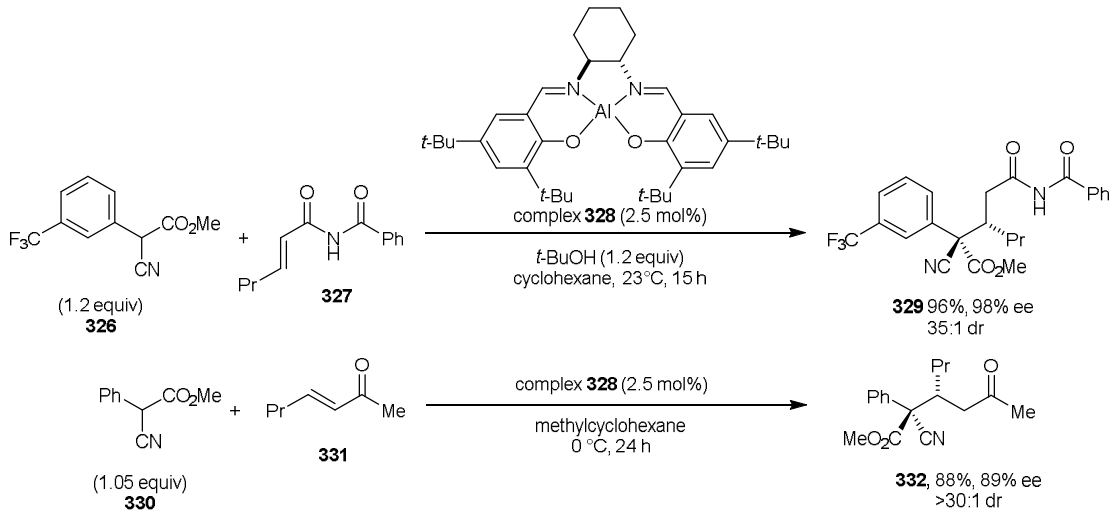
Sodeoka and co-workers described the generation of chiral palladium enolates of 1,3-dicarbonyl compounds and its application to the efficient catalytic enantioselective Michael reaction with α,β-unsaturated ketones.[114] With a novel palladium aqua complex catalyst **324**, 1,3-dicarbonyl compounds were transformed to chiral dicarbonyl adducts with all carbon quaternary centres (**Scheme 2.3**). The unique mechanism proposed that the palladium aqua complex allows successive supply of a Brønsted base and a Brønsted

acid. The former activates the dicarbonyl compound to give the chiral palladium enolate and the latter cooperatively activates the enone.



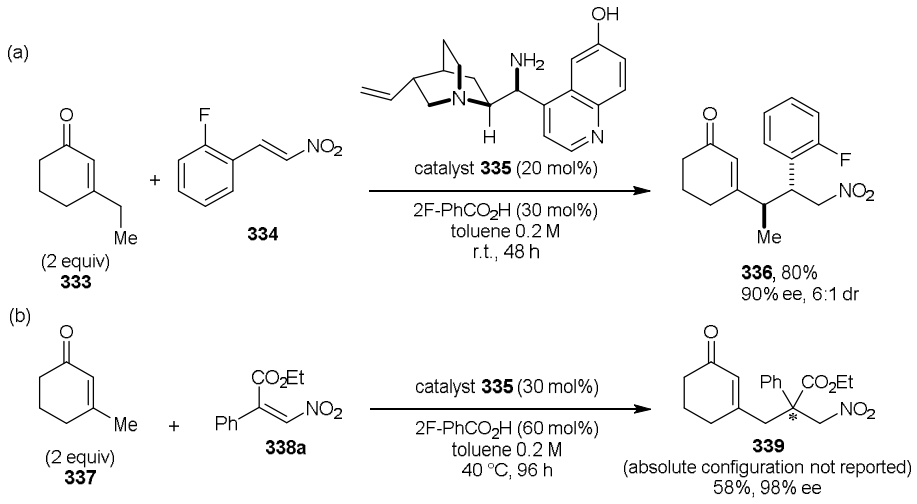
Scheme 2.3: Palladium-catalysed enantioselective Michael reaction with enones.

Jacobsen and co-workers[115] reported asymmetric Michael additions of electron-deficient nitrile derivatives to acyclic α,β-unsaturated carbonyl compounds catalysed by a chiral (salen)-aluminum complex **328**. This catalyst tolerated a large variety of α-aryl and heteroaryl cyanoacetates with substituted enones or imides. Although the reaction of methyl cyanoacetate gave chiral products in a roughly 1:1 mixtures of diastereomers because α-cyanoester stereocentre undergoes epimerisation, the use of substituted cyanoacetates provided adducts containing carbon- and heteroatom-substituted quaternary stereocentres in high enantio- and diastereoselectivities (**Scheme 2.4**). Moreover, the authors believed that a simple one-point binding of carbonyl compounds to the catalyst is sufficient for high enantioselectivity in catalytic processes.



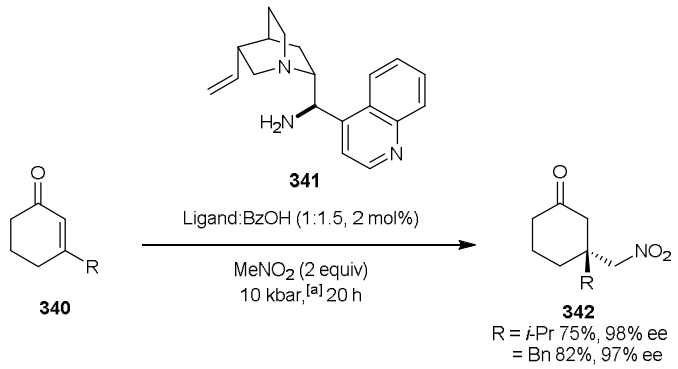
Scheme 2.4: Enantioselective Michael additions to *α,β*-unsaturated carbonyls catalysed by a salen-Al complex **328**.

In recent years, organocatalysed Michael reactions have also been broadly studied to generate chiral all-carbon quaternary stereogenic centres. For example, Melchiorre and co-workers[116] reported an intermolecular vinylogous Michael addition of unmodified cyclic *β*-substituted ketones to nitroalkenes promoted by diamine catalysts. Notably, the two stereocentres at the *γ* and *δ* positions of the carbonyl moiety were formed with very high levels of diastereo- and enantioselectivities (**Scheme 2.5(a)**). The reaction proceeded smoothly *via* *γ*-site-selective addition of *β*-substituted cyclohexanone derivatives to nitroalkene acceptors. When *β*-substituted nitroacrylate **338a** was used the Michael product **339** containing all-carbon quaternary stereocentre was obtained (**Scheme 2.5(b)**).



Scheme 2.5: Direct asymmetric vinylogous Michael addition of cyclic enones to nitroalkenes *via* dienamine catalysis.

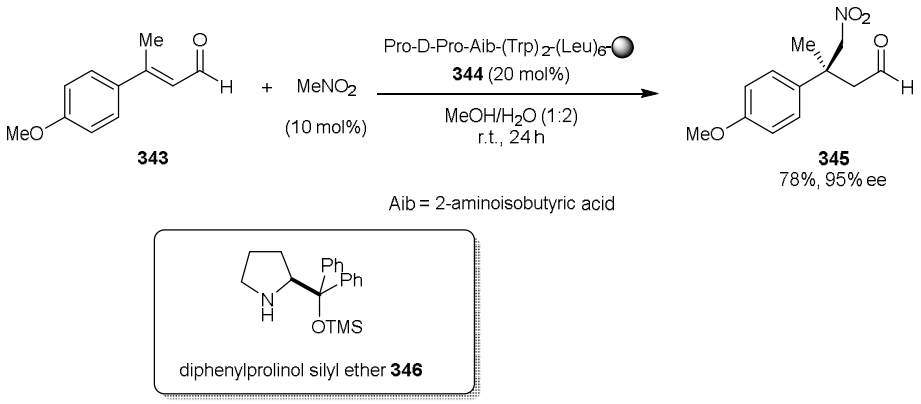
Kwiatkowski and co-workers developed an efficient high-pressure enantioselective organocatalytic 1,4-conjugate addition of nitroalkanes to prochiral *β*,*β*-enones.[117] This approach worked successfully with various acyclic and cyclic enones to afford *γ*-nitroketones containing chiral all-carbon quaternary stereogenic centres (**Scheme 2.6**). The loading of simple chiral primary amine catalysts was only 1-5 mol%. This work demonstrates the significant effect of hydrostatic pressure on the rate of an organocatalytic reaction while the enantioselectivity was retained.



[a] using a direct, single-stage piston-cylinder apparatus with a hydraulic press.

Scheme 2.6: Organocatalytic asymmetric Michael reaction of enone **340**.

In 2012, the asymmetric Michael addition of nitromethane to β-disubstituted α,β-unsaturated aldehydes was investigated using a resin-supported peptide catalysts.[118] The use of an aqueous solvent system was found to be essential for effective reactions in comparison with running the reaction in THF which afforded products with poor conversions. Moreover, the hydrophobic helical part of the peptide significantly affected the reaction rate and enantioselectivity. With the optimised peptide catalyst **344**, highly enantioenriched products with all-carbon quaternary stereocentres were obtained with reasonable yields (**Scheme 2.7**). The report demonstrates the high potential of peptide catalysis for organocatalytic reactions, in which a conventional low molecular weight catalyst such as diphenylprolinol silyl ether (**346**) is ineffective.

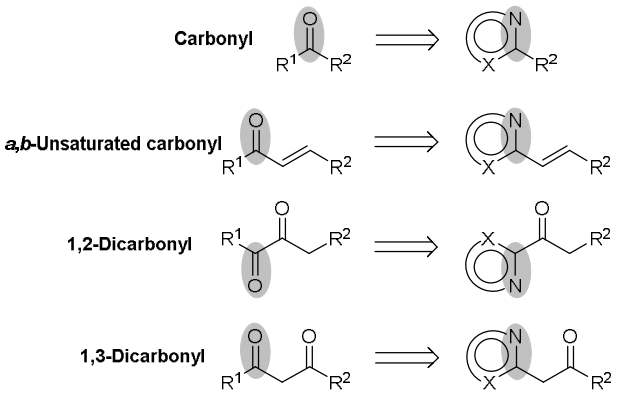


Scheme 2.7: Peptide-catalysed asymmetric Michael addition of nitromethane to β-disubstituted α,β-unsaturated aldehyde **343**.

As discussed above, there are many different approaches to obtain chiral compounds containing all-carbon quaternary stereocentres, either by using metal catalysts or organocatalysts. However, in terms of azaarenes bearing chiral all-carbon quaternary substituents, they are rarely investigated and explored. These compounds may serve as intermediates for the synthesis of complex target molecules. In order to highlight the importance of azaarenes in asymmetric Michael reactions, the use of azaarenes as activating groups in stereoselective transformations is discussed in **Section 2.3**.

2.3 Introduction to Heteroarenes as Activating Groups in Enantioselective Reactions

Generally, chiral compounds containing azaarenes can be synthesised by using either catalytic asymmetric reactions or chiral auxiliaries.[119-121] However, within most of those reports the azaarene acts as a nonparticipating bystander in a reaction. Therefore the development of methods that exploit or utilise the unique chemical properties of the azaarene itself to promote the reaction should provide powerful, complementary tools for synthesis. Interestingly, if the structure of an azaarene is considered carefully, it is found that this functional group is isoelectronic with respect to the carbonyl motif. For example, the C=N bond of azaarenes could mimic carbonyl (C=O) containing groups such as *α,β*-unsaturated carbonyl, 1,2-dicarbonyl and 1,3-dicarbonyl (**Scheme 2.8**). Therefore this section will provide an overview of the relevant literature demonstrating that azaarenes can activate both electrophiles and nucleophiles as shown below.

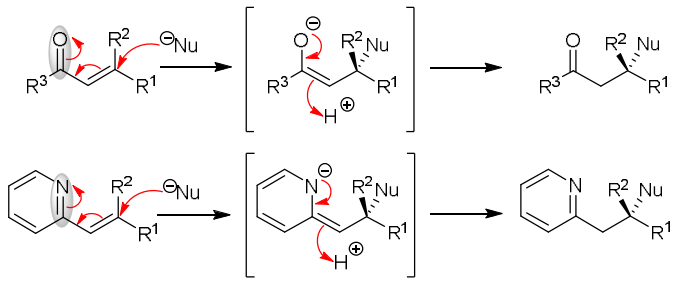


Scheme 2.8: Azaarenes mimic carbonyl compounds.

2.3.1 Azaarenes as Activating Groups for Electrophilic Additions

The conjugate addition of a nucleophile to a C=C bond electrophile normally requires the alkene be activated by a range of π-electron withdrawing groups. Theoretically, C=N containing azaarenes can activate adjacent conjugated π-systems by withdrawing electron density from those unsaturated double bonds (**Scheme 2.9**). Using this concept,

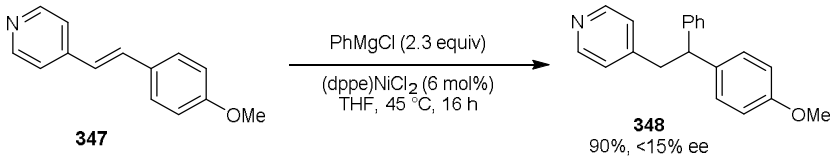
several research groups have functionalised alkenylazaarenes with various nucleophiles although most of these works produced only achiral products.[122]



Scheme 2.9: Electronic homology concept between α,β-unsaturated carbonyl motives and alkenylazaarenes.

Conjugate Additions of Nucleophiles to Alkenylazaarenes

In 1998, Houpis and co-workers[123] reported a nickel catalysed conjugate addition of Grignard reagents to substituted alkenylpyridines (**Scheme 2.10**). Yields of the reaction were improved by the gentle heating from room temperature to 45 °C. Unfortunately, when the asymmetric version of these reactions were investigated by using chiral ligands such as *bis*-phosphines, diamines, *bis*-sulfonamides, aminoalcohols, and diols, unsatisfactory results were received (<15% ee). These results highlight the possibility the catalytic asymmetric conjugate addition of nucleophiles to alkenylazaarenes.

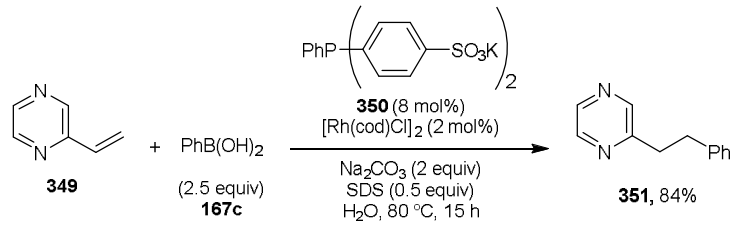


347 **348** 90%, <15% ee

Scheme 2.10: Nickel-catalysed conjugate addition of Grignard reagents to alkenylazaarene **347**.

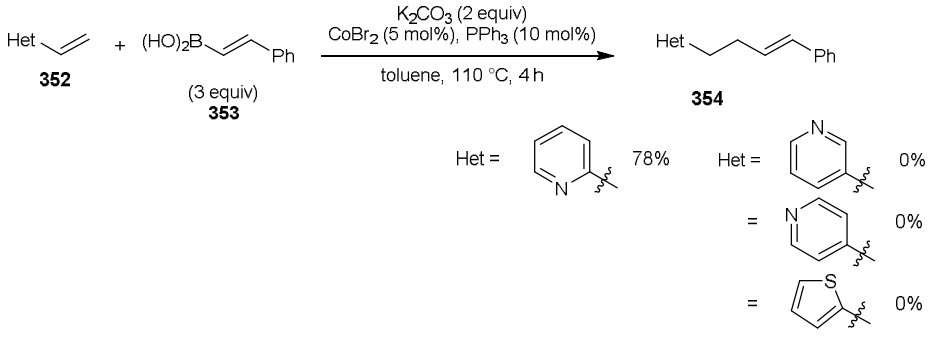
A few years later, Lautens and co-workers[124] developed an aqueous rhodium-catalysed coupling reaction of arylboronic acids and olefins. The aqueous conditions were crucial

for reactivity since the reaction was unsuccessful in organic solvents. Moreover, sodium dodecyl sulfate (SDS) and water soluble phosphine ligand were used as a phase transfer catalyst to generate products in high yield (**Scheme 2.11**).



Scheme 2.11: Rhodium-catalysed conjugate addition of vinylazaarenes.

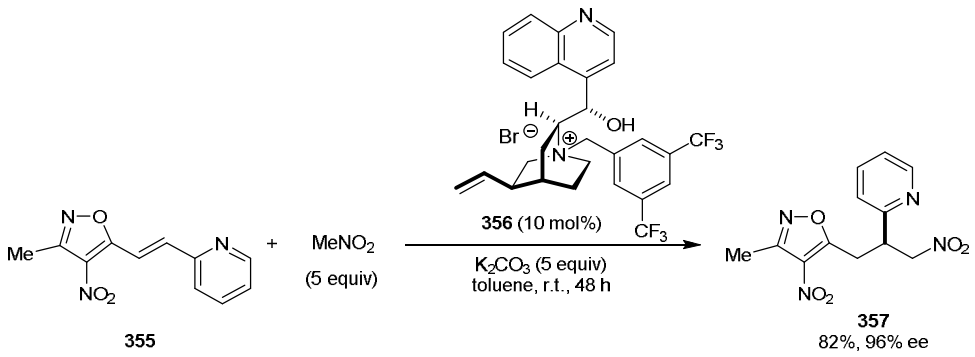
In 2011, Yorimitsu and Oshima[125] developed a cobalt-catalysed addition of alkenylboronic acids to 2-vinyl heteroarenes. It was found that the C=N of azaarenes adjacent to the vinyl group was crucial to promote the reaction. It is possible that the nitrogen accelerated the addition of the styrylcobalt species, generated by transmetalation, onto the vinyl double bond to give alkenylation products in modest yields. The reactions of other azaarenes or other heteroarenes were unsuccessful (**Scheme 2.12**).



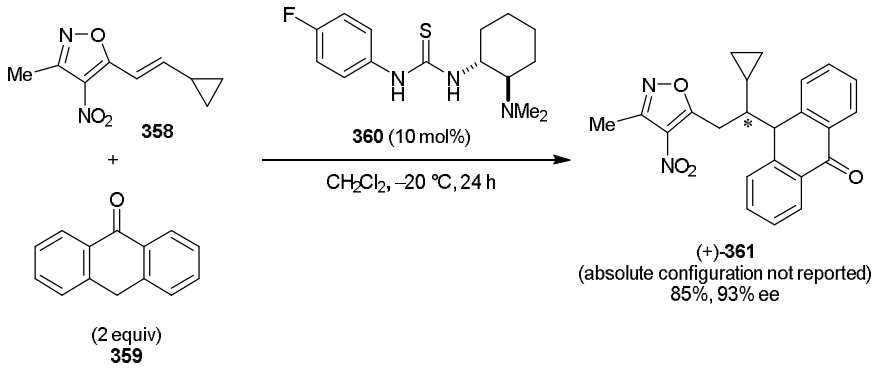
Scheme 2.12: Cobalt-catalysed conjugate alkenylation of 2-vinylazaarenes.

Regarding an asymmetric conjugate addition, in 2009, Bernardi and Adamo[126] reported an enantioselective Michael addition of nitroalkanes to 5-styrylisoxazoles such as **355** with Cinchona alkaloid-derived organocatalyst **356**. This work demonstrated a novel

family of nitroisoxazoles with dual activating groups in asymmetric Michael reaction of various nitroalkanes and 3-methyl-4-nitro-5-styrylisoxazoles (**Scheme 2.13**).



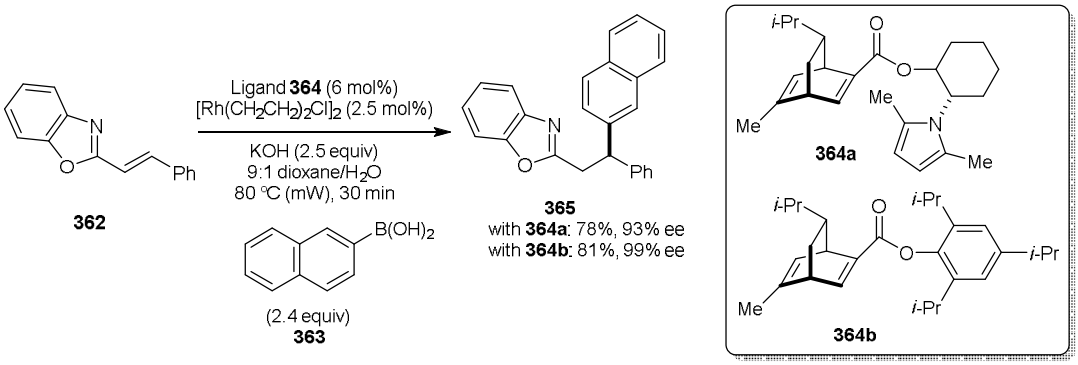
Scheme 2.13: Organocatalysed asymmetric conjugate addition of nitroalkanes to β-substituted alkenylnitroisoxazoles.



Scheme 2.14: Organocatalysed asymmetric conjugate addition of anthrone **359** to β-substituted alkenylnitroisoxazole **360**.

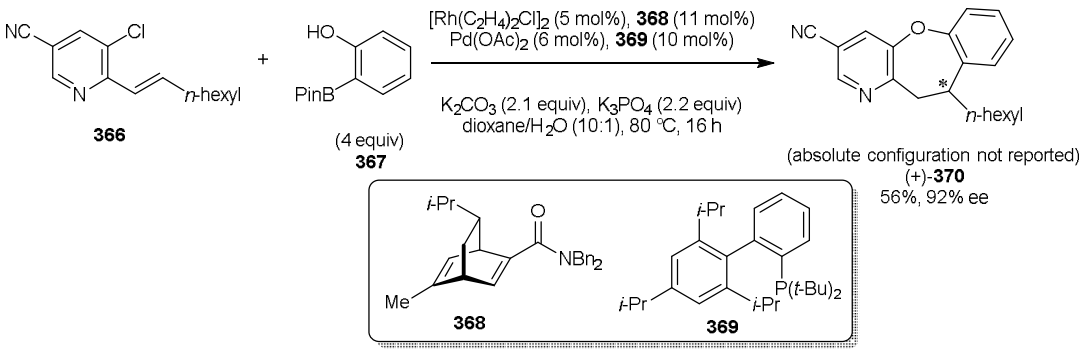
Similar to the work reported by Bernardi and Adamo, a simple and efficient method for the enantioselective 1,6-Michael addition reaction of anthrone **359** to a series of 3-methyl-4-nitro-5-alkenyl-isoxazoles was reported by Yuan and co-workers[127] (**Scheme 2.14**). With the use of bifunctional thiourea-tertiary amine **360** as the catalyst, the transformation proceeded smoothly and resulted in Michael adducts with high yields (up to 99%) and enantioselectivities (up to 96% ee).

In 2010, Lam and co-workers studied an enantioselective rhodium-catalysed addition of arylboronic acid **363** to *β*-monosubstituted alkenylheteroarene **362**.[128] Chiral products containing heterocycles were obtained with modest to high yields and high enantioselectivities when employing a secondary amide-containing chiral diene ligand **364a** (**Scheme 2.15**). Following that report, a comprehensive investigation of second-generation ligands showed that a simpler novel chiral ligand **364b** provided results superior to those obtained using the first generation ligand.[129]



Scheme 2.15: Enantioselective rhodium-catalysed addition of arylboronic acids to alkenylheteroarenes.

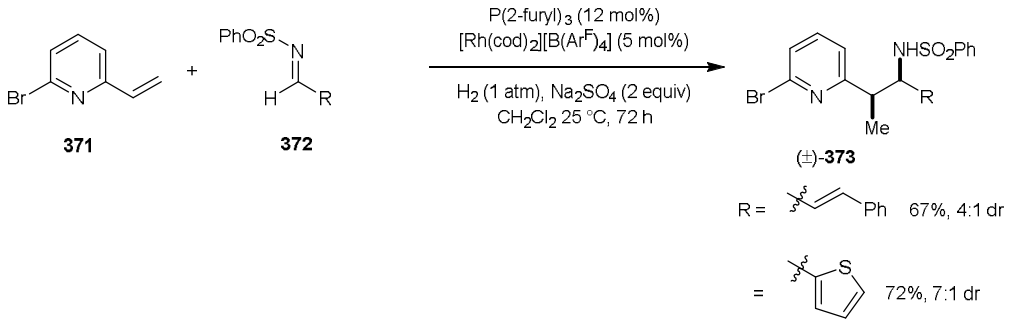
Lautens and co-workers[130] subsequently developed the time-resolved domino reaction of 3-chloro-2-vinylpyridine (**366**) with 2-hydroxy-phenylboronic ester (**367**) to give chiral aza-dihydrodibenzoxepine **370** (**Scheme 2.16**). This domino process composed of 2-catalytic systems in one pot. The first step is the rhodium-catalysed arylation which is similar to the one previously reported by Lam.[128,129] The second step is the Pd-catalysed intramolecular C−O coupling mediated by the Buchwald ligand *t*-BuXPhos **369**.[131]



Scheme 2.16: Domino synthesis of chiral aza-dihydrodibenzoxepine **370**.

Reductive Couplings and Conjugate Reductions

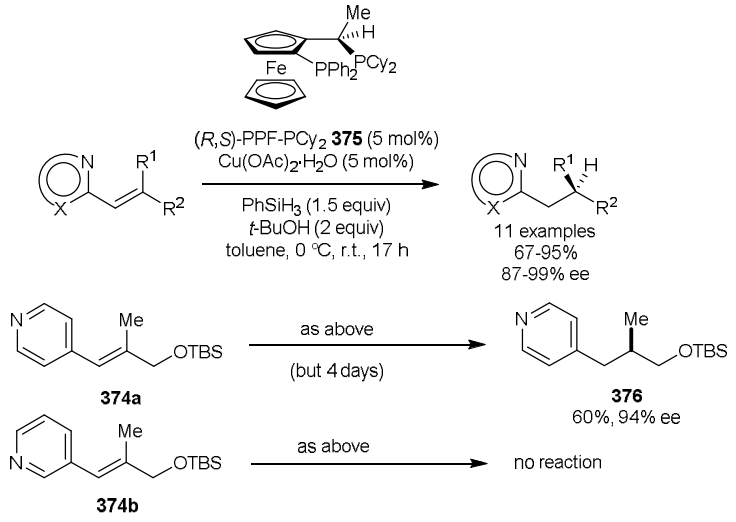
Krische and co-workers[132] reported the first metal-catalysed reductive couplings between vinyl azines and *N*-sulfonylaldimines. Employing the use of a rhodium−phosphine catalyst, branched products were obtained with modest to high yields and diastereoselectivities as single regioisomers. However, pyridines bearing a 6-substituent and quinolines seemed to be privileged substrates while other azines had low reactivity. Fortunately, this coupling process tolerated a wide range of imine substituents especially when Na_2SO_4 was added to prevent their hydrolysis (**Scheme 2.17**).



Scheme 2.17: Rhodium-catalysed reductive coupling of alkenylazaarenes with imines.

In 2009, copper-catalysed asymmetric conjugate reductions of β,β'-disubstituted 2-alkenyl heteroarenes were reported by Lam and co-workers.[133] This work

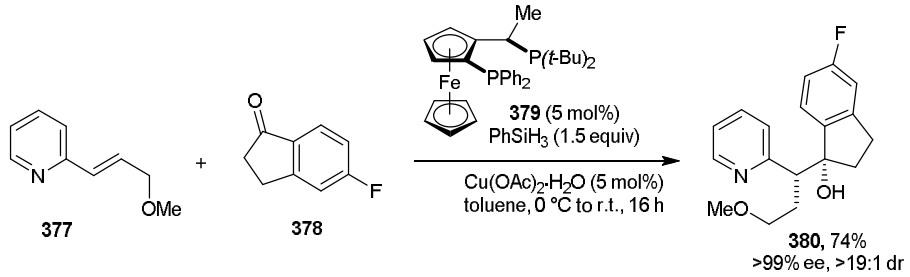
demonstrated that nitrogen-containing aromatic heterocycles could provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate addition reactions (**Scheme 2.18**). Furthermore, to prove the hypothesis that C=N is crucially important for electrophilic activations, the reduction of 3- and 4-alkenylpyridines were attempted. Interestingly, it was found that 4-alkenylpyridine provided chiral adduct **374a** with 60% yield and 94% ee, even though the reaction time was longer than the standard condition. This result suggests that the copper hydride reduction process can occur without assistance of a directing effect from the nitrogen atom. In contrast, 3-alkenylpyridine **374b** was unreactive. This indicates the importance of conjugation of the alkene to a C=N moiety for reactivity.



Scheme 2.18: Enantioselective copper-catalysed reduction of 2-alkenylheteroarenes.

In addition to the trapping chemistry reported by Krische in which rhodium catalyst was used,[132] Lam and co-workers[134] reported copper-catalysed enantioselective reductive coupling reactions of alkenylazaarenes with ketones. The idea is the combination of the utility of copper hydride catalysis[133] with the ability of C=N-containing azaarenes to activate adjacent alkenes toward nucleophilic additions. By the use of chiral biphosphine ligands, aromatic heterocycles bearing stereogenic tertiary alcohols were obtained with high levels of diastereo- and enantioselectivity. Both acyclic and cyclic ketones were

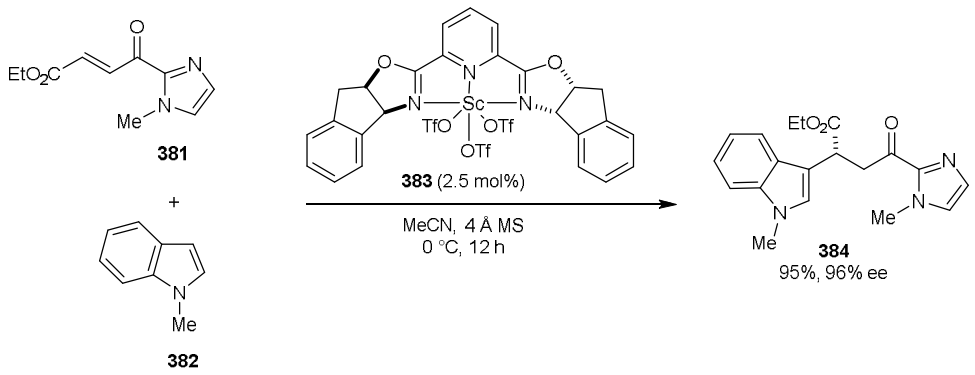
effective substrates and *β*-substitution on the alkene was also tolerated under standard reaction conditions (**Scheme 2.19**).



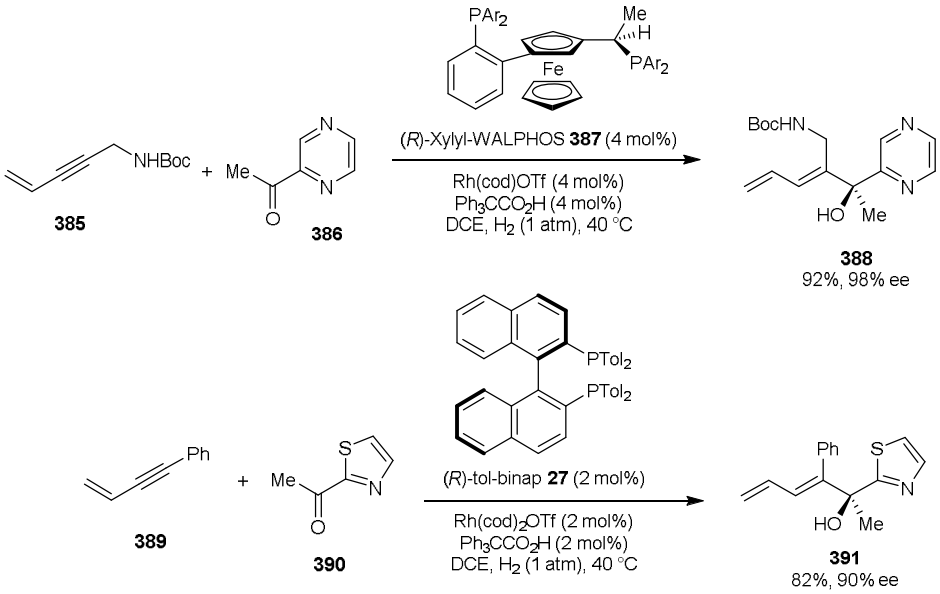
Scheme 2.19: Copper-catalysed asymmetric reductive coupling of alkenylazaarene **377** with ketone **378**.

Electrophilic Activation with Two-Point Binding to Catalysts

Azaarenes have been used as an electrophilic activating group for over a decade, especially in a homology of 1,2-dicarbonyl compounds. There are many examples showing that *α*,*β*-unsaturated acylazaarenes are potential electrophiles for enantioselective processes that rely upon two-point binding of these azaarenes to chiral metal complexes for activation and enantioinduction.[135] For example, in 2005, Evans and co-workers reported an enantioselective Friedel−Crafts alkylation of *α*,*β*-unsaturated 2-acyl imidazoles catalysed by chiral *bis*(oxazolinyl)pyridine (PyBox)-scandium(III) triflate complex **383**.[120c] Reactions proceeded smoothly with furan, pyrrole and indole derivatives to afford chiral adducts with high yields and high enantioselectivities (**Scheme 2.20**).



Scheme 2.20: Scandium-catalysed enantioselective Friedel−Crafts alkylations of *α*,*β*-unsaturated 2-acyl imidazole **381**.

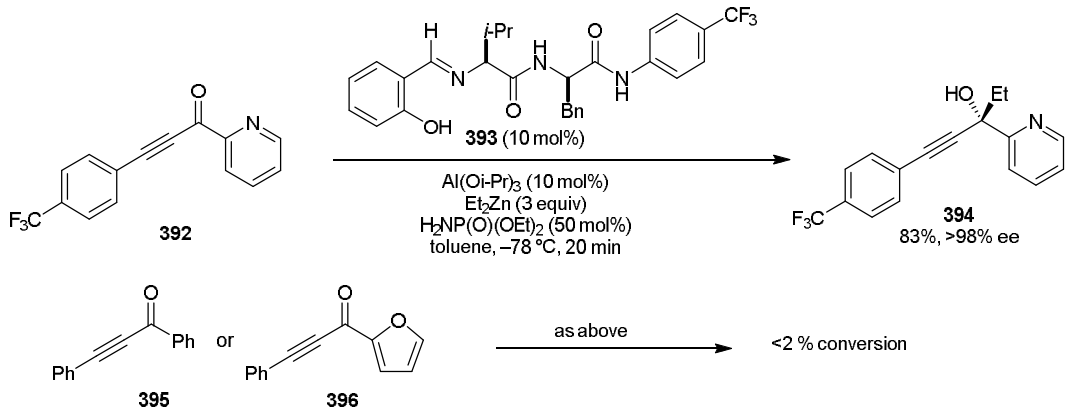


Scheme 2.21: Rhodium-catalysed enantioselective reductive coupling of 1,3-enynes to heterocyclic aromatic aldehydes and ketones.

In 2006, Komanduri and Krische[136] studied an enantioselective rhodium-catalysed reductive coupling of 1,3-enynes to heterocyclic aromatic aldehydes and ketones. It was speculated that heteraromatic aldehydes and ketones might be viable electrophilic partners for hydrogen-mediated alkyne couplings because they are isoelectronic with

vicinal dicarbonyl substrates. By using chiral rhodium catalysts, chiral alcohols were obtained with high yields and enantioselectivities (**Scheme 2.21**).

Two years later, Hoveyda and co-workers[137] developed protocols for catalytic enantioselective aluminium-catalysed alkylations of alkynones bearing a pyridyl substituent with Et_2Zn and Me_2Zn reagents. The reactions were promoted by amino acid-based chiral ligands, which were easily prepared on gram-scale (**Scheme 2.22**). However, there was <2% conversion when aryl ketone **395** and furyl ketone **396** were employed. It was believed that the two point chelation, which involved Lewis acidic Al and the Lewis basic carbonyl and N atom of the pyridine, is crucial.



Scheme 2.22: Aluminium-catalysed asymmetric alkylations of pyridyl-substituted alkynyl ketones with dialkylzinc reagents.

The reaction mechanism was proposed to proceed *via* model **397a** (cationic complex) or **397b** (neutral complex) as illustrated in **Figure 2.2**. The Lewis acidic Al associates with and activates the substrate molecule. Then the dialkylzinc adds to the Al-bound pyridyl ketone to afford chiral tertiary propargyl alcohols. The authors also suggested that the strongly Lewis basic phosphoramidate additive increases Al Lewis acidity and catalytic activity. This activation involves the amide carbonyl interaction with the dialkylzinc reagent. Moreover, molecular mechanics calculations suggest that a zinc bridge leads to

a high degree of rigidity in complexes **397a** and **397b**, resulting in the enhanced enantioselectivity.

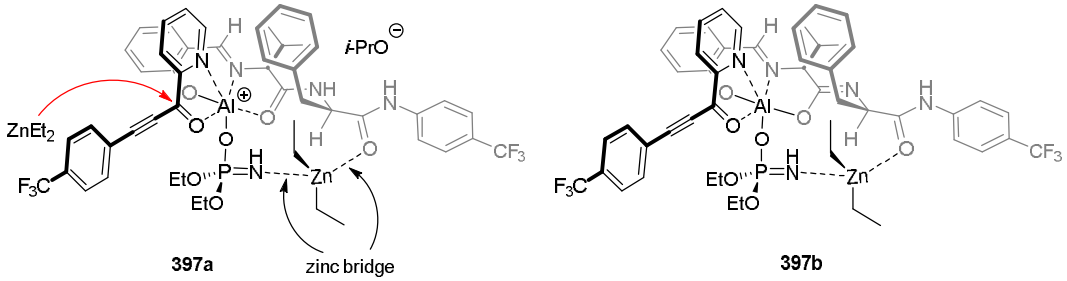
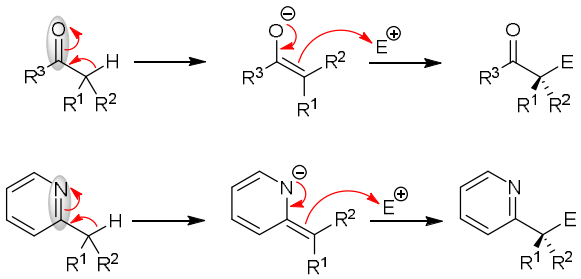


Figure 2.2: Mechanistic model.

2.3.2 Azaarenes as Activating Groups for Nucleophilic Additions

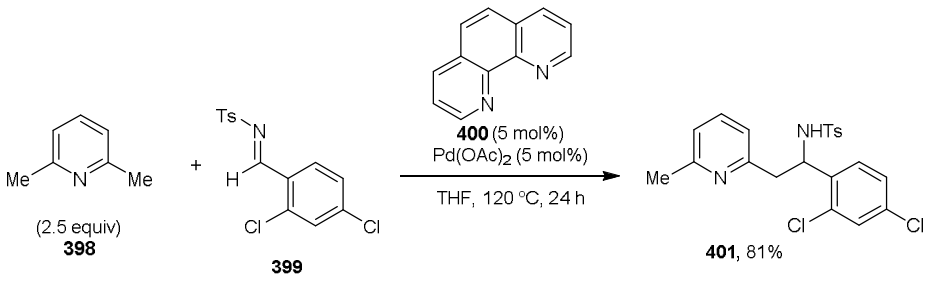
In addition to acting as an activating group for electrophiles, azaarenes can alternatively be used as an activating group for nucleophiles. Similar to C=O, the electron deficient C=N of azaarenes withdraws electron density facilitating α-deprotonation adjacent alkyl pronucleophile. This enolate-equivalent anion can then undergo either direct (1,2-) or conjugate (1,4-) nucleophilic addition to a suitable electrophile (**Scheme 2.23**).



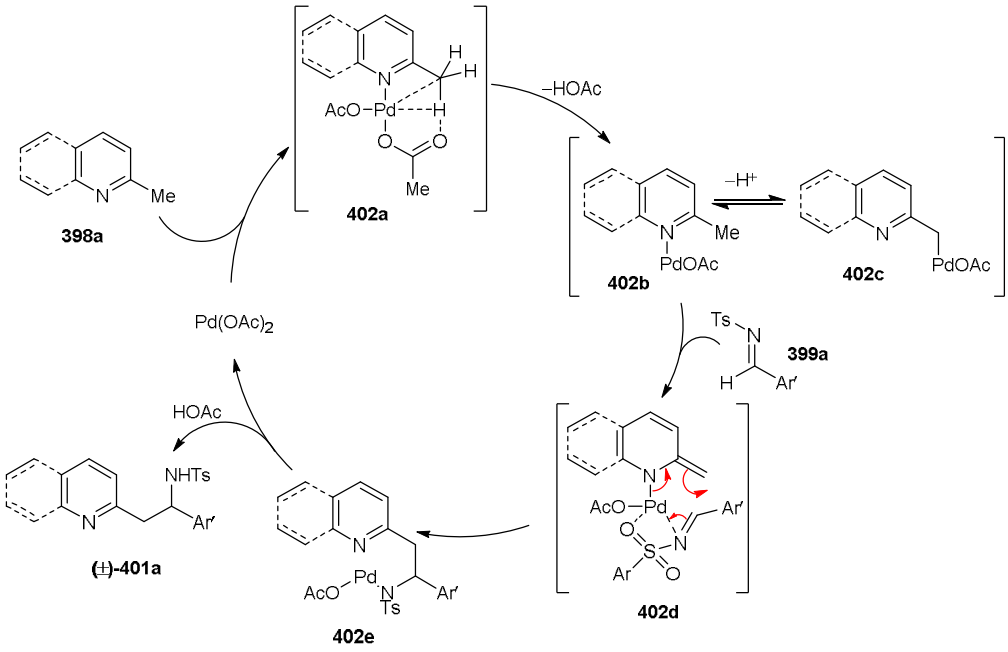
Scheme 2.23: Electronic homology concept between enolisable carbonyl motifs and alkylazaarenes.

Previously, most reports of this type of activation rely upon Lewis acids together with harsh conditions such as high pressure and temperatures in order to achieve useful reactivity. For example, in 2010, Huang and co-workers[138] reported the racemic

palladium-catalysed benzylic addition of 2-methyl azaarenes to aldimines. The mixture of substrates, palladium catalyst and THF was heated at 120 °C in a sealed vessel for 24-30 h to obtain racemic amines with reasonable yields (**Scheme 2.24**).



Scheme 2.24: Palladium-catalysed direct benzylic addition of **398** to imine **399**.



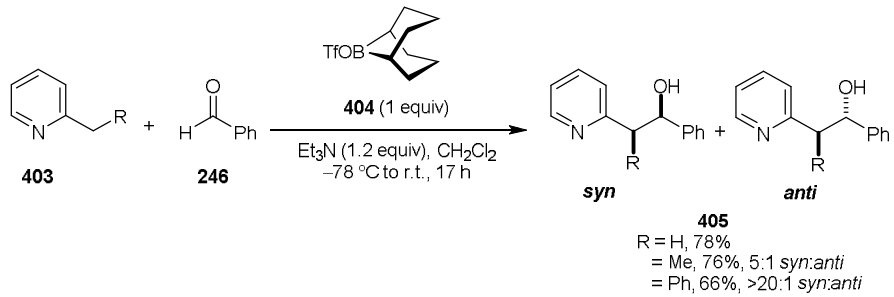
Scheme 2.25: Proposed mechanism.

The proposed mechanism involves coordination between the azaarene and $Pd(OAc)_2$ to form complex **402a**. This complex then undergoes C−H bond cleavage *via* a three-centre-two-electron interaction to form the intermediate **402b** or **402c**, which then coordinates with imine **399a**, resulting in intermediate **402d** or **402e**. This complex

undergoes nucleophilic addition to obtain addition product **401a** after protonolysis (**Scheme 2.25**). Moreover, closely related reactions were then reported by the groups of Huang,[139] Rueping[140] and Matsunaga and Kanai[141] using various metalcatalysts such as $Cu(OTf)_2$, $Sc(OTf)_3$, $Y(OTf)_3$ and $Fe(OAc)_2$ as well as other electrophiles such as α,β-unsaturated carbonyls and α,β-unsaturated nitriles.

Alkylazaarenes Activated by Boron Additives

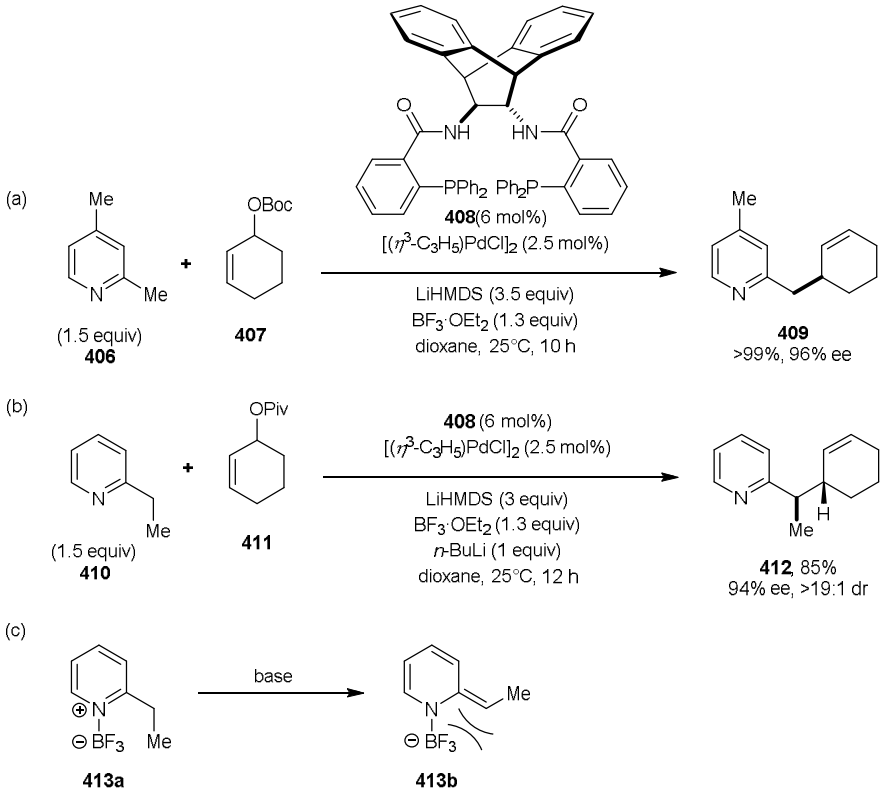
Apart from the metal-based Lewis acid catalysts mentioned above, non-metallic Lewis acids such as dialkylboryl triflates can also promote the deprotonation of alkylazaarenes under relatively mild conditions. For example, Hamana and Sugasawa[142] investigated the diastereo- and regioselective reaction of alkylpyridines with benzaldehyde (**246**) in the presence of 9-BBN triflate and triethylamine. This racemic, aldol-like process gave alcohol adducts with reasonable yields and modest to high diastereoselection (**Scheme 2.26**).



Scheme 2.26: Mild aldol type reaction of alkylpyridines and benzaldehyde **246**.

In 2008, Trost and Thaisrivongs[143] reported a palladium-catalysed enantioselective allylic alkylation of 2-alkylpyridines. Employing the use of a BF_3 promoter, soft carbon nucleophiles such as 2-methylazaarenes underwent allylation with five-, six- and seven-membered endocyclic allylic carbonates to generate chiral products with high yields and stereoselectivities (**Scheme 2.27(a)**). A year later,[144] they investigated an analogous reaction with higher 2-alkylpyridines. This idea originated from the hypothesis that the coordination of the pyridyl nitrogen atom with BF_3 followed by

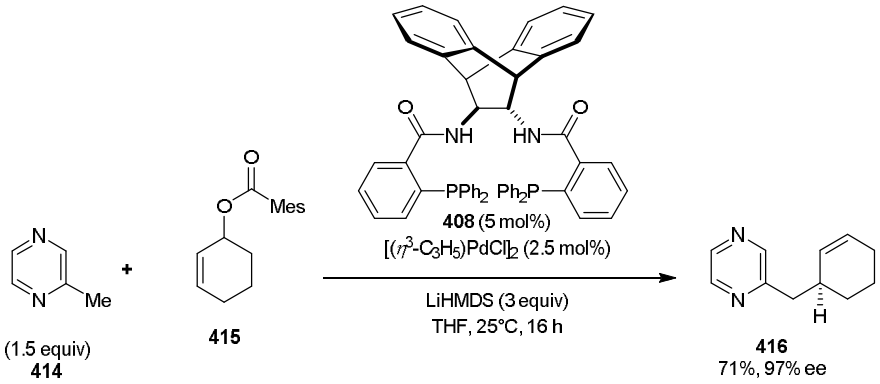
benzylic deprotonation leads to a nucleophile existing as a single geometric isomer (**Scheme 2.27(c)**). Using optimised reaction conditions, with chiral ligand **408** and $[(\eta^3\text{-}C_3H_5)PdCl]_2$, chiral products were obtained with high level of regio-, diastereo-, and enantioselectivities (**Scheme 2.27(b)**).



Scheme 2.27: Palladium-catalysed regio-, diastereo-, and enantioselective benzylic allylation of 2-substituted pyridines.

In order to expand the scope of substrates, Trost and co-workers[145] subsequently investigated the asymmetric allylic alkylation under the previously optimised conditions discussed above. Unfortunately, higher azines such as pyrazine and pyrimidine were unreactive. It was believed that complexation of these substrates to BF_3 rendered them too electron-deficient to undergo nucleophilic attack to the allyl carbonates. However, when the reaction was repeated without adding Lewis acid, the desired product was observed with low yields. Moreover, when allylic mesitylate esters were used as

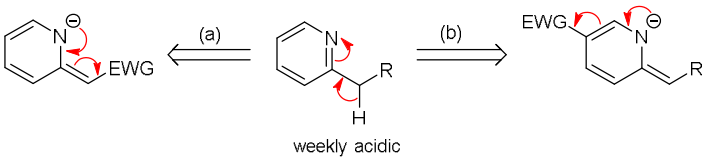
electrophiles the reaction yields improved significantly (**Scheme 2.28**). The reason behind this was that bulky leaving groups such as mesitylate esters prevents the competitive elimination of the acyl group of the electrophile.



Scheme 2.28: Palladium-catalysed asymmetric allylic alkylation of polynitrogen-containing aromatic heterocycles.

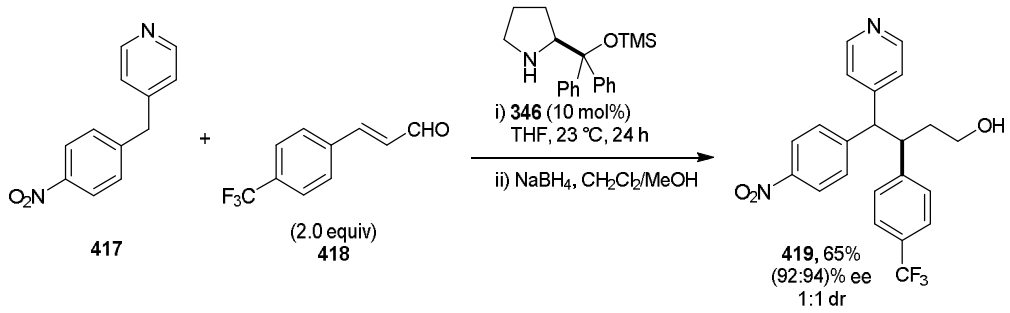
Nucleophilic Addition of Electron-Deficient Alkylazaarenes

Alternatively, electron-deficient substituents are able to activate alkylazaarene pronuclephiles (**Scheme 2.29**). This strategy relies upon the additional inductive or mesomeric effect of an electron-withdrawing group either on the azaarene rings or on the alkyl group. Thus, the proton at the alkyl α-position becomes more acidic and more easily deprotonated by weakly basic anions. Recently, there are some examples demonstrating the use of this mode of activation as shown below.



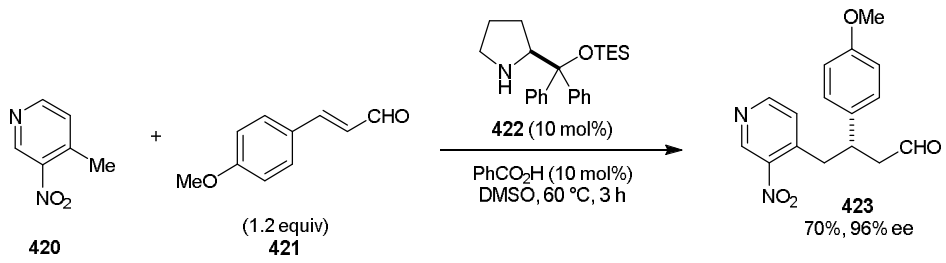
Scheme 2.29: Alkylazaarenes activated by an additional electron-withdrawing groups.

In 2011, the asymmetric Michael addition of nitrobenzyl pyridines to *α,β*-unsaturated aldehydes was reported by Melchiorre and co-workers.[146] This transformation demonstrated the use of dually activated methylene nucleophiles in which the methylene group is not activated by classical electron-withdrawing substituents (such as a carbonyl moiety). Interestingly, the mode of activation is the combination of electronic effects of a *p*- or *o*-nitro-substituted aromatic and a pyridine system (**Scheme 2.30**).



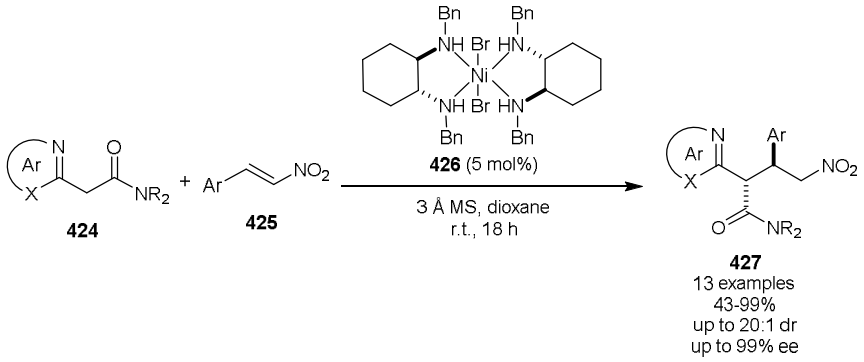
Scheme 2.30: Asymmetric Michael addition of nitrobenzyl pyridines to enals *via* iminium catalysis.

Similarly, Wang and co-workers[147] reported an organocatalytic enantioselective Michael reaction of 4-methyl-3-nitropyridine to enals. In the presence of an analogous chiral amine catalyst under mild reaction conditions, various *α,β*-unsaturated aldehydes were converted to chiral adducts with modest to high yields and high enantioselectivities (**Scheme 2.31**). These reactions were developed based on a hypothesis that a methyl substituent of pyridine pronucleophiles was activated by a strongly electron-withdrawing nitro group on the aromatic ring.



Scheme 2.31: Organocatalysed conjugate addition of 4-methyl-3-nitropyridine (**420**) to *α*,*β*-unsaturated aldehyde **421**.

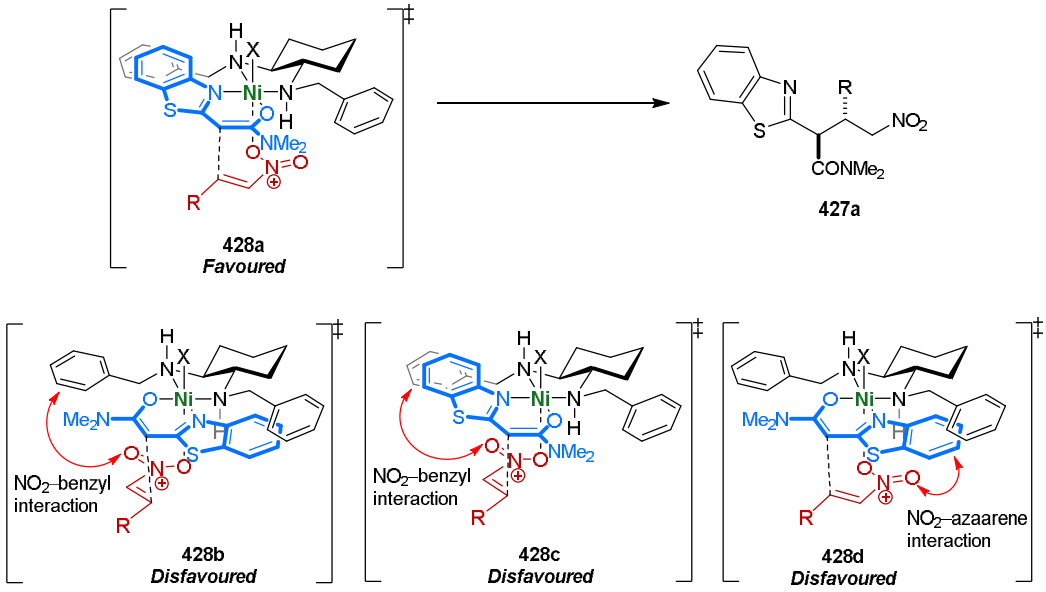
Fallan and Lam[148] studied the catalytic enantioselective Michael additions of azaaryl carboxylic acid derivatives to nitroalkenes using a chiral nickel(II)-*bis*(diamine) complex catalyst.[149] With pronucleophiles containing a wide variety of azaarenes, enantioenriched chiral azaarene-containing building blocks were obtained with high yield and enantioselectivities (**Scheme 2.32**). The authors also suggested that the analogy between the C=O group and the C=N moiety in azaarenes may serve as a rich platform for the development of additional catalytic enantioselective reactions.



Scheme 2.32: Enantioselective nickel-catalysed Michael additions of azaarylacetamides to nitroalkenes.

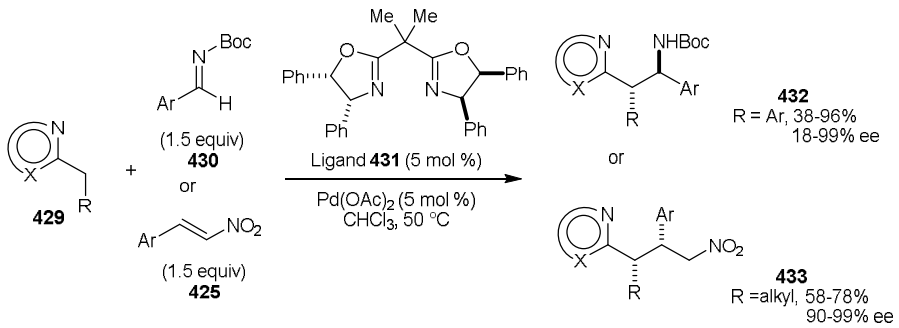
It was believed that the reaction mechanism is similar to a mechanism of the Michael addition of 1,3-dicarbonyls to nitoalkenes, originally proposed by Evans and co-workers (see **Scheme 2.48**).[149] Firstly, the catalyst **426** releases one diamine ligand to generate

the catalytically active species. This active nickel species binds to the amide oxygen and the azaaryl nitrogen atoms to generate a reactive nickel enolate after deprotonation. Subsequently, the nickel enolate undergoes Michael addition to a coordinated nitroalkene to afford a chiral product. The *anti*-selectivity observed was explained by the four plausible transition states (**Scheme 2.33**). The unfavoured transition states **428b** and **428c** showed steric interactions between nitroalkenes and the benzyl groups of ligand. In transition **428d**, there is a steric interaction between the nitro group and the benzene ring of the azaarene, while in **428a**, the nitro group is relatively free from unfavourable steric repulsions.



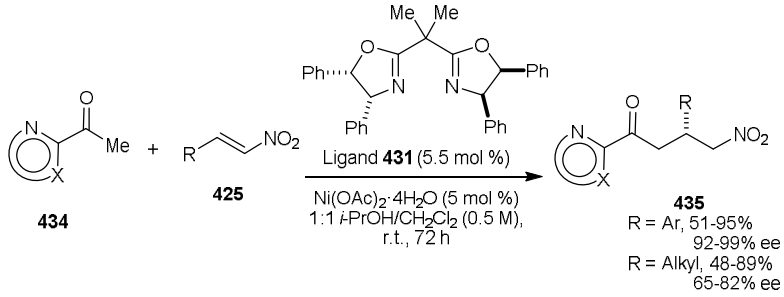
Scheme 2.33: Stereochemical model.

The first palladium-catalysed diastereo- and enantioselective addition of alkylazaarenes to *N*-Boc aldimines and nitroalkenes was reported by Lam and co-workers.[150] The reactions were promoted by a chiral palladium(II)-*bis*(oxazoline) complex at mild temperature in undried solvent under an air atmosphere. By exploiting the acidifying effect of nitro, cyano, or ester groups on the azaarenes, chiral adducts were synthesised with high levels of diastereo- and enantioselections (**Scheme 2.34**).



Scheme 2.34: Diastereo- and enantioselective palladium(II)-catalysed additions of 2-alkylazaarenes to *N*-Boc imines and nitroalkenes.

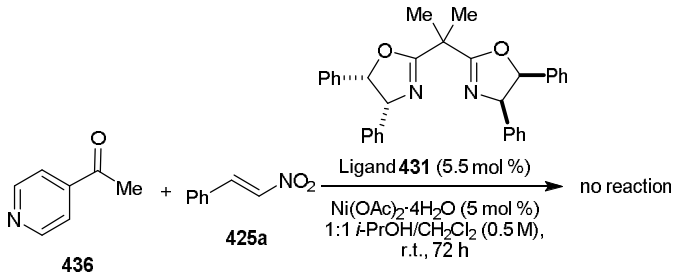
Simpson and Lam also developed an enantioselective nickel-catalysed Michael additions of 2-acetylazaarenes to nitroalkenes.[151] This process was tolerant of a range of azaarenes in the pronucleophilic component, and the reactions proceeded under mild conditions. Although the enantioselectivities were modest with β-alkyl-substituted nitroalkenes, a range of β-(hetero)aryl-substituted nitroalkenes reacted smoothly to result in Michael products with much higher enantiopurity (**Scheme 2.35**).



Scheme 2.35: Enantioselective nickel-catalysed Michael additions of 2-acetylazaarenes to nitroalkenes.

The result mentioned above demonstrated the utilisation of the C=N moiety for participating in the activation of adjacent alkenyl or alkyl groups by mimicking a 1,2-dicarbonyl compound. This reactivity was confirmed by the attempted reaction of

4-acetylpyridine (**436**) with *β*-nitrostyrene (**425a**), which gave no Michael product under the same conditions (**Scheme 2.36**).



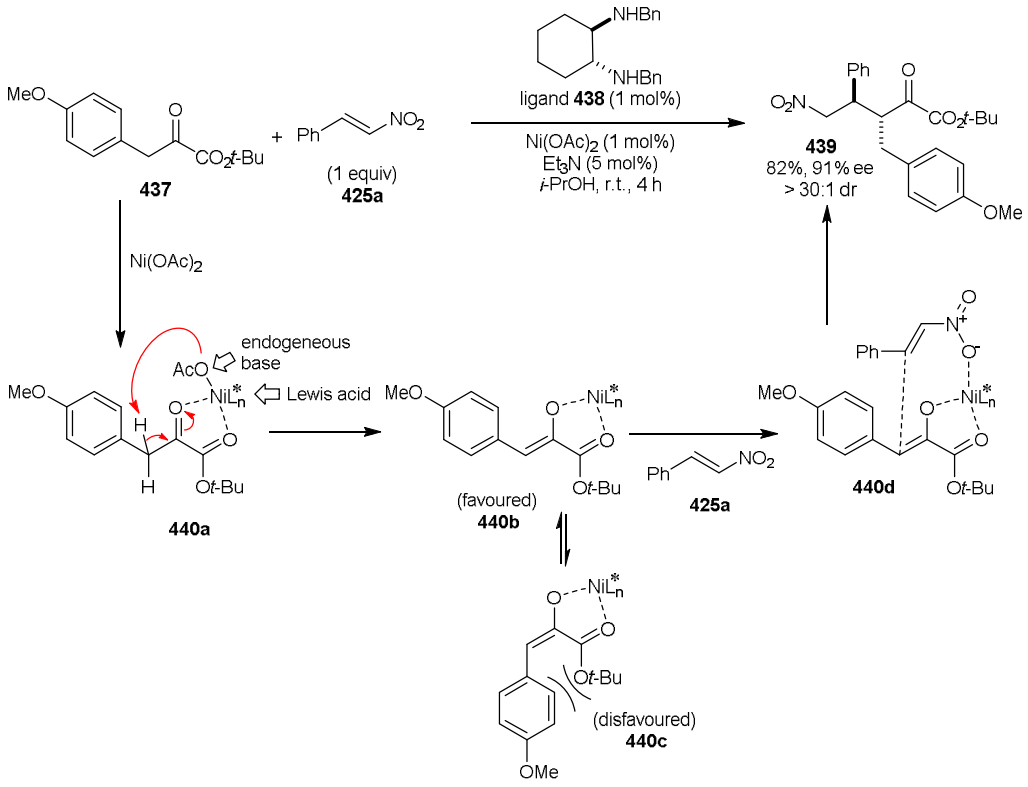
Scheme 2.36: Enantioselective nickel-catalysed Michael additions of 4-acetylpyridine (**436**) to *β*-nitrostyrene (**425a**).

Azaarenes have been used as activating groups in enantioselective transformations. The utility of the electronic analogy between C=N bond of azaarenes and C=O bond of carbonyls provides access to novel azaarene-containing compounds, and allows alternative modes of catalytic activation to be explored. The Lam group has reported in detail the most recent contribution to the field; the enantioselective Michael addition of 2-acetylazaarenes to *β*,*β*-disubstituted nitroalkenes (**Section 2.7**). Therefore, in the next **Section 2.4**, an overview of previously reported Michael additions of 1,2-dicarbonyls and 2-acetylheteroarenes to nitroalkenes is discussed.

2.4 Michael Addition of 1,2-Dicarbonyl Compounds and 2-Acetylheteroarenes to Nitroalkenes

1,2-Dicarbonyl compounds are important in the eyes of both biochemists and organic chemists. Pyruvic acid, for example, is one of the simple 1,2-dicarbonyl compounds believed to be involved in biosynthesis by nature.[152] In terms of synthetic utility, 1,2-dicarbonyls are less developed than 1,3-dicarbonyl compounds because they are less acidic. Recently, however, these functional groups have gained a lot of attention in the synthetic community.[153]

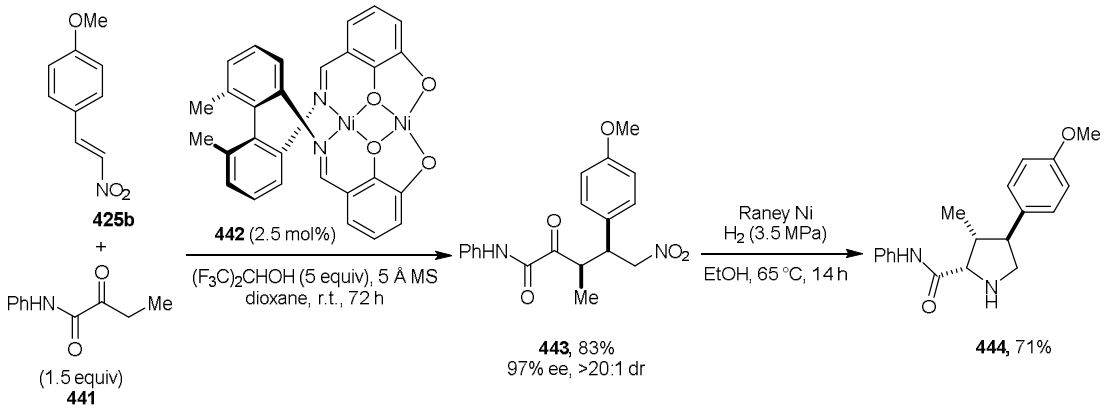
Sodeoka and co-workers[154] reported a diastereo- and enantioselective Michael addition of 1,2-dicarbonyl compounds to nitroalkenes catalysed by a chiral $Ni(OAc)_2$ complex. The reaction was applicable to various α-ketoester pronucleophiles and proceeded well in very mild reaction conditions. It was expected that acetate counteranion is sufficient to produce a chiral metal enolate **440b** with a *Z*-enolate geometry. This enolate is then trapped by the nitroalkene in a stereoselective manner (**Scheme 2.37**).



Scheme 2.37: Nickel-catalysed diastereo- and enantioselective conjugate addition of α-ketoesters to nitroalkenes.

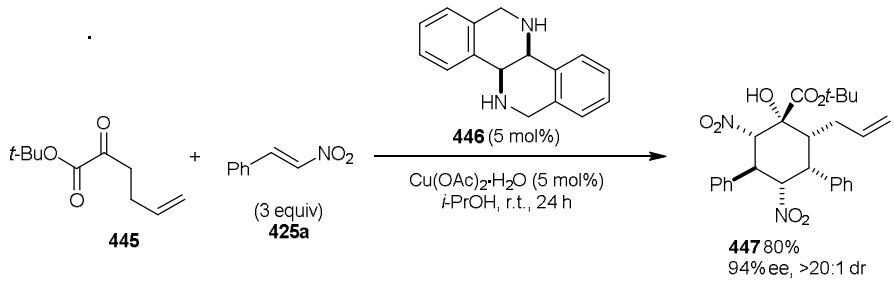
In 2010, Shibasaki and co-workers reported a *syn*-selective catalytic asymmetric Michael addition of α-ketoanilides to nitroalkenes using a dinuclear Ni-Schiff base catalyst (**442**).[155] Under optimised reaction conditions, chiral products were obtained with 61-92% yields, 8-20:1 *syn*-selectivity, and 72-98% ee. A stereoselective

transformation of the 1,4-adduct **443** to a pyrrolidine derivative **444** was performed to demonstrate the utility of this methodology (**Scheme 2.38**).



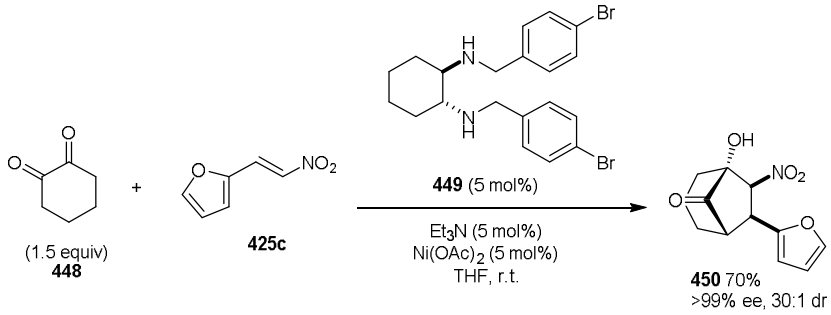
Scheme 2.38: *Syn*-selective catalytic asymmetric 1,4-addition of α-ketoanilides to nitroalkenes under dinuclear nickel catalysis.

Although nickel is a good metal for enantioselective Michael reaction of 1,2-dicarbonyl compounds to nitroalkenes, copper is also a useful catalyst for this transformation. For example, Huang and co-workers[156] demonstrated the copper-catalysed asymmetric formal [2+2+2] annulation between α-ketoesters and nitroalkenes (**Scheme 2.39**). This high efficiency domino process resulted in six stereocentres under mild and environmentally friendly reaction conditions. The reason for the high stereoselectivity was the use of a chiral copper catalyst derived from the rigid chiral diamine which produced a highly diastereo- and enantioselective adduct in the first Michael addition. The high stereoselectivity is conserved in the following Michael/Henry reaction steps.



Scheme 2.39: Copper-catalysed Michael/Michael/Henry domino annulation.

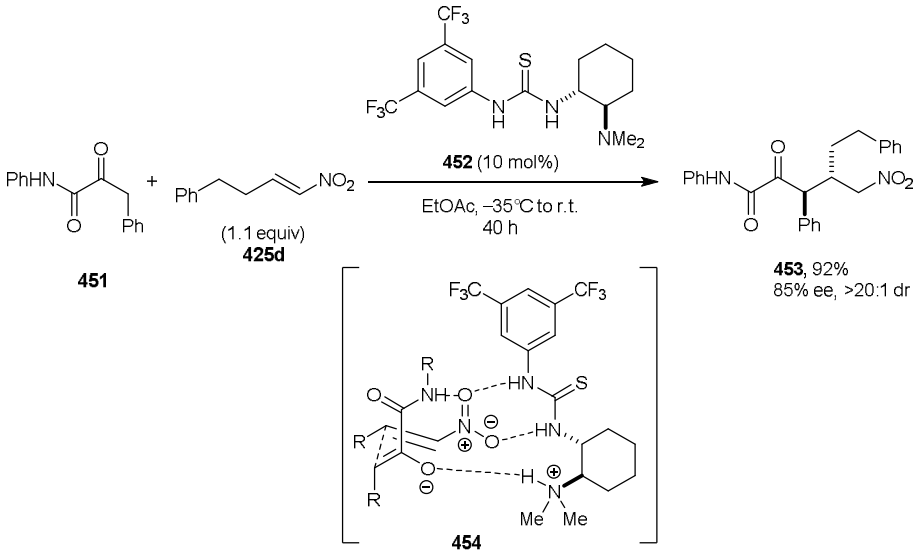
Wang and co-workers[157] reported a catalytic asymmetric Michael-Henry reaction of 1,2-diones with substituted nitroalkenes. With the use of a highly efficient catalyst system derived from $Ni(OAc)_2$ and chiral diamine ligands under aprotic conditions, a series of polyfunctionalised bicycle compounds containing four consecutive stereogenic centres were obtained with generally excellent enantio- and diastereoselectivities with reasonable yields (**Scheme 2.40**). Moreover, when the reaction time was prolonged from six hours to 48 hours the diastereomeric outcome of a product was maintained. This result suggested that the base-induced epimerisation could be minimised.



Scheme 2.40: Ni-catalysed Michael/Henry domino annulation.

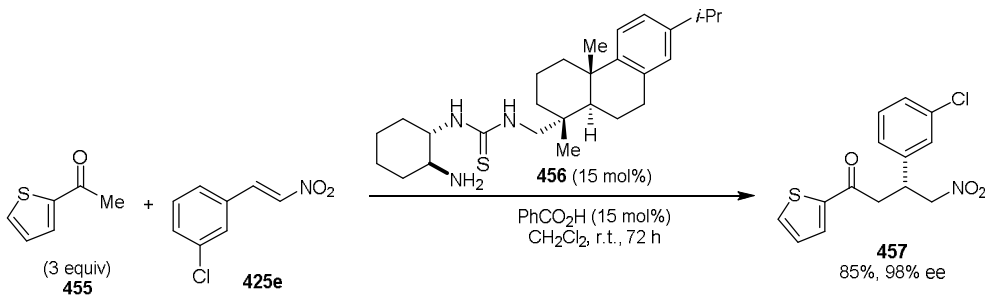
In comparison to transition metal-catalysed Michael addition of 1,2-dicarbonyl compounds to nitroalkenes, the corresponding organocatalysed additions have been more widely studied. Rodriguez and co-workers were the first to investigate the organocatalysed enantio- and diastereoselective conjugate additions of α-ketoamides to nitroalkenes.[158] Using a bifunctional amino thiourea catalyst, the Michael anti-adducts

were synthesised in high yields and stereoselectivities (**Scheme 2.41**). Notably, the substrate amide proton was believed to play a critical role in the formation of product with *anti*-selectivity. The bifunctional catalyst activates the nitroolefin *via* a bidentate H−bond interaction and the tertiary amine group deprotonates the amide nucleophile, resulting in the ion pair transition state **454**. In the transition state, the Si face of the *Z*-enolate is preferentially delivered to the Re face of the nitroalkene to give the observed stereochemistry. Moreover, the described method was applied to α-ketoester substrates.[159]



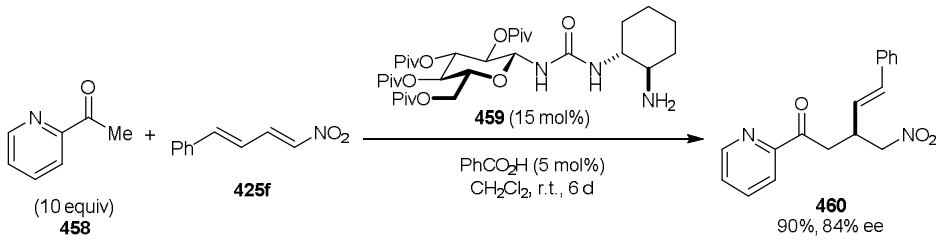
Scheme 2.41: Organocatalysed asymmetric Michael addition of α-ketoamide **451** to nitroalkene **425d**.

Although aromatic ketones are very common substrates for organocatalysed asymmetric Michael reactions to nitroalkenes, the corresponding heteroaromatic ketones are rarely investigated. In 2009, Wang and co-workers[160] designed and synthesised a new class of bifunctional primary amine-thiourea catalysts. The new catalysts were applied for the asymmetric Michael addition of ketones containing heteroaryl groups such as furyl, thienyl and thiazolyl to nitroalkenes to afford γ-nitro heteroaromatic ketones with reasonable yields and excellent enantioselectivities (up to >99% ee) (**Scheme 2.42**).



Scheme 2.42: Organocatalysed asymmetric Michael addition of 2-acetylthiophene (**455**) to nitrodiene **425e**.

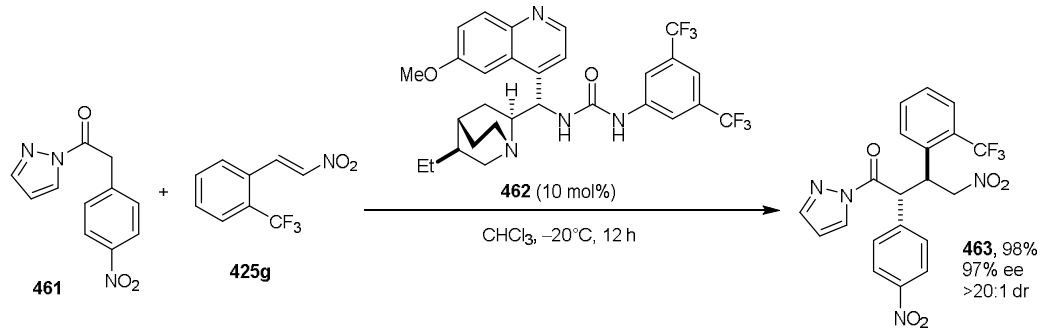
In addition to the potential of bifunctional thiourea catalysts as mentioned above, Ma and co-workers[161] reported the Michael addition of ketones to conjugated nitrodienes by using catalysts derived from commercially available saccharides and chiral diamines. Not only akyl- and arylketones, but heteroaryl ketones, were also investigated (**Scheme 2.43**). Moreover, in all cases, 1,4-addition selectively occurred without any trace of the 1,6-adducts.



Scheme 2.43: Organocatalysed asymmetric Michael addition of 2-acetylpyridine (**458**) to nitrodiene **425f**.

Barbas and co-workers[162] developed an organocatalytic asymmetric Michael reaction through the rational design of pyrazoleamides as Michael donors. In contrast to the works reported by Ma and Wang in which the heteroaryl rings behaved as simple substituents, the study by Barbas demonstrated a rare example of the use of pyrazoleamides as an ester equivalent, an activating group, and a directing group, as well as a good leaving group for further transformation. In general, amides are

considered to be challenging substrates due to their relatively low acidity. However, in this study, the authors demonstrated that pyrazoleamide derivatives could undergo the Michael addition to nitroalkenes in the presence of Cinchona alkaloid-based urea catalyst **462** (**Scheme 2.44**).



Scheme 2.44: Organocatalysed asymmetric Michael addition of pyrazoleamide **461** to nitroalkene **425g**.

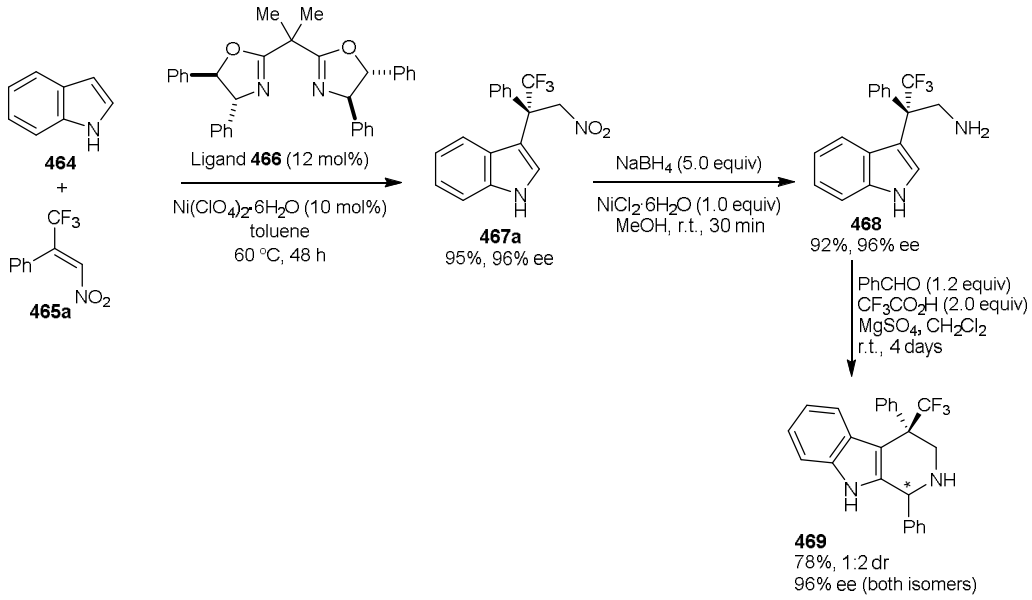
Asymmetric Michael additions of 1,2-dicarbonyls to nitroalkenes have been investigated. Most of these transformations relied upon organocatalysts. Only some examples used transition metal catalysts and nickel is amongst the most popular metals, presumably, because nickel has good catalytic properties. To justify this claim, in **Section 2.5**, nickel-catalysed enantioselective nucleophilic addition of nucleophiles to nitroalkenes will be discussed.

2.5 Introduction to Nickel-Catalysed Enantioselective Addition of Nucleophiles to Nitroalkenes

Nickel is one of the most widely studied transition metals in organic synthesis. It is comparatively cheaper than other transition metals such as Ru, Rh, Pd, Ir, Pt and Au etc. Moreover, nickel has very unique catalytic properties that make it very useful for the chemical industries. For example, nickel has been used as a catalyst in chemical processes such as Kumada coupling and Negishi coupling. It has been shown to be highly effective in enantioselective transformations of nitroalkenes as discussed below.

2.5.1 Friedel–Crafts alkylations

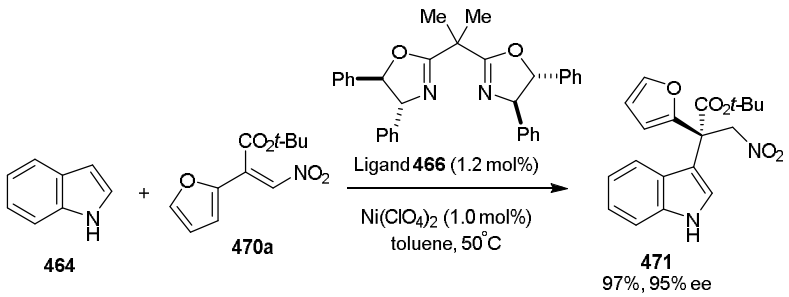
In 2013, Jia and co-workers[163] reported an enantioselective nickel-catalysed Friedel–Crafts alkylation reaction of indoles with *β*-trifluoromethyl-*β*-disubstituted nitroalkenes. Under the optimised reaction conditions, a wide range of substituted indoles and nitroalkenes were investigated. Indole-bearing chiral compounds with all-carbon quaternary stereocentres were obtained with good yields and good enantioselectivities. In order to demonstrate the utility of this methodology, the synthesis of a tetrahydro-*β*-carboline was carried out by the reduction of chiral nitro product **467** to trifluoromethylated tryptamine (**468**), followed by Pictet–Spengler cyclisation of this amine to afford **469** with complete preservation of enantiopurity (**Scheme 2.45**).



Scheme 2.45: Nickel-catalysed Friedel–Crafts alkylation of nitroalkene **465a** toward the synthesis of compound **469**.

To expand the scope of nitroalkenes in the previous work,[163] Jia and co-workers studied an enantioselective Friedel–Crafts alkylation reaction of indoles with acyclic *α*-substituted *β*-nitroacrylates using $Ni(ClO_4)_2$-*bis*(oxazoline) complex catalyst.[164] Chiral *β*-nitroesters bearing all-carbon quaternary stereocentres were obtained with excellent

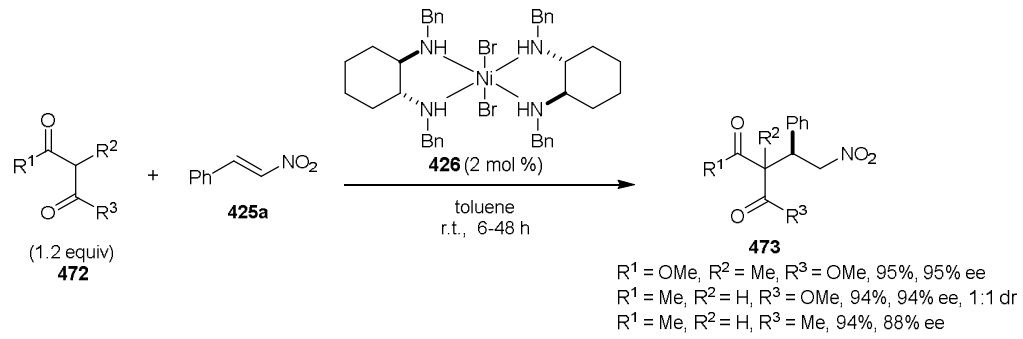
yields and enantiopurities. It should be noted that this result was obtained with a very low catalyst loading of 0.1 mol % (**Scheme 2.46**), which represents a rare case of highly active Lewis acid catalyst in the asymmetric Friedel−Crafts reaction.



Scheme 2.46: Asymmetric Friedel−Crafts alkylation of α-substituted β-nitroacrylate **470a**.

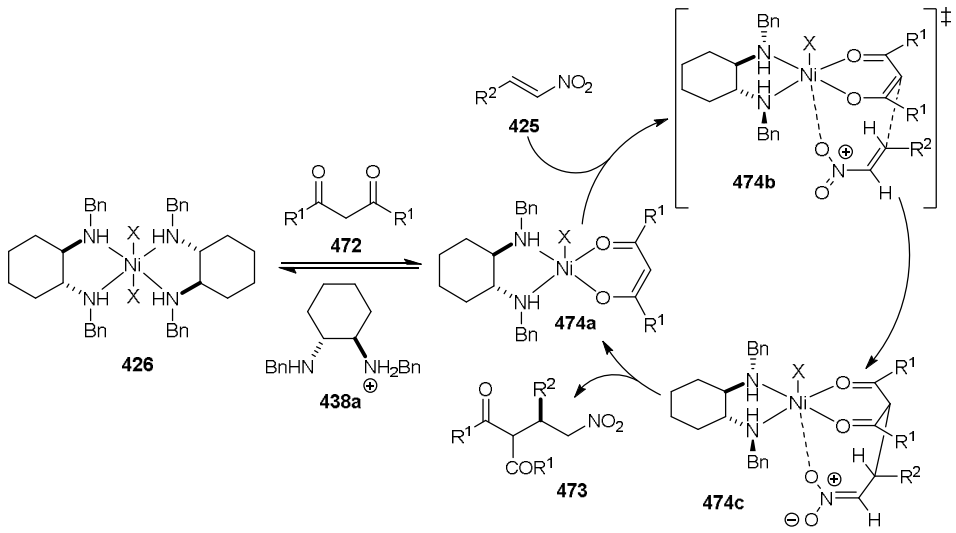
2.5.2 Michael Additions

The Michael reactions of nucleophiles to nitroalkenes have been broadly investigated. There are many reported examples of Ni-catalysed Michael addition of nucleophiles to nitroalkene receptors. Apart from 1,2-dicarbonyl pronucleophiles (**Section 2.4**), there are several examples of the use of 1,3-dicarbonyl compounds as a Michael donors.[165] For example, Evans and co-workers[149] screened various types of cyclohexanediamine ligands and Ni(II), and it was found that the complex **426** showed the best results. Moreover, the reaction was conveniently performed under mild conditions at room temperature without the need to exclude air or moisture. Under the optimised reaction conditions, chiral products were obtained with high yields and enantioselectivities from a broad range of 1,3-dicarbonyl compounds and nitroalkenes (**Scheme 2.47**).



Scheme 2.47: Nickel-catalysed enantioselective Michael additions of 1,3-dicarbonyl compounds to conjugated nitroalkenes.

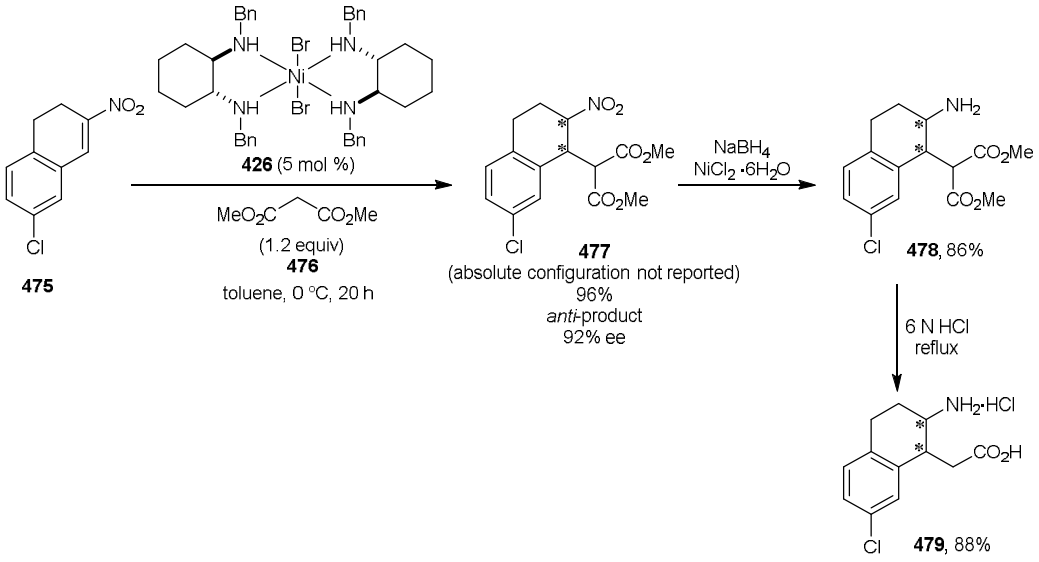
The results from an NMR experiment, together with an X-ray structure analysis of complex **474a** suggested that the two diamine ligands in this system each play a distinct role. The first one serves as a chiral ligand to provide stereoinduction in the addition step. The second diamine functions as a base to deprotonate the metal-bond substrate to generate the chiral enolate nucleophile. The resulting chiral enolate subsequently adds enantioselectively to a range of nitroalkenes (**Scheme 2.48**).



Scheme 2.48: Proposed mechanism.

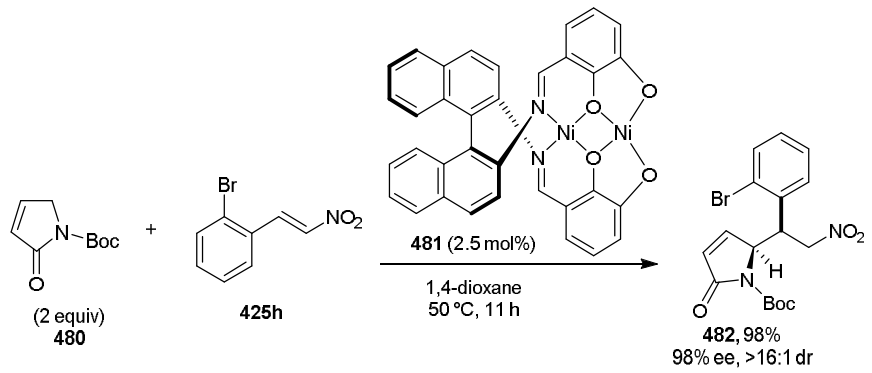
Chen and co-workers investigated an enantioselective Michael reaction of 1,3-dicarbonyl compounds to 3-nitro-2*H*-chromenes catalysed by chiral nickel

complexes.[166] After extensive ligand screening, they found that the chiral nickel complex **426** exhibited high stereoselectivity and catalytic activity to generate corresponding enantioenriched products (**Scheme 2.49**). To demonstrate the utility of this procedure, Michael product **477** was transformed to chiral cyclo *γ*-amino butyric acid derivative **479**.



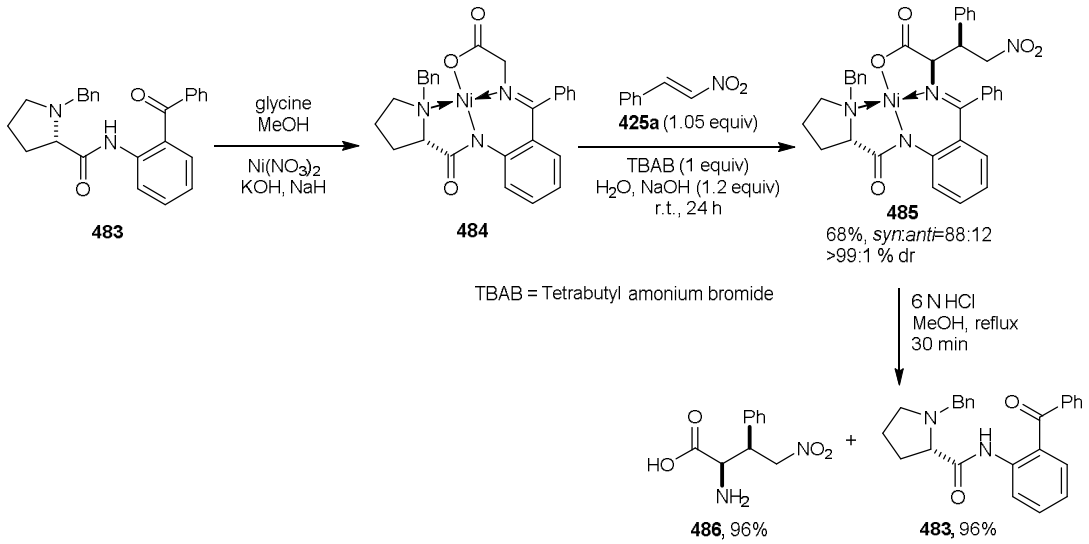
Scheme 2.49: Enantioselective Michael reaction of 1,3-dicarbonyl compounds to 3-nitro-2*H*-chromenes catalysed by chiral nickel complex **426**.

Shibasaki and co-workers developed a catalytic asymmetric vinylogous Michael reaction of *α*,*β*-unsaturated *γ*-butyrolactam **480** to nitroalkenes under homodinuclear nickel catalysis (**Scheme 2.50**).[167] It was shown that the reactions proceeded selectively at the *γ*-position, giving vinylogous Michael adducts in high diastereoselectivities (16-30:1 dr) and high enantioselectivities (93-99% ee).



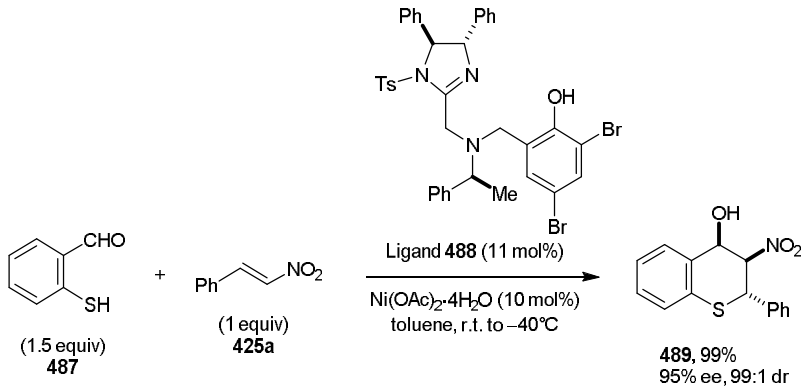
Scheme 2.50: Catalytic asymmetric vinylogous Michael reactions of α,β-unsaturated γ-butyrolactams to nitroalkenes under dinuclear nickel catalysis.

Liu and co-workers reported the first diastereoselective Michael reaction of chiral nickel(II) glycinate with nitroalkenes.[168] The reactions proceeded smoothly under mild conditions in the presence of TBAB (tetrabutyl ammonium bromide). A broad range of aryl-, heteroaryl-, and alkyl-substituted nitroalkenes were transformed to chiral β-substituted α,γ-diaminobutyric acid derivatives in a single reaction step with high yield and excellent stereoselectivity (**Scheme 2.51**).



Scheme 2.51: Diastereoselective Michael reaction of chiral nickel(II) glycinate with nitroalkenes.

Arai and Yamamoto studied a tandem asymmetric Michael/Henry reaction between 2-mercaptobenzaldehydes and *β*-nitrostyrenes using an imidazoline-aminophenol-nickel complex catalyst.[169] Using the optimised reaction conditions, the corresponding (2*S*,3*R*,4*R*)-2-aryl-3-nitrothiochroman-4-ols were obtained with up to 99% dr with 95% ee. (**Scheme 2.52**).



Scheme 2.52: Stereochemically divergent synthesis of thiochromanes using an imidazoline-aminophenol-nickel catalysed Michael/Henry reaction.

In summary, many research groups have developed stereoselective Michael additions of 1,2-dicarbonyls to nitroalkenes using transition metal catalysts or organocatalysts. Under the very mild reaction conditions, both methods of catalysis allow selective access to chiral products with impressive results. However, for the organocatalysed Michael reactions the amount of catalyst loadings are normally higher than that of the metal-catalysed process.

Additionally, in terms of the Michael addition of 2-alkylazaarenes to nitroalkenes, the challenge is the weaker activation property of C=N bound in comparison with C=O. Therefore, only some examples of enantioselective Michael additions of acetylheteroarenes to nitroalkenes have been reported recently and most of them rely upon organocatalysis. In the Lam group,[151] we investigated nickel-catalysed Michael addition of 2-acetylazaarenes to nitroalkenes with the exploitation of the activation properties of azaarene units (**Section 2.3.2**). However, it is currently unclear whether

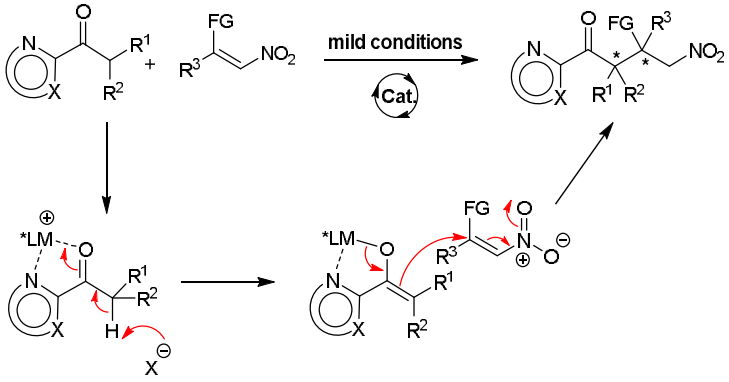
this mode of activation could be applied to the more complex substrates. To address this issue, the enantioselective Michael addition of 2-acylazaarenes to sterically *β*,*β*-disubstituted nitroalkenes will be discussed in detail in **Section 2.7**.

2.6 Aims and Objectives

As shown in the previous sections, molecules containing chiral all-carbon quaternary stereocentres are useful in terms of their biological properties. However, chiral compounds containing both azaarenes and an all-carbon quaternary centre in the same molecule are rarely explored and studied. Moreover, it should be noted that the Michael reaction is one of the most practical approaches to obtain all-carbon quaternary stereocentres. Thus, constructing azaarenes bearing chiral all-carbon quaternary substituents by the Michael addition reaction would be a promising and challenging idea.

Importantly, the use of azaarenes as activating groups in enantioselective transformations is one of the main research goals in the Lam group. Since the first report of the copper-catalysed enantioselective reduction of 2-alkenylazaarenes in 2009,[133] many novel methods for the asymmetric functionalisation of azaarene-containing compounds have been investigated in our group.[128,129,133,134,148,150,151] Besides, according to the recent work by Simpson and Lam,[151] the Michael reaction between 2-acetyl azaarenes and *β*-substituted nitroalkenes afforded chiral products containing heteroarenes with reasonable yields and selectivities (**Scheme 2.35**). This report demonstrates the ability of C=N group to stabilise a negative charge and activate the nucleophilicity of 2-acetylazaarenes. Therefore, following the same concept, the aim of our research was to apply this novel mode of activation for the asymmetric functionalisation of 2-acyl substituted azaarenes using the more sterically hindered electrophiles, *β*,*β*-disubstituted nitroalkenes to generate azaarene derivatives containing chiral all-carbon quaternary stereocentres. It was envisaged that employing *α*,*α*-disubstituted 2-acetyl heteroarenes instead of 2-acetyl azaarenes, chiral products

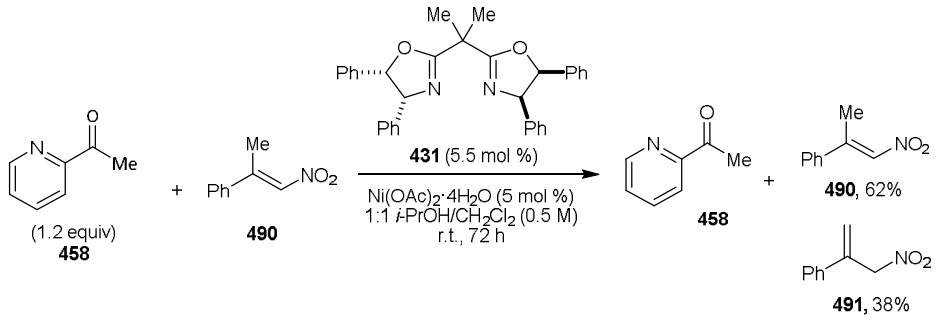
with vicinal all-carbon quaternary stereocentres could be obtained as shown in **Scheme 2.53**.



Scheme 2.53: Enantioselective nickel-catalysed Michael additions of 2-acetylazaarenes to nitroalkenes.

2.7 Results and Discussions

As discussed in **Scheme 2.35**, the Lam group had developed the enantioselective nickel-catalysed Michael addition of 2-acetylazaarenes to *β*-substituted nitroalkenes by exploitation of the mode of activation of azaarenes.[151] However, the use of *β*,*β*-disubstituted nitroalkenes as electrophiles is very challenging due to the sterically hindered nature of these substrates. In order to fulfil our goal (see **Scheme 2.53**) of generating azaarenes featuring a chiral all-carbon quaternary stereocentre, initially, the Michael addition of 2-acetylpyridine (**458**) to a *β*,*β*-disubstituted nitroalkene **490** was studied by Alain J. Simpson (a former PhD student in Lam group) using the same reaction conditions as in our previous report.[151] Unfortunately, no Michael product was observed, only the isomerisation of alkene **490** was formed (**Scheme 2.54**).[170,171]



[a] Reaction was conducted by Alain J. Simpson (a former PhD colleague).

Scheme 2.54: Attempted Michael addition with a *β*-methy-*β*-phenyl nitroalkene (**490**).

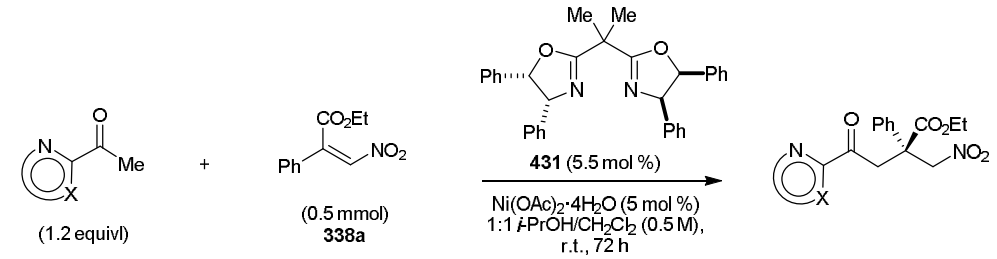
The low reactivity of nitroalkene **490** was ascribed to its more hindered *β*-position. To overcome the increased steric crowding and gain sufficient activation,[172] the methyl group of *β*,*β*-substituted nitroalkene **490** was replaced by electron-withdrawing substituents, such as carbonyl,[173] phosphonate[174] and CF_3[163] groups. The nickel-catalysed Michael addition of 2-acetylazaarenes to these activated nitroalkenes will be featured in the following sections.

2.7.1 The Michael Addition of 2-Acetylazaarenes to Aromatic *α*-Substituted *β*-Nitroacrylates

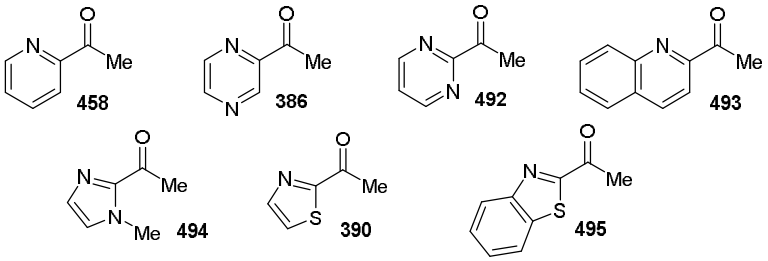
As discussed in **Scheme 2.54**, the Michael addition of 2-acetylpyridine (**458**) to nitroalkene **490** was unsuccessful presumably due to the low reactivity of this hindered nitroalkene. However, it was anticipated that electron deficient substituted nitroalkenes could be compatible substrates. To continue this work, Alain J. Simpson investigated the Michael addition of 2-acetylpyridine (**458**) to nitroalkene **338a** under the reported optimal reaction conditions (the complex composed of $Ni(OAc)_2 \cdot 4H_2O$ (5 mol %) and the *bis*-oxazoline ligand **431** in i-PrOH/CH_2Cl_2 at room temperature).[151] Gratifyingly, it was found that the Michael adduct **496a** was obtained with 93% yield and 95% ee (**Table 2.1**). Various other 2-acetylazaarenes containing quinoline, pyrazine, thiazole, benzothiazole, or *N*-methylimidazole groups also reacted smoothly with **338a** to provide chiral products, with all-carbon quaternary stereocentres, with 78-89% yield and 95-99% ee. Unfortunately, the use of 2-acetylpyrimidine (**492**) as the nucleophilic partner was problematic, giving product with poor yield (46%) and selectivity (49% ee). The origin of the detrimental effect of pyrimidine ring is still unclear; although this dinitrogen-containing ring may lead to an alternative binding mode, resulting in diminished catalytic activity.

To expand the substrate scope, the Michael additions of various azaarenes to other aromatic or heteroaromatic *β*-acylnitroalkenes were also studied. For *m*- and *p*-substituted aromatic *β*-acylnitroalkenes (**Table 2.2**) with both electron rich and poor substituents such as methyl, methoxy and chloro groups the reactions proceeded smoothly providing chiral products with high yields (80-96%) and excellent enantioselectivities (94-99% ee).

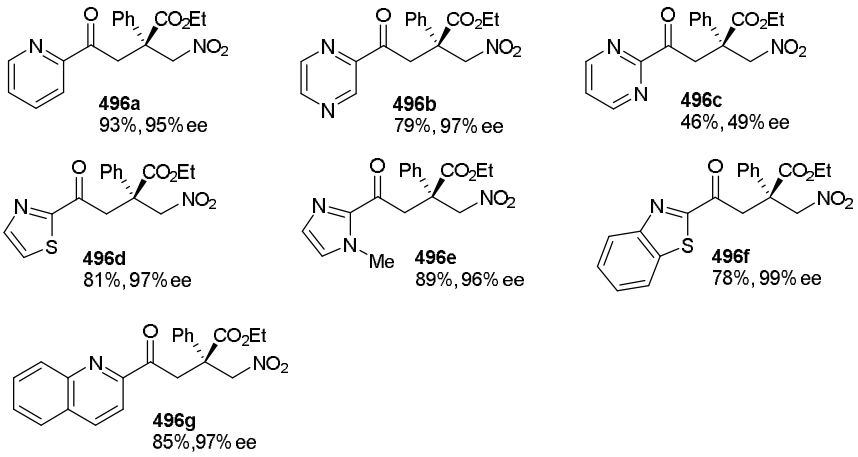
Table 2.1: Enantioselective nickel-catalysed Michael additions of 2-acetylazaarenes to phenyl *β*-acylnitroalkene **338a**.[a]



Azaarenes

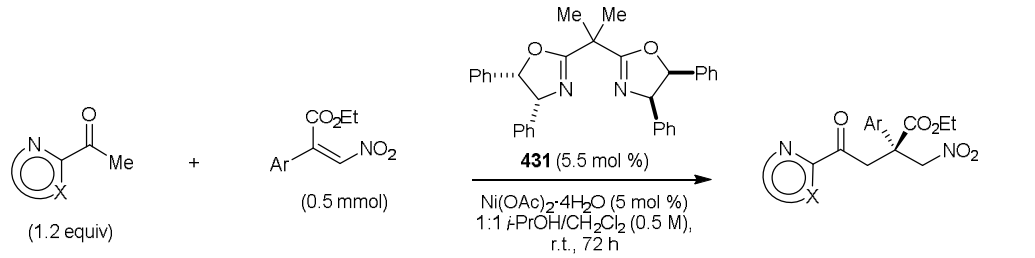


Products

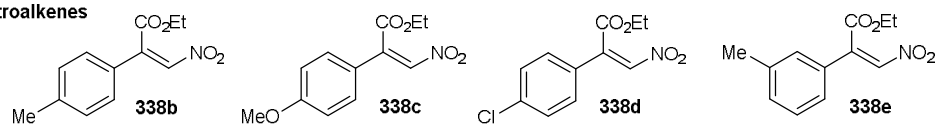


[a] Reactions were conducted by Alain J. Simpson.

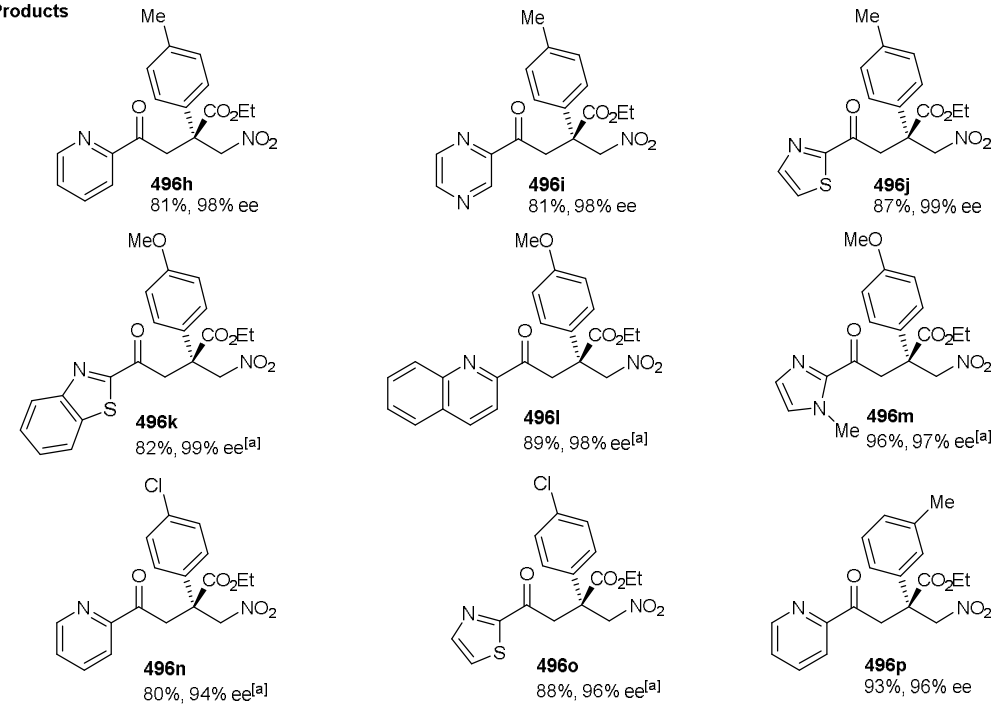
Table 2.2: Enantioselective nickel-catalysed Michael additions of 2-acetylazaarenes to aryl β-acylnitroalkenes.



Nitroalkenes



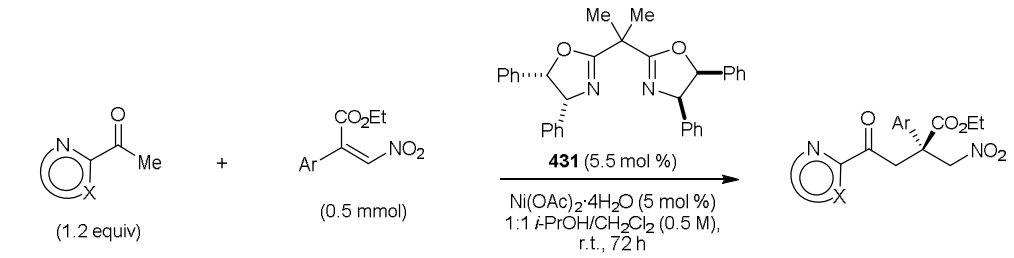
Products



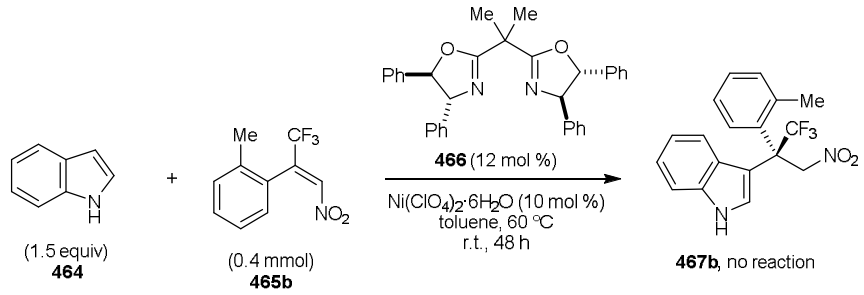
[a] Reactions were conducted by Alain J. Simpson.

In the case of *o*-substituted aromatic *β*-acylnitroalkenes with either electron-rich or -poor groups such as methoxy or chloro substituents, the reaction was unsuccessful leading to recovering only the starting materials (**Table 2.3**). This result suggested that substituents at the *o*-position of aromatic nitroalkenes render the system too bulky to react with azaarenes. This kind of steric effect has also been observed by Jia and co-workers in the nickel-catalysed enantioselective Friedel−Crafts alkylation of indoles with nitroalkenes: although *m*- and *p*-substituted aromatic nitroacrylate esters were successfully reacted (see **Scheme 2.45**), the reaction of nitroalkene **465b** containing an *o*-tolyl substituent gave no product (**Scheme 2.55**).[163]

Table 2.3: Enantioselective nickel-catalysed Michael additions of 2-acetylazaarenes to phenyl *β*-acylnitroalkenes.

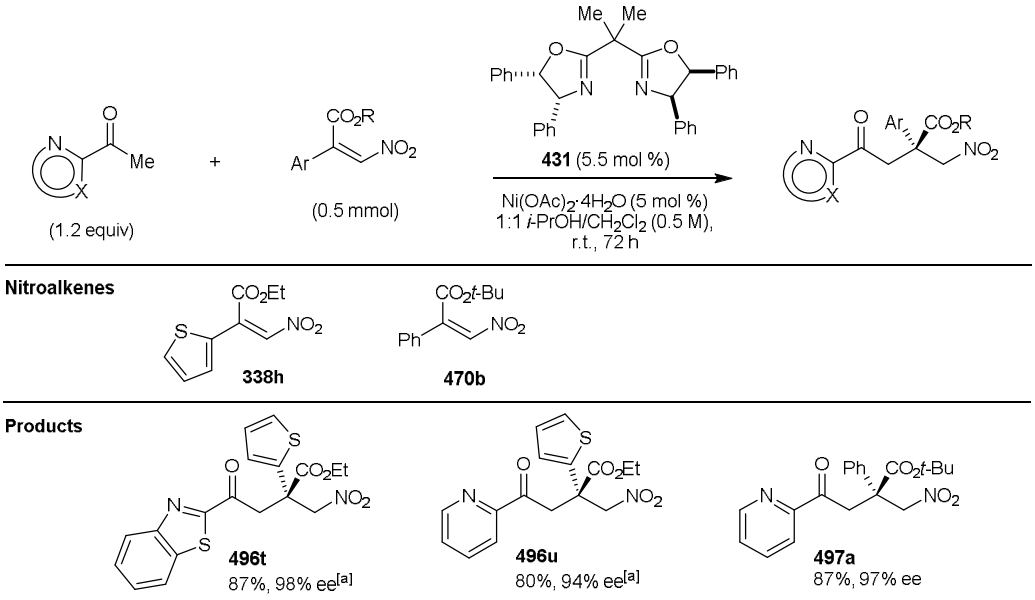


[a] The reaction was conducted by Alain J. Simpson.



Scheme 2.55: Enantioselective nickel-catalysed Friedel−Crafts alkylation of indole (**464**) with β-CF_3-β-disubstituted nitroalkene **465b**.[163]

Table 2.4: Enantioselective nickel-catalysed Michael addition of 2-acetyl azaarenes with heteroaromatic β-substituted nitroalkenes and aromatic β-acylnitroalkene.



[a] Reactions were conducted by Alain J. Simpson.

Further investigations were made using heteroaromatic instead of aromatic β-substituted nitroalkenes. Notably, it was revealed that 2-thiophenyl β-substituted nitroalkene **338h** underwent Michael addition with satisfactory results. Both 2-acetylbenzothiazole (**495**) and 2-acetylpyridine (**458**) afforded heteroaromatic adducts with high yields and

enantioselectivities. Moreover, the ester substituent could be varied as well. For example, the nitroalkene containing a bulky *tert*-butyl ester **470b** afforded chiral product **497a** with 87% yield and 97% ee (**Table 2.4**).

In light of these encouraging results with aromatic α-acyl-β-nitroacrylates, the Michael addition of 2-acetylazaarenes to α-alkyl-β-nitroacrylates appeared to be a promising avenue for future research. Therefore in the following section, the Michael reaction of aliphatic α-substituted β-nitrocrylates was investigated.

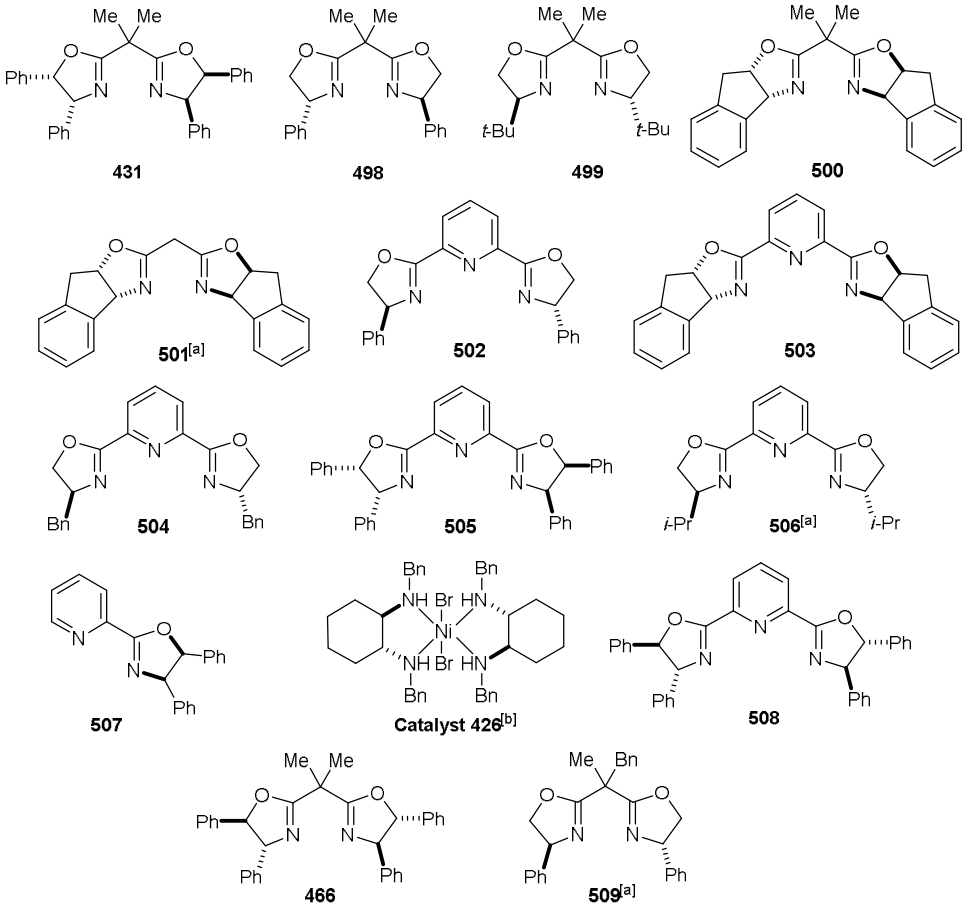
2.7.2 The Michael Addition of 2-Acetylazaarenes to Aliphatic α-Substituted β-Nitroacrylates

Ligand Screening

Initial attempts (**Table 2.5**) focused on the Michael addition between 2-acetylpyridine (**458**) and α-octyl β-nitroacrylate (**510a**) using the same catalyst as was used for aromatic α-substituted β-nitroacrylates. The result showed that both yield and enantioselectivity were modest (79% NMR yield, 74% ee, entry 1). In order to improve enantioselectivity, a number of Box and PyBox ligands (**Figure 2.3**) were investigated. Firstly, 2,2-dimethylmalonic acid-derived *bis*-oxazoline ligands (**498**, **499** and **500**) were screened, however, inproved results were not observed (entries 2-4). Ligand **501**, derived from unsubstituted malonic acid, was also screened and the reaction remained incomplete after 48 h (it gave only 27% yield and 8% ee; entry 5).

At this point, *bis*-oxazoline ligands with a different central linker, for example PyBox ligands with aliphatic or aromatic substituents at the oxazoline ring, were investigated. Fortunately, the use of ligand **503** gave superior result; 83% yield and 78% ee (entry 7). Thus, pyridinyl oxazoline (PyOx) ligand **507** was also tested; however, it was found to give a modest yield (74%) and a low level of selectivity (14% ee, entry 11). Nickel−diamine catalyst **426**, which is a very good catalyst for the Michael addition of 1,3-dicarbonyl compounds, azaarylacetates and acetamides to nitroalkenes,[148,149,166] gave low yield and racemic product (entry 12). This catalyst seemed to behave as a stronger

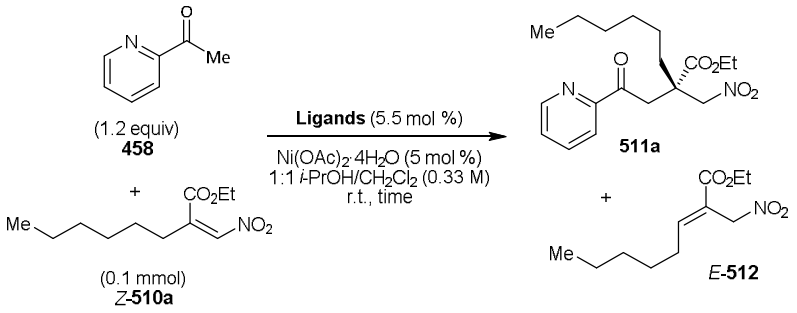
base than oxazoline ligands because an isomerised nitroalkene **512** was observed in a significant amount (34%) (this is consistent with the requirement for loss of one diamine ligand to generate a reactive nickel enolate, see **Scheme 2.35** and **Scheme 2.48**).[148,149] Ligands **508** and **466** (having substituents pointing in opposite directions) were then evaluated, as this type of ligand has been previously reported as an effective ligand for a nucleophilic addition to nitroalkenes.[163,164] However, neither improved the yield or selectivity (entries 13 and 14). A *bis*-oxaxoline ligand **509** was then studied and it was found that this ligand gave low yield and enantioselectivity as well (entry 15). Other classes of ligands such as biphosphines were not investigated because they tended to be unreactive to this chemistry.[151]



[a] Commercial ligands. [b] This catalyst was prepared by Alain J. Simpson.

Figure 2.3: *Bis*-oxazoline ligands and catalyst for screening.

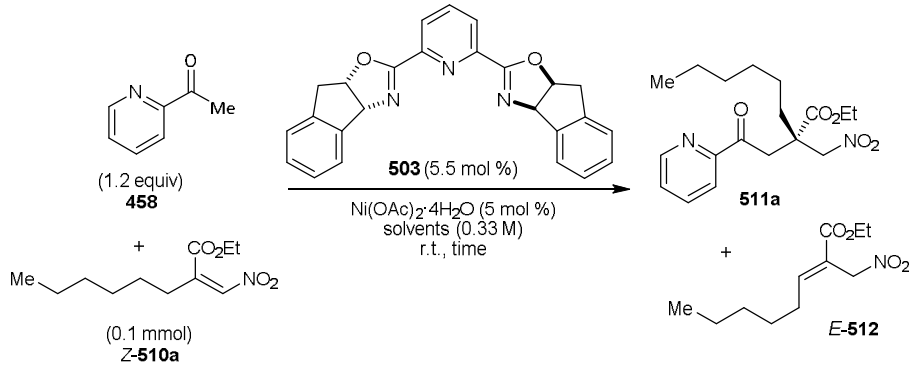
Table 2.5: Ligand screening.



Entry	Ligand	Time (h)	Con.(%) (NMR)[a]	NMR Yield (%)[a]		ee (%)[b]
				511a	***E*-512**	
1	**431**	96	100	79	18	−74
2	**498**	96	73	46	22	−24
3	**499**	96	61	22	13	0
4	**500**	96	64	31	27	12
5	**501**	96	48	27	10	−8
6	**502**	48	100	78	22	−70
7	**503**	40	100	83	15	78
8	**504**	48	67	53	11	−50
9	**505**	68	100	82	15	68
10	**506**	96	80	57	19	−50
11	**507**	40	100	74	19	14
12[c]	Catalyst **426**	40	100	60	34	0
13	**508**	62	95	81	13	54
14	**466**	96	37	24	12	5
15	**509**	72	78	59	18	12

[a] Determined by NMR analysis of the crude product using 1,3,5-tetramethoxybenzene as an internal standard. [b] Enantiomeric excess were determined by chiral HPLC analysis. [c] Catalyst **426** was used in place of $Ni(OAc)_2 \cdot 4H_2O$ and ligand.

Table 2.6: Solvent screening



Entry	Solvent	Time (h)	Con.(%) (NMR)[a]	NMR Yield (%)[a]		ee (%)[b]
				511a	***E*-512**	
1	CH_2Cl_2	48	34	16	14	74
2	$CHCl_3$	48	43	27	7	70
3	MeOH	48	94	55	7	22
4	*i*-PrOH	48	100	82	15	32
5	BuOH	48	100	84	14	52
6	Et_2O	48	18	8	7	30
7	THF	48	97	84	7	58
8	dioxane	48	31	22	4	60
9	MeCN[d]	48	100	35	44	54
10	toluene	48	20	11	6	65
11	EtOAc	48	19	13	4	58
12	DMF[d]	48	100	44	28	38
13	BuOH:CH_2Cl_2 (1:1)	40	100	79	12	75
14	THF:CH_2Cl_2 (1:1)	96	74	55	12	70
15[c]	*i*-PrOH:CH_2Cl_2 (1:1)	40	100	83	15	78

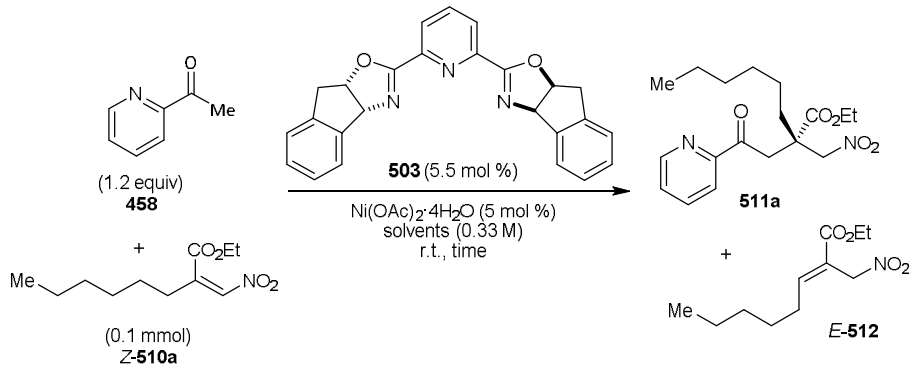
[a] Determined by NMR analysis of the crude product using 1,3,5-tetramethoxybenzene as internal standard. [b] Enantiomeric excess were determined by chiral HPLC analysis. [c] The result from **Table 2.5.** [d] starting materials were possibly degraded to generate unidentified compounds which stuck on the silica gel.

Solvent Screening

With the best ligand **503** revealed, a range of solvents was screened (**Table 2.6**). Halogenated solvents such as dichloromethane and chloroform gave modest conversion, with the highest enantioselectivities (entries 1-2). Protic solvents or alcohols such as methanol, isopropanol and butanol resulted in high to complete conversion (maybe because of a good solubility of catalyst) but low selectivities were observed and larger alcohols gave higher enantioselectivities (entries 3, 4 and 5). Most ether solvents showed low reactivity except THF, which underwent 97% conversion, but disappointingly, with only 58% ee (entry 7). Although toluene and ethyl acetate brought about a moderate ee, these solvents afforded very low conversions (entries 10-11). Acetonitrile and DMF were also investigated and gave complete conversion; however, very high levels of isomerised nitroalkene were observed (entries 9 and 12). Apart from single solvents, which produced poor results, mixed solvents were also tested. However, both BuOH:CH_2Cl_2 and THF:CH_2Cl_2 mixtures were poor in comparison with the use of *i*-PrOH:CH_2Cl_2 (entries 13-15).

According to the result in **Table 2.6**, a mixed *i*-PrOH:CH_2Cl_2 solvent system afforded the best result. Notably, this resulted in higher enantioselectivity than the use of pure *i*-PrOH or CH_2Cl_2. This result suggested a synergistic phenomenon between *i*-PrOH and CH_2Cl_2. Thus, different ratios of these two solvents were investigated (**Table 2.7**). Undoubtedly, a synergistic effect was observed when 40% and 50% of dichloromethane in isopropanol were used as a mixed solvent giving product in 78% ee (entries 5 and 6). However the yields of these reactions were unsatisfactory. A possible reason for this problem would be the isomerisation of the nitroalkene starting material. To solve this issue, the *Z*-nitroalkene **510a** was added in excess (1.5 equiv) and 2-acetylpyridine (**458**) was used as the limiting substrate. Gratifyingly, the result showed that Michael adduct **511a**, with all-carbon quaternary stereogenic centre, was achieved with excellent yield (>99% NMR yield) and retained a reasonable enantioselectivity (78% ee, entry 12). Therefore these conditions were considered as the optimal conditions for this reaction.

Table 2.7: Cosolvent proportion screening.



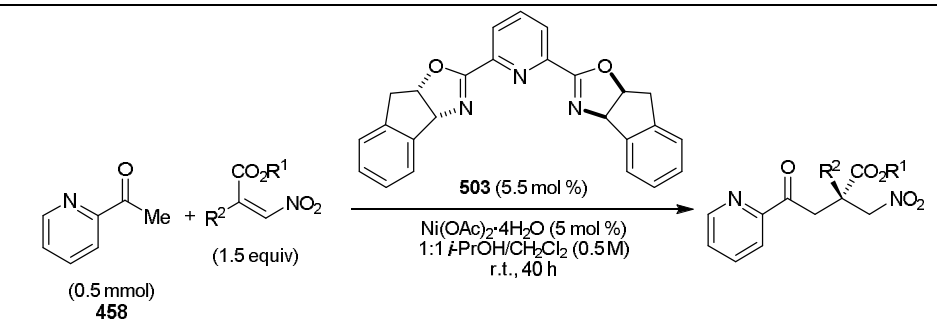
Entry	*i*-PrOH:CH_2Cl_2	Time (h)	Con.(%) (NMR)[a]	NMR Yield (%)[a]		ee (%)[b]
				511a	***E*-512**	
1[d]	10 : 0	48	100	82	15	32
2	9 : 1	40	100	84	16	56
3	8 : 2	40	100	81	13	68
4	7 : 3	40	100	83	14	68
5	6 : 4	40	100	78	17	78
6[[c]	5 : 5	40	100	83	15	78
7	4 : 6	40	100	81	18	74
8	3 : 7	48	91	70	19	73
9	2 : 8	48	72	40	17	74
10	1 : 9	48	63	34	19	73
11[d]	0 : 10	48	34	16	14	74
12[e]	5 : 5	40	100	>99	-	78

[a] Determined by NMR analysis of the crude product using 1,3,5-tetramethoxybenzene as internal standard. [b] Enantiomeric excess were determined by chiral HPLC analysis. [c] The result from **Table 2.5**. [d] The results from **Table 2.6**. [e] 0.1 mmol of 2-acetylpyridine (**458**) and 0.15 mmol of nitroalkene **510a** were used.

Scope of Azaarenes and Nitroalkenes

With the optimised reaction conditions in hand, several aliphatic substituted nitroalkenes were investigated using 2-acetylpyridine (**458**) as a model pronucleophile (**Table 2.8**). Firstly, for 2*Z*-2-(nitromethylidene)octanoates with methyl-, ethyl- or *tert*-butyl-substituents at ester group, the results indicated that the bulkier the substituents, the lower enantioselectivities of products were obtained (81%, 78%, and 52% ee respectively). Next, ethyl β-nitroacrylates with different substituents at the α-position were studied. Both methyl and 3-butenyl substituted nitroalkenes gave products with modest percent enantiomeric excess. However, substrates with larger substituents resulted in products with higher yields than substrates with smaller substituents.

Table 2.8: Enantioselective nickel-catalysed Michael addition of 2-acetylpyridine (**458**) with aliphatic β-acylnitroalkenes.



The scope of both azaarenes and nithroalkenes were further investigated. In addition to 2-acetylpyridine (**458**), other 2-acetylazaarenes with different heterocyclic cores (namely thiazole, benzothiazole, pyrazine, *N*-methylimidazole and quinolone) were studied whilst varying the aliphatic nitroalkene partners (**Table 2.9**). The results showed that most of these azaarenes were significantly less reactive than 2-acetylpyridine (**458**). Moreover, nitoalkene **510f** reacted with azaarenes **494** and **495** to afford chiral products **511d** and **511e** with high enantioselectivities but modest yields even though the reaction time was extended to four days. The more reactive 2-acetylpyrazine (**386**) underwent Michael addition to nitroalkene **510d** and **510g** giving products **511f** and **511g** with reasonable yields and selectivities. Fortunately, nitroalkene **510e** containing two ester groups also reacted with 2-acetylthiazole (**390**) to give product **511h** with 63% yield and 78% ee. The least reactive 2-acetylquinoline (**493**) could react with nitroalkenes **510a** and **510c** generating Michael adducts **511i** and **511j** with moderate ee, however, the yields of these reactions were very low.

To demonstrate the versatility of this methodology, three other electron deficient substituted-nitroalkenes were investigated, namely keto-substituted, phosphonate ester-substituted and trifluoromethyl-substituted nitroalkenes (**Table 2.10**). Extending the reaction time to seven days, keto-substituted nitroalkene **515** reacted slowly with 2-acetylpyrazine (**386**), 2-acetyl *N*-methyl imidazole (**494**) and 2-acetylbenzothiazole (**495**) to give products in reasonable yields (67-82%) and excellent enantioselectivities (97-99% ee). Regarding the synthesis of the chiral compounds **518a** and **518b** from phosphonate ester-substituted nitroalkene **516**, a number of PyBox and Box ligands as well as solvents were screened (data not show). The best result was the use of ligand **502** in a mixture of dioxane and CH_2Cl_2. Although the enantioselectivities were very high, the yields were disappointingly low. The reaction did not go to completion even with extension of the reaction time to 96 h. Pleasingly, using ligand **502** in THF, CF_3-substituted nitroalkene **465a** underwent Michael addition with reasonable yields and stereoselectivities.

Table 2.9: Enantioselective nickel-catalysed Michael addition of 2-acetylazaarenes with aliphatic β-acylnitroalkenes.

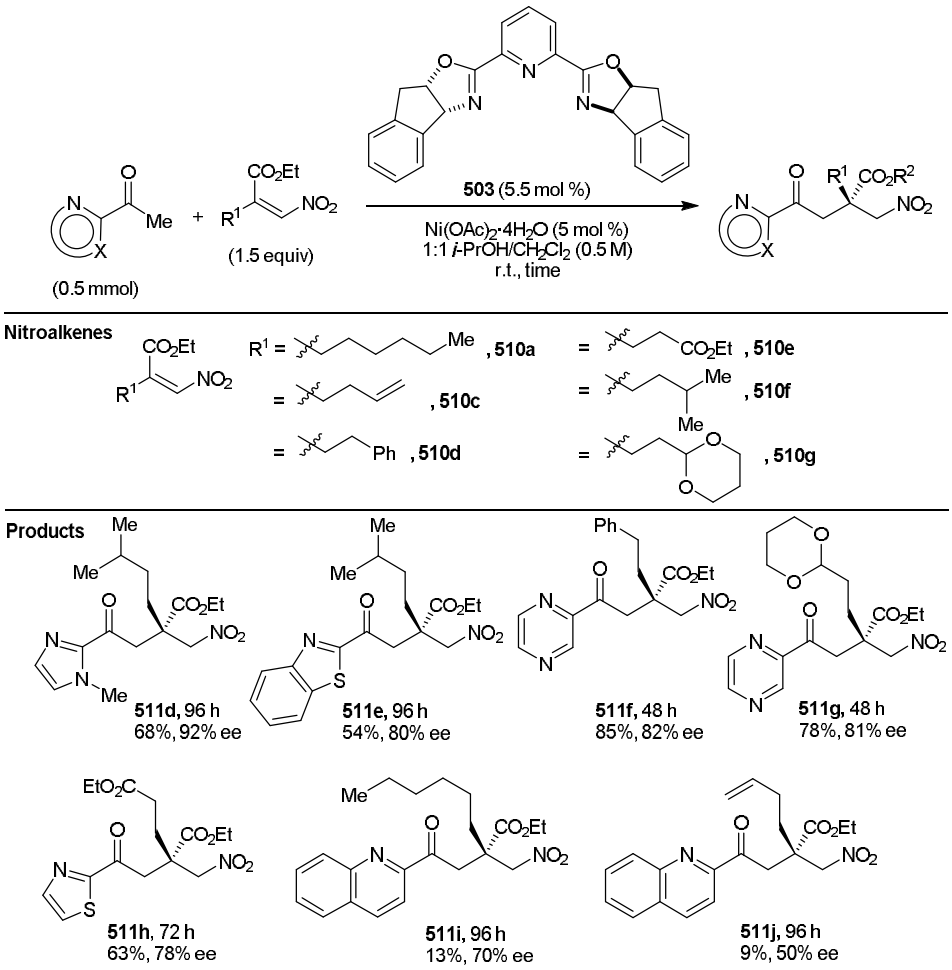
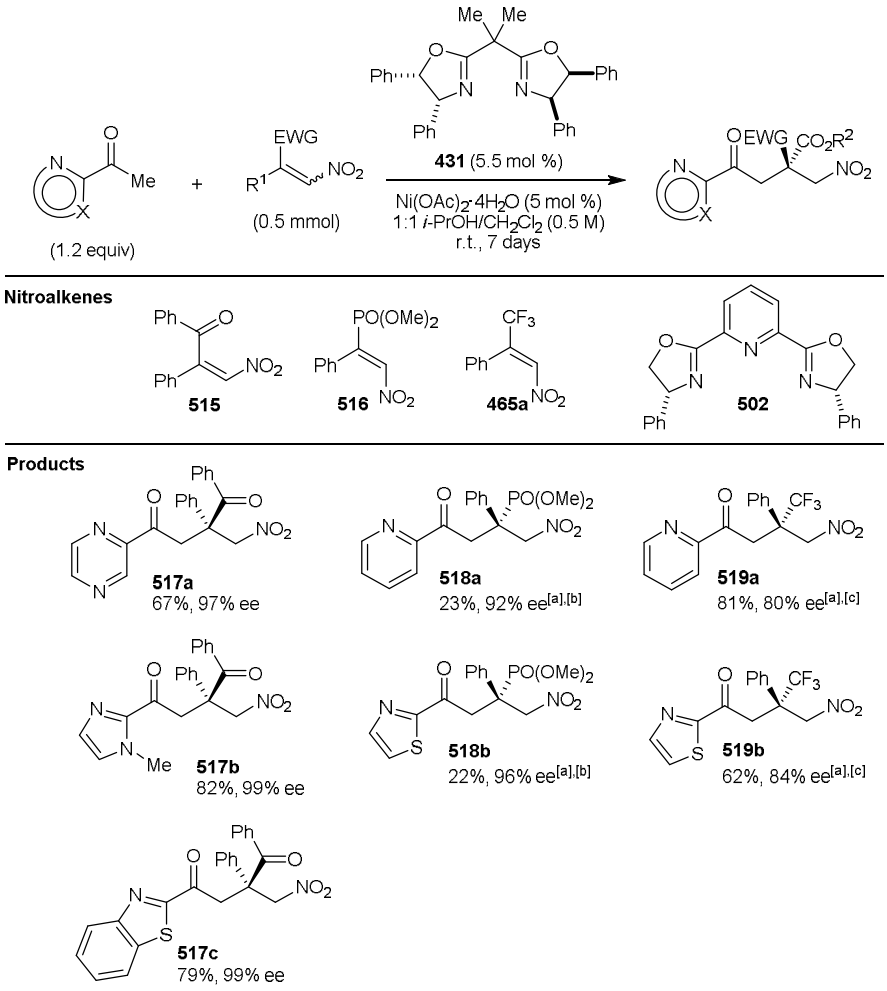


Table 2.10: Enantioselective nickel-catalysed Michael addition of 2-acetylazaarenes with other β-substituted nitroalkenes.



[a] Ligand **502** was used. [b] Reactions were run in 1:1 dioxane:CH_2Cl_2 for 96 h. [c] Reactions were run in THF for 72 h and using 1.5 equivalent of 2-acetylazaarenes.

2.7.3 Unsuccessful Heteroarenes and Nitroalkenes

To investigate the scope of both Michael donors and Michael acceptors, a number of azaarenes and nitroalkenes were studied (**Figure 2.4**). The result showed that acyl pyridine derivatives in which the alkyl substituent is bigger than methyl group such as ethyl, isopropyl or bromomethyl were unsuccessful. This result suggested that steric

effects have a crucial role in this catalytic process. Also other heteroaromatic group apart from azaarenes, for example, 2-acetylthiophene (**455**) or 2-acetylfuran (**523**), were incompatible substrates. If the carbonyl group was derivatised to an imine group such as in compound **524**, the reaction was also unsuccessful. The reason for this would be because of the steric effect of the bulky *p*-methoxy phenyl substituent. Also this substrate would behave like a Schiff base ligand and slow the rate of this reaction.

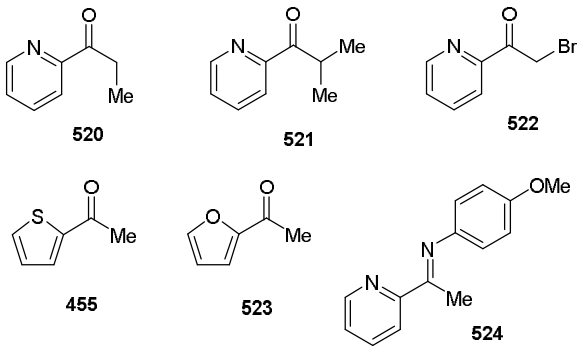
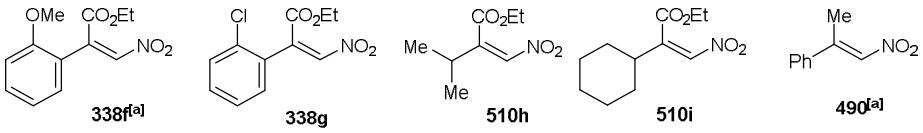


Figure 2.4: Unreactive heteroarenes.

As mentioned in **Table 2.3**, *o*-substituted aromatic *β*-acylnitroalkenes were unreactive. Aliphatic nitroalkenes with bulky substituents such as *iso*propyl or cyclohexyl groups were also unreactive (**Figure 2.5**), it could be rationalised that having a massive substituent on the nitroalkenes renders the system too bulky to react with azaarenes. Last but not least, as mentioned in **Scheme 2.54**, the nitroakene without an ester group such as nitroalkene **490** could not undergo Michael addition either. From NMR analysis of a crude mixture, this nitroalkene seems to isomerise to alkene **491**.[170,171]



[a] The reaction was conducted by Alain J. Simpson.

Figure 2.5: Unsuccessful nitroalkenes.

Absolute Configuration Determination

The absolute configurations of Michael products **511e**, **517b**, **518a** and **519a** were determined by X-ray crystallography (**Figure 2.6**). The relative stereochemistry of the remaining products was assigned by analogy with the observed sense of enantioinduction in the representative products.

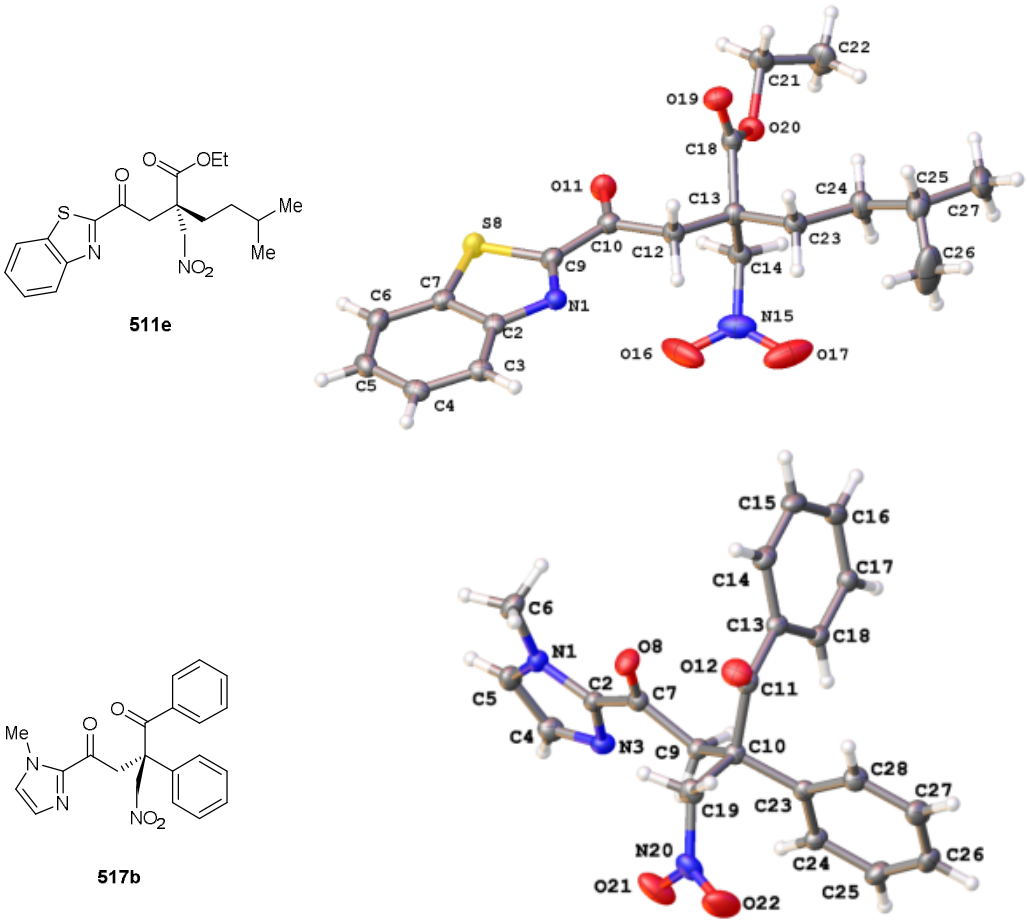


Figure 2.6: Crystal structures of Michael adducts **511e**, **517b**, **518a** and **519a**.

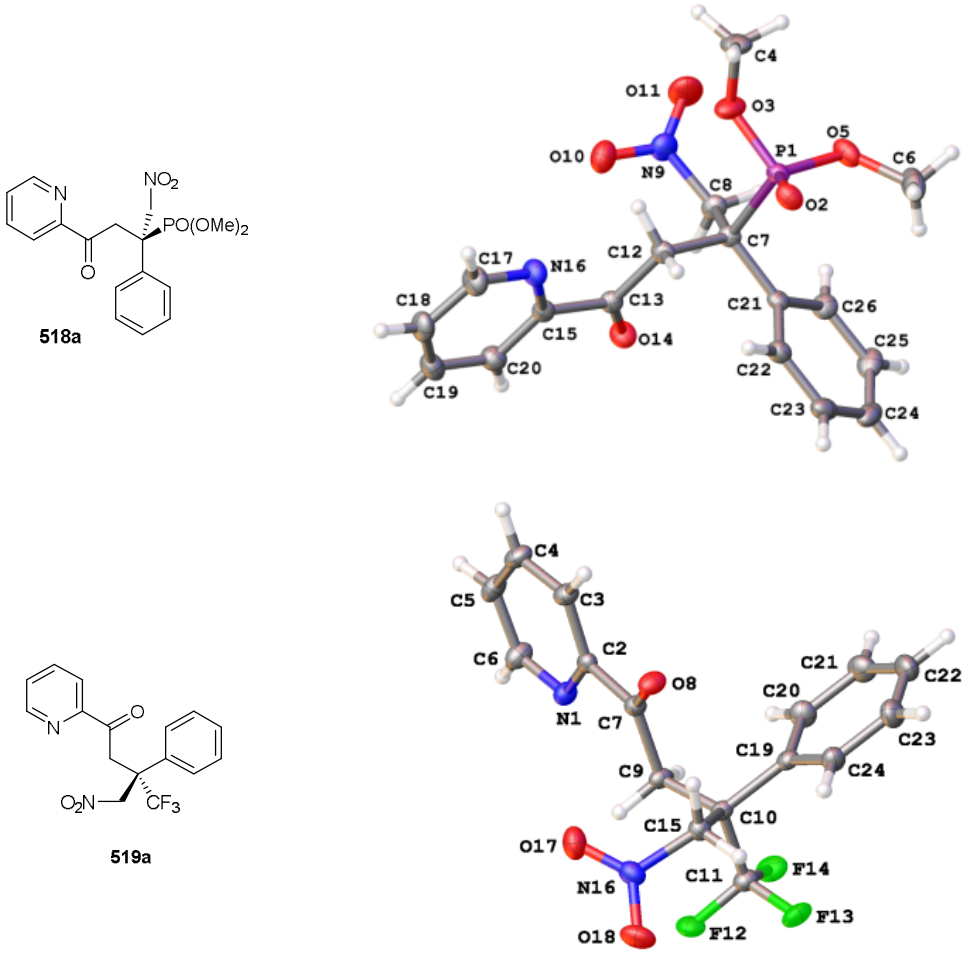
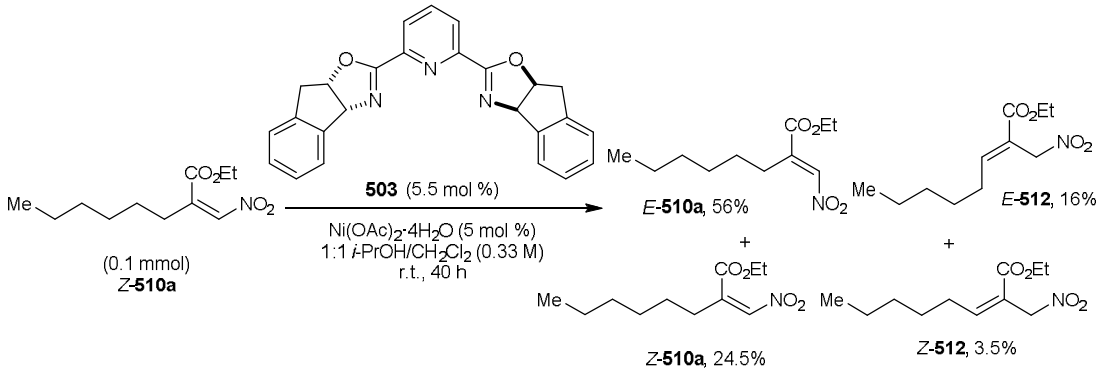


Figure 2.6: Crystal structures of Michael adducts **511e**, **517b**, **518a** and **519a** (Continued).

2.7.4 Mechanistic Discussion

It was shown that the catalyst might cause an isomerisation of *α*-alkyl-*β*-nitroacrylates. This resulted in a low yield of the Michael adducts (**Table 2.5**). To investigate this problem, *Z*-nitroalkene **510a** was mixed with the nickel catalyst without an acetylazaarene substrate. After 40 h of continuous stirring, four nitroalkenes were found in a crude mixture. There were 56% of *E*-**510a**, 24.5% of *Z*-**510a**, and 16% and 3.5% of

alkenes *E*-**512** and *Z*-**512** respectively (**Scheme 2.56**). This result demonstrated that *Z*-nitroalkene **510a** undergoes isomerisation over the course of the reaction.



[a] yields were relative to total nitroalkene signals.

Scheme 2.56: Isomerisation of *Z*-nitroalkene **510a**.[a]

The four alkenes were determined by the ^{1}H-^{1}H NOESY experiments. For the *E*-**510a**, there was no cross peak observed between C**H**$_2$ and =C**H**NO$_2$. However, a strong correlation was detected between C**H**$_2$ and =C**H**NO$_2$ of *Z*-**510a**. Regarding *Z*-alkene **512**, there was a strong NOE correlation between =C**H** and C**H**$_2$NO$_2$. However, for *E*-alkene **512** there was a cross peak between C**H**$_2$ and C**H**$_2$NO$_2$ instead (**Figure 2.7**).

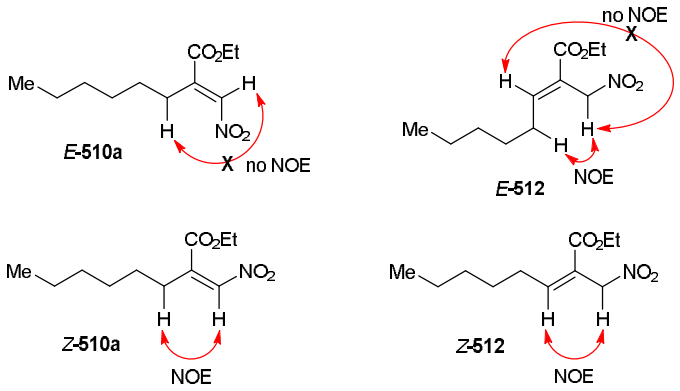
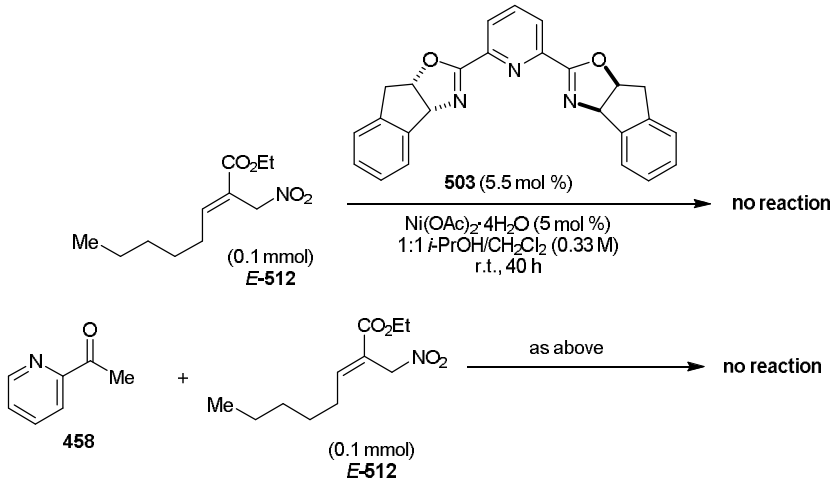


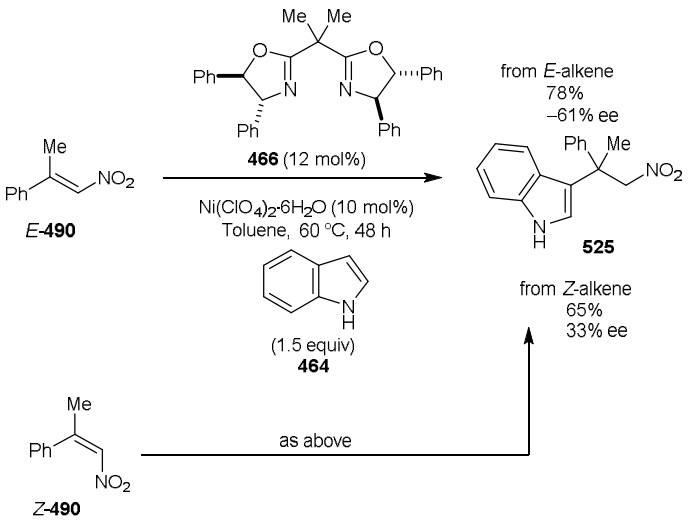
Figure 2.7: ^{1}H-^{1}H NOESY experiments of **510a** and **512**.

As shown in **Table 2.5** (entry 7), the NMR yield in the presence of azaarene **458** was only 83%, and the isomerised alkene *E*-**512** was about 15% (entry 7). This result indicated that alkene *E*-**512** could not isomerise back to nitroalkene **510a** to generate a higher quantity of chiral product **511a**. To test this hypothesis, the isomerised alkene *E*-**512** was investigated by putting this alkene in the same catalytic system as shown above with or without 2-acetylpyridine (**458**) (**Scheme 2.57**). Michael product **511a**, isomerised alkene *Z*-**512** or nitroalkenes **510a** were not observed in the reaction mixture apart from the starting material *E*-**512**. This result proved that alkene *E*-**512** does not undergo isomerisation in this reaction medium.



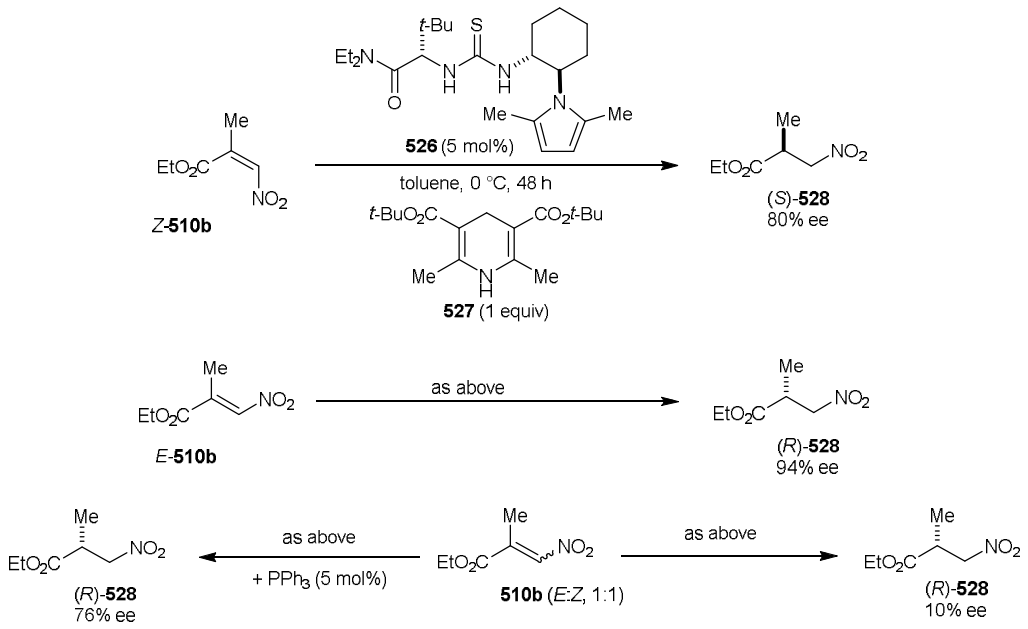
Scheme 2.57: Reaction of alkene *E*-**512**.

It was therefore decided to investigate the effect of nitroalkene configuration on the yield and stereochemical outcome of the reaction. Usually, in most asymmetric reactions involving activated alkenes as electrophiles, *E*- and *Z*-olefins provide stereodivergent products or products with opposite absolute configurations.[175] For example, in the enantioselective nickel-catalysed Friedel−Crafts alkylation reaction of indoles with *β*-methylnitrostyrenes investigated by Jia and co-workers,[163] *E*- and *Z*-*β*-methylnitrostyrenes gave opposite stereoisomers with significantly lower ee values (33% and -61% ee)(**Scheme 2.58**).



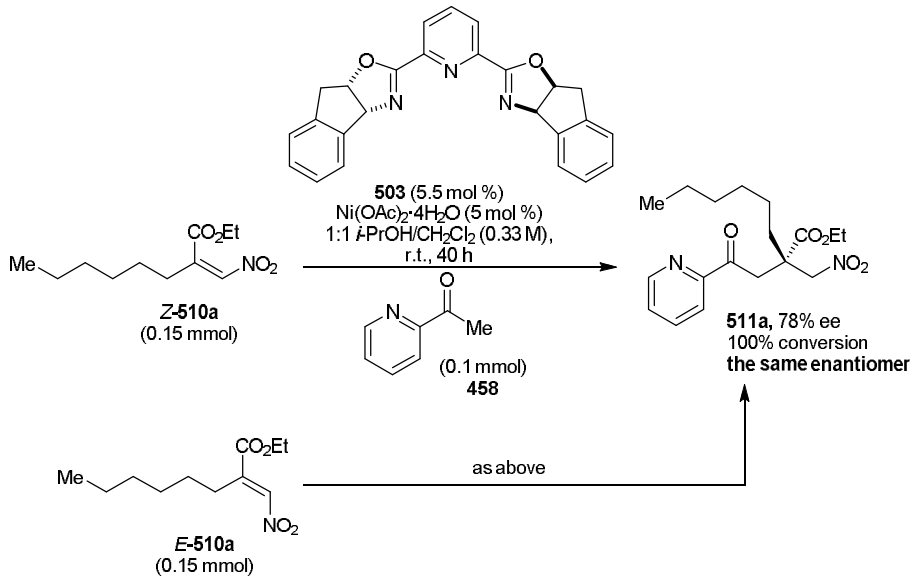
Scheme 2.58: Enantioselective nickel-catalysed Friedel−Crafts alkylation of indole (**464**) to *E*- and *Z*-nitroalkenes **490**.[163]

Moreover, in the study of organocatalytic asymmetric transfer hydrogenations of *β*-nitroacrylates by List and co-workers[173] it was shown that the stereochemical outcome of nitroolefin reduction strongly depends on the substrate olefin geometry, with *E*- and *Z*-nitoalkenes **510b** giving products with opposite enantiomers (**Scheme 2.59**). The authors proposed that the addition of triphenylphosphine creates a rapid equilibrium between *E*-**510b** and *Z*-**510b** *via* a conjugate addition/elimination pathway and *E*-starting material dominates the equilibrium of the two olefin isomers resulting in (*R*)-**528** as the major product.



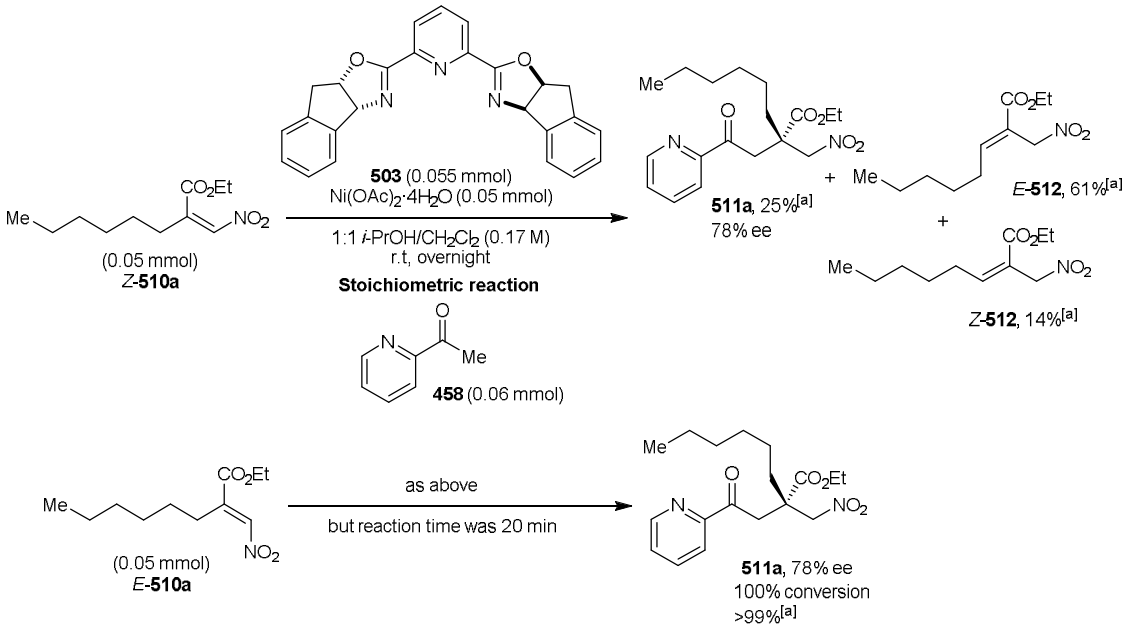
Scheme 2.59: Organocatalytic asymmetric transfer hydrogenation of *β*-nitroacrylates **510b**.[173]

In the present chemistry, if *Z*- and *E*-nitroalkenes reacts with 2-acetylazaarene in a similar manner, opposite enantiomers would be obtained. Moreover, if one nitroalkene isomer reacts faster than the other, the enantiomeric excess obtained would be different for the two nitroalkene isomers. To test this hypothesis, the Michael reactions of both *Z*- and *E*-nitroalkenes **510a** with 2-acetylpyridine (**458**) were investigated. Surprisingly, both *Z*- and *E*-nitroalkenes **510a** gave the same enantiomer of **511a** (78% ee) which suggests that one isomer is either much more reactive than the other, or maybe the *Z*-isomer is unreactive and isomerises slowly to the reactive *E*-isomer (**Scheme 2.60**).



Scheme 2.60: Nickel-catalysed enantioselective Michael addition of 2-acetylpyridine (**458**) to *Z*- and *E*-nitroalkenes **510a**.

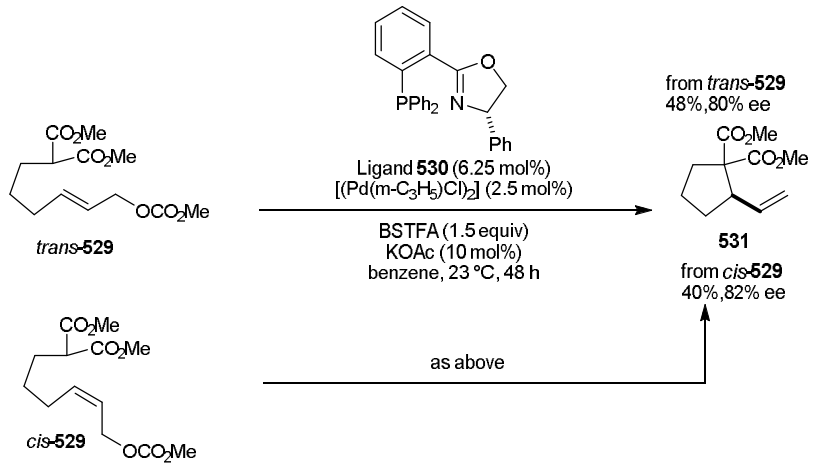
In order to determine which is the more reactive nitroalkene, two stoichiometric reactions were set up separately using *Z*- and *E*-nitroalkenes **510a** as starting materials. The reaction using *Z*-**510a** generated Michael adduct **511a** with only 25% yield (78% ee) for the reaction time of 24 h. In addition, there were two isomerised alkenes, *E*-**512** and *Z*-**512**, observed at 61% and 14% respectively in the reaction mixture. In the reaction using *E*-**510a**, a quantitative yield of the same product was obtained with the same enantioselectivity as with *Z*-**510a**, in only 20 minutes (**Scheme 2.61**). This result indicated that *E*-nitroalkene **510a** is the more reactive isomer of this stereoconvergent process.



[a] Determined by NMR analysis of the crude product using 1,3,5-tetramethoxybenzene as internal standard

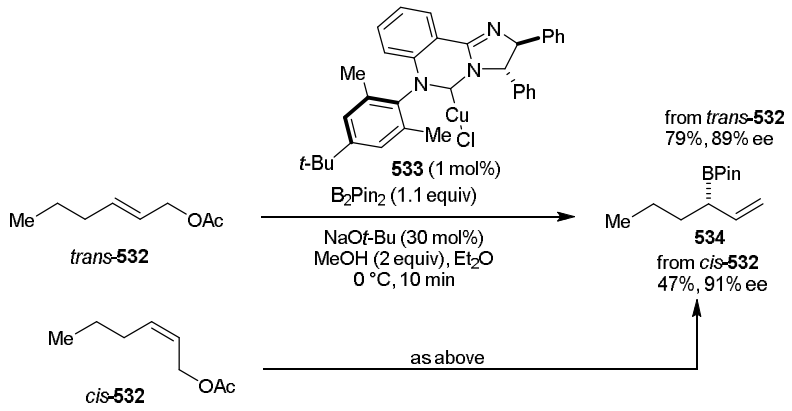
Scheme 2.61: Stoichiometric reactions of *Z*- and *E*-**510a**.

Although stereoconvergent reactions of *E*- and *Z*- alkenes are rare, a few examples of metal-catalysed stereoconvergent enantioselective addition of nucleophiles to alkenes have been reported.[176] For example, in 1996, Koch and Pfaltz[177] studied the intramolecular Pd-catalysed allylic alkylations of 1,3-dicarbonyl compounds using chiral phosphinooxazoline ligands (**Scheme 2.62**). It was proposed that the reaction pathway involves a rapid equilibration of allylpalladium intermediates, with the enantioselectivity determined in the subsequent slow cyclisation step.



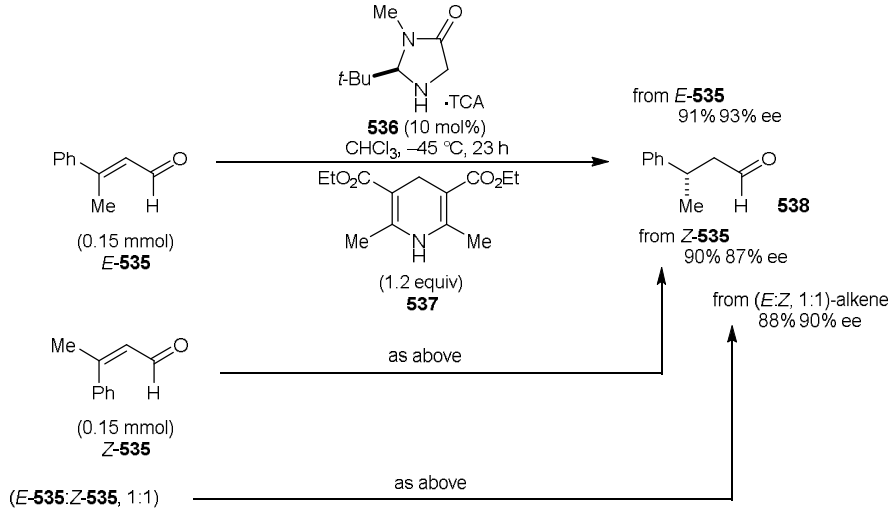
Scheme 2.62: Palladium-catalysed intramolecular allylic alkylations of 1,3-dicarbonyl compound **529**.[177]

McQuade and co-workers[178] reported the enantioselective synthesis of chiral α-substituted allylboronates from allylic ethers using a 6-NHC-Cu(I) catalyst (**Scheme 2.63**). Both *trans*- and *cis*-alkenes or a *trans*-/*cis*-alkene mixture provided chiral products with the same absolute configuration (without showing *trans*-*cis* isomerisation by NMR analysis of *cis*-starting material). Moreover, this stereoconvergent reaction occurred with high yields, high ee, high S_N2' selectivity, and exhibited wide functional group tolerance. After monitoring the reaction by GC and ^{1}H NMR spectroscopy using a 1:1 *trans*-/*cis*- mixture of alkenes, they observed that the reaction of *trans*-**532** was faster than that of *cis*-**532**. On the basis of this result, they speculated that the *trans*-**532** has a lower-barrier transition state than the *cis*-**532** and that the catalyst reacts with the same face of the *trans*- and *cis*-alkenes.



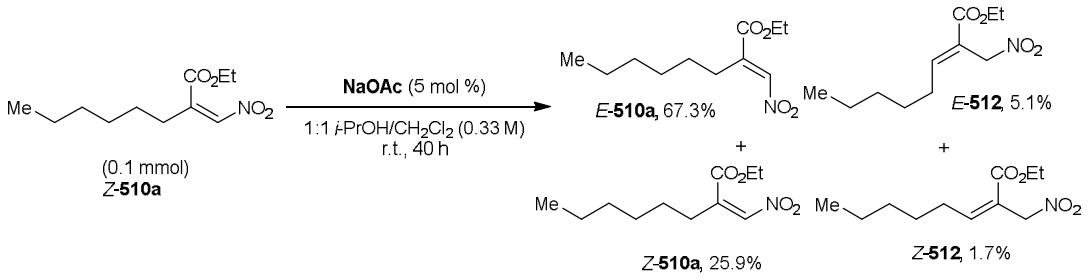
Scheme 2.63: Stereoconvergent synthesis of chiral α-substituted allylboronates from allylic ethers using a 6-NHC-Cu(I) catalyst **533**.[178]

Organocatalysis has also been reported in stereoconvergent reactions of alkene electrophiles.[179] MacMillan and co-workers[180] developed the first enantioselective organocatalytic hydride reduction of enal-olefins with chiral amine catalysts using Hantzsch esters as a hydride source (**Scheme 2.64**). It was suggested that the origin of stereoconvergence arises from catalyst accelerated *E*-*Z* isomerisation prior to selective hydride reduction of the *E*-olefin.



Scheme 2.64: Organocatalytic hydride reduction of *E*-and *Z*-enals **535**.[180]

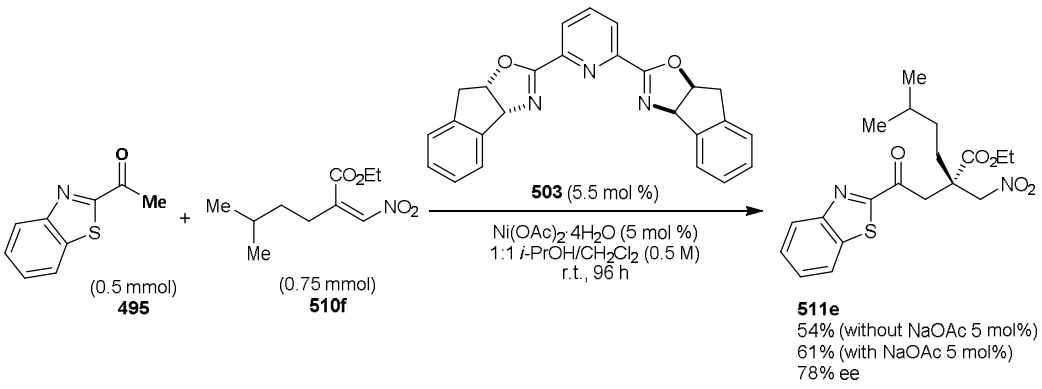
At this point, it was clear that the isomerisation of the nitroalkene is problematic for the reaction yield. Another question regarding this result was whether the catalyst (metal−ligand complex) causes unwanted isomerisation, or only base (AcO^-). To determine this, a weak base, NaOAc, was used instead of the nickel catalyst and the reaction was run for 40 h (**Scheme 2.65**). As before, four compounds were detected in the crude mixture in a different ratio from the use of nickel-ligand complex catalyst in **Scheme 2.56**. The result suggested that this is a base-mediated isomerisation.



[a] yields were relative to total nitroalkene signals.

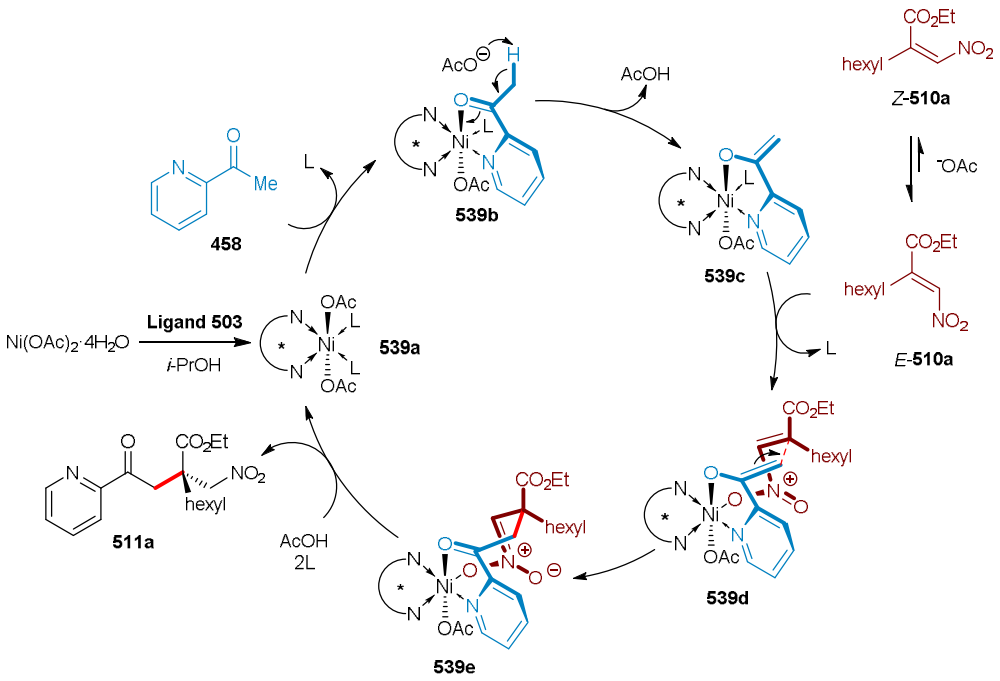
Scheme 2.65: NaOAc mediates isomerisation of nitroalkene *Z*-**510a**.[a]

NaOAc gave a higher ratio of nitroalkenes *Z*-**510a** and *E*-**510a** (67.3% and 25.9% respectively) and a lower ratio of alkenes *E*-**512** and *Z*-**512** (5.1% and 1.7%) than when $Ni(OAc)_2 \cdot 4H_2O$ was used. From this observation, it was postulated that NaOAc would improve the reaction yield because it generates the more reactive nitroalkene *Z*-**510a** *in situ*. To test this hypothesis, compound **511e** was resynthesised by adding 5.0 mol% of NaOAc in the reaction in addition to the catalyst. Fortunately, the yield was improved significantly and the ee remained the same (**Scheme 2.66**).



Scheme 2.66: NaOAc as a yield-improving compound for enantioselective Michael reaction.

On the basis of the results mentioned above, a possible catalytic cycle for these reactions, using 2-acetylpyridine (**458**) and nitroalkene **510a** for illustrative purposes, is shown in **Scheme 2.67**. Presumably, coordination of 2-acetylpyridine (**458**) to the nickel catalyst allows acetate anion (AcO^-) to deprotonate the α-proton of the acetyl group to generate the nucleophile nickel enolate complex **539c**. In the presence of base (AcO^-), *Z*-nitroalkene **510a** undergoes isomerisation to generate *E*-nitroalkene **510a**, which is the reactive electrophile. This electrophile engages in ligand exchange with the complex **539c**. It is believed that the Michael addition proceeds in a way that minimises unfavourable steric interactions between the alkene and ligand to give complex **539e**, which is then protonated through proton transfer from AcOH to release the product and regenerate the catalyst **539a**.



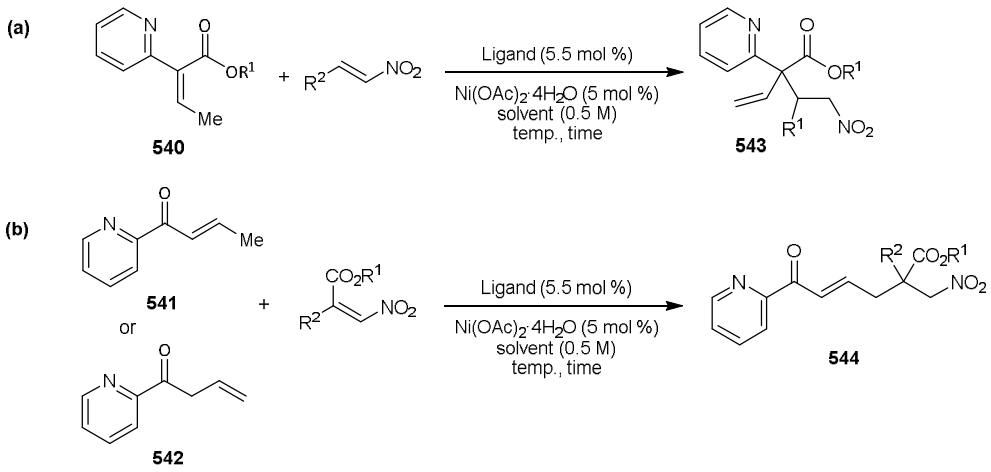
Scheme 2.67: Proposed mechanism.

2.8 Conclusion and Future Studies

In summary, Michael additions of azaarenes to nitroalkenes have been investigated by using a chiral nickel(II)−*bis*(oxazoline) complex. The process is tolerant of a range of azaarene pronucleophiles and nitroalkene electrophiles, and the reactions proceed under mild, experimentally convenient conditions. Aromatic nitroacrylates react smoothly to give products bearing all carbon quaternary stereocentres with high yields and excellent enantioselectivities. However, aliphatic nitroacrylates only give products with moderate to high yields and selectivities. Although nitroalkenes with acyl and trifluoromethyl substituents give products with reasonable yields and enantioselectivities, the nitroalkene with phosphonate ester generates product in very low yield.

Further investigations of this isomerisation chemistry will be a Michael addition of azaarenes containing unsaturated groups in order that varieties of new products can be explored. For instance, with *α,β*-unsaturated carbonyl compound **540** as starting

material, the complex product **543** could be accessed (**Scheme 2.68(a)**). Interestingly, this product has two contiguous stereogenic centres. Moreover, one carbon is a quaternary carbon having four different functional groups (pyridyl, vinyl, carbonyl and alkyl) attached. The other two azaarenes **541** and **542** are also interesting because they could generate chiral all-carbon quaternary adducts containing *α*,*β*-unsaturated carbonyl and azaarene in their structures (**Scheme 2.68(b)**).



Scheme 2.68: New potential heteroarenes.

Not only new azaarenes, but also new nitroalkenes will receive considerable attention. As mentioned in the previous section, *β*-methyl *β*-phenyl-nitroalkene **490** was unsuccessful (see **Scheme 2.54**). However, *β*-heteroaryl *β*-alkylnitroalkene **545** and *β*,*β*-diarylnitroalkene **546** could give chiral products. Also nitrodiene **547** is worth studying as it could afford an interesting product as well as pyridine-*N*-oxide substrate **548**.

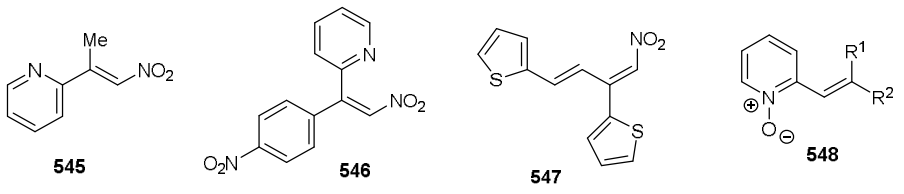


Figure 2.8: New potential nitroalkenes.

3. Experimental

General information

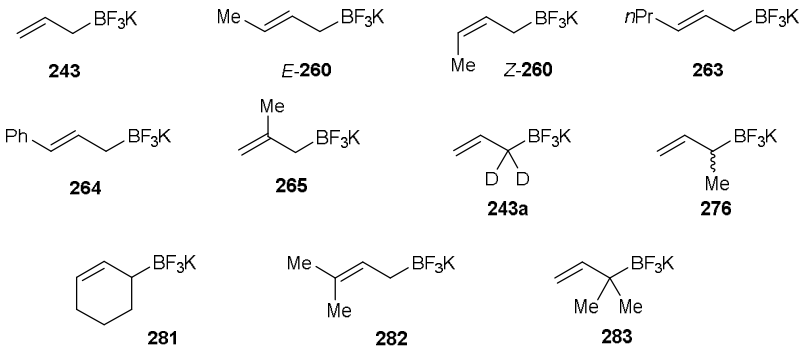
Unless otherwise stated, all commercially available reagents were used without further purification. Solvents were dried and purified by passage through activated alumina columns using a solvent purification system. Unless specified otherwise, all of non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried glassware. Microwave-assisted reactions were carried out in thick-wall glass vials using a Biotage Initiator. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualised by UV light at 254 nm, and subsequently developed using potassium permanganate, vanillin or ninhydrin solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron) employing the method of Still and co-workers.[181] Melting points were recorded on a Gallenkamp or Griffin melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Shimadzu IRAffinity-1 instrument. All ^{1}H NMR spectra were recorded on a Bruker AVA400 (400 MHz), a Bruker AVA500 (500 MHz) or a Bruker AVA600 (600 MHz). Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (Acetone-d_6 at 2.05 ppm, $CDCl_3$ at 7.27 ppm, CD_3OD at 3.31 ppm and DMSO-d_6 at 2.50 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad), m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA400 (100.6 MHz) spectrometer, a Bruker AVA500 (125.8 MHz) spectrometer or a Bruker AVA600 (150.8 MHz) spectrometer. Assignments were made using the DEPT sequence with secondary pulses at 90º and 135º. For proton-decoupled ^{19}F NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of $CFCl_3$. For proton-decoupled ^{31}P NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (aqueous 85% H_3PO_4 at 161.9 MHz with respect to tetramethylsilane at

400.00 MHz). Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter. Chiral HPLC analysis was performed on an Agilent 1100 instrument using 4.6 x 250 nm columns. Authentic racemic samples of products for chiral HPLC assay determinations were obtained using $[Rh(cod)Cl]_2$ (2.5 mol%) as an achiral precatalyst (or $Ni(OAc)_2 \cdot 4H_2O$/ *rac*-**498** for the nickel catalysed Michael addition project). High-resolution mass spectra were recorded using electrospray ionisation (ESI) or electron impact (EI) techniques at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLTspectrometer at the School of Chemistry, University of Edinburgh.

3.1 Enantioselective Rhodium-Catalysed Addition of Allylboron Reagents to Cyclic Imines

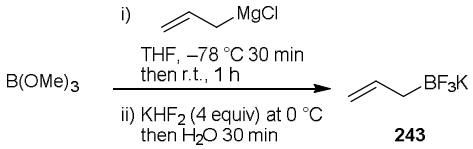
3.1.1 Preparation of Organoboron Reagents, Chiral Ligands and Rhodium-Catalysts

Organoboron Reagents



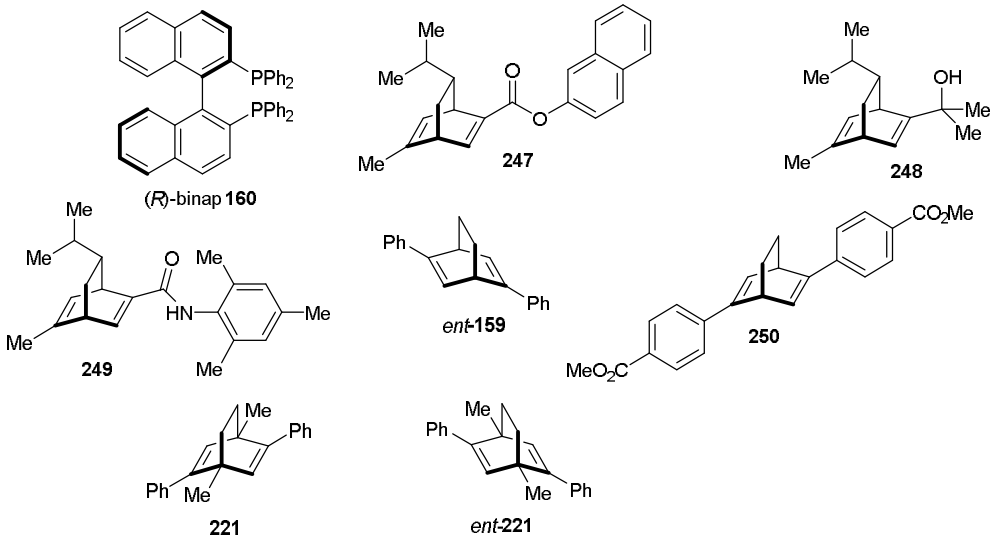
Compounds *E*-**260**,[182] Z-**260**,[182a,183] **263**,[182a,184] **264**,[184,185] **265**,[185] **243a**,[182a] **276**,[185] **281**,[184,185] **282**[182a,184] and **283**[185] were prepared by Hamish B. Hepburn and Dr Yunfei Luo following a slight modification of previously reported procedures. Yields and reaction times reported in this Section are unoptimised.

Potassium allyltrifluoroborate (243)



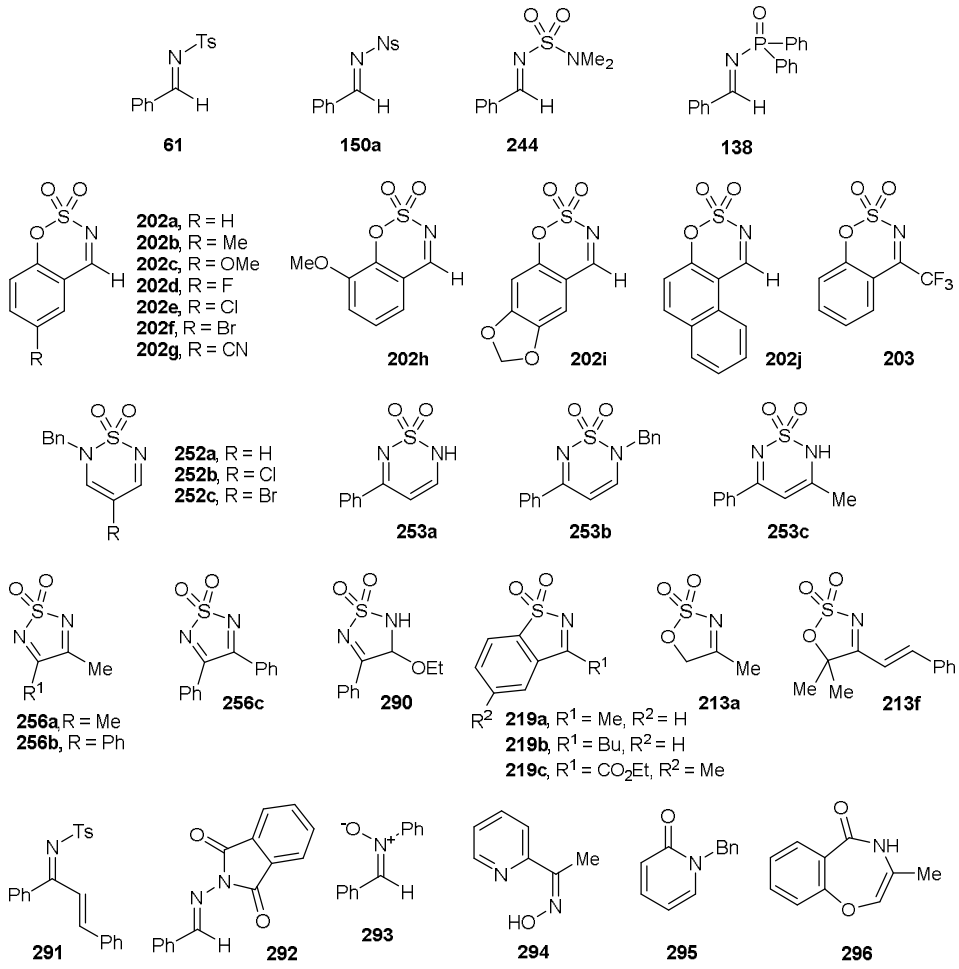
In a modification of a previously reported procedure,[186] to a solution of $B(OMe)_3$ (6.44 g, 62.0 mmol) in THF (42 mL) was added dropwise allylmagnesium chloride (2.0 M in THF, 25 mL, 50.0 mmol) at –78 ºC. The mixture was stirred at this temperature for 30 min then the ice bath was removed. The yellow solution with a white precipitate was allowed to reach room temperature over a 1 h period. Then, it was cooled to 0 ºC and KHF_2 (19.5 g, 250 mmol) was added in one portion. This was followed by the dropwise addition of H_2O (27 mL). The mixture was stirred at room temperature for 30 min and then concentrated *in vacuo* until no water remains. The crude solid was extracted with hot acetone (4 x 100 mL). The extracts were filtered through a Celite pad. The filtrate was concentrated to afford a white solid. This solid was purified by dissolving in the minimum amount of hot acetone (5 mL), followed by cooling to room temperature and precipitation with Et_2O. The precipitate was collected and dried under high vacuum to yield 2.56 g (35%) of a powdery white solid. **^{1}H NMR** (500 MHz, Acetone-d_6) δ (1H, dq, *J* = 10.0, 7.9 Hz, C**H**=), 4.70-4.62 (1H, m, C**H**$_2$=), 4.55 (1H, dd, *J* = 10.0, 2.6 Hz, C**H**$_2$=), 1.15-1.02 (2H, m, C**H**$_2$); **^{13}C NMR** (125.8 MHz, Acetone-d_6) δ 142.6 (CH), 109.4 (CH_2). The NMR data were in agreement with the literature.[186]

Chiral Ligands and Rhodium-Catalysts



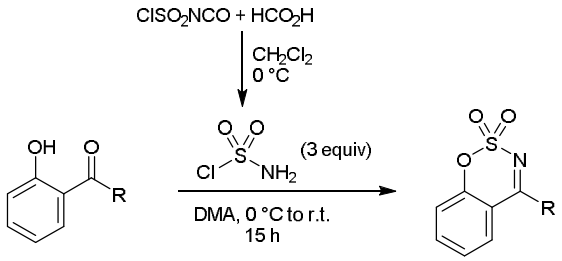
(*R*)-Binap **160** was purchased from Acros. Diene *ent*-**159** was purchased from Manchester Organics. Dienes **247**,[73] **248**,[73] and *ent*-**221**[94] were prepared by Hamish B. Hepburn according to previously reported procedures. Diene **249**[129] was prepared by Iain D. Roy according to previously reported procedure. Diene **221**,[94] **250**,[187] Catalysts $[Rh((R)\text{-}\mathbf{221})Cl]_2$[94] and $[Rh(\textit{ent}\text{-}\mathbf{221})Cl]_2$[94] were were prepared by Dr. Yunfei Luo according to previously reported procedures. Yields and reaction times reported in this Section are unoptimised.

3.1.2 The Synthesis of Imines and Related Substrates

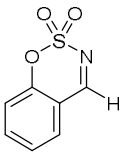


Compounds **61**,[188] **150a**,[189] and **202b**-**202j**[81] were prepared by Dr Yunfei Luo according to previously reported procedures. Compounds **244**[188] and **138**[190] were prepared by Dr Daneil Best according to previously reported procedures. Compounds **256a**[191] and **213a**[192] **219a**,[193] **219b**,[194] **219c**[78] were prepared by Hamish B. Hepburn according to general reported procedures. Yields and reaction times reported in this Section are unoptimised.

General Procedure A: Synthesis of 1,2,3-Benzoxathiazine-2,2-dioxides



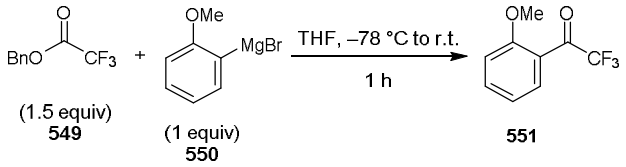
In a modification of a previously reported procedure,[195] to a solution of chlorosulfonyl isocyanate (21.14 g, 150 mmol) in dry dichloromethane (100 mL) at 0 ºC was added solution of formic acid (6.87 g, 150 mmol) in dry dichloromethane (40 mL) dropwise (**Caution**: the apparatus should be well vented as gas evolution ensues upon addition of formic acid). The mixture was stirred for 1 h at 0 ºC. The cold dichloromethane was then removed with the aid of cannula. The resulting solid was dried *in vacuo* to give sulfamyl chloride (H_2NSO_2Cl) in quantitative yield. Then, to a solution of appropriate aldehydes or ketones (50 mmol) in DMA (150 mL) at 0 ºC was transferred solid sulfamyl chloride (150 mmol) (**Caution**: a mild exotherm is generally noted upon combination of these reagents). The mixture was allowed to warm up to ambient temperature and stirred overnight. The reaction was quenched by a pH 7 NaH_2PO_4/NaOH aqueous buffer solution (100 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed successively with H_2O (2 x 20 mL) and saturated NaCl (aq) (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography to afford the imine substrates.



1,2λ^6,3-Benzoxathiazine-2,2-dione (202a). The title compound was prepared according to General Procedure A from salicylaldehyde (6.11 g, 50 mmol) and was purified by column chromatography (20-60% EtOAc/Hexane) to afford the imine **202a** as a white solid (8.31 g, 91%). R_f = 0.40 (40% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.68 (1H, s, C**H**=N), 7.77 (1H, ddd, *J* = 8.4, 7.5, 1.6 Hz, Ar**H**), 7.70 (1H, dd, *J* = 7.7, 1.5 Hz, Ar**H**), 7.44 (1H, td, *J* = 7.6, 1.0 Hz, Ar**H**), 7.32-7.29 (1H,m, Ar**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$)

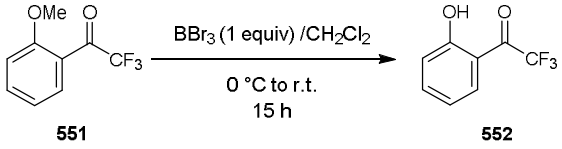
δ 167.6 (CH), 154.2 (C), 137.6 (CH), 130.8 (CH), 126.2 (CH), 118.6 (CH), 115.4 (C). The NMR data were in agreement with the literature.[195b]

2,2,2-Trifluoro-2-methoxyacetophenone (551)



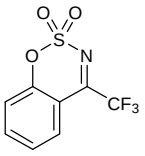
In a modification of a previously reported procedure,[196] to a solution of phenyltrifluoro acetate (**549**) (15 g, 80 mmol) in THF at –78 ºC (40 mL) was dropwise added a THF solution of 4-methoxyphenylmagnesium bromide (**550**) (1.0 M, 53 mL, 53 mmL). After stirring for 1 h at this temperature, the reaction was quenched with sat. NH_4Cl (50 mL) and the whole mixture was extracted with EtOAc (3 x 100 mL). The obtained organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (4-12% EtOAc/hexane) and distilled to give product **551** as a colourless oil (5.26 g, 49%). R_f = 0.26 (10% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70-7.64 (1H, m, Ar**H**), 7.63-7.56 (1H, m, Ar**H**), 7.09-6.96 (2H, m, Ar**H**), 3.92 (3H, s, OC**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 183.0 (q, J = 36.4 Hz, C), 159.8 (C), 135.9 (CH), 131.3 (CH), 121.7 (C), 120.7 (CH), 116.2 (q, J = 291.0 Hz, CF_3), 112.1 (CH), 55.8 (CH_3); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –74.1 ppm. The NMR data were in agreement with the literature.[196]

2-Trifluoroacetylphenol (552)



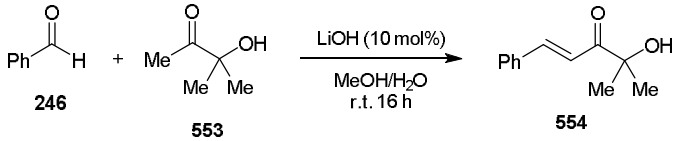
In a modification of a previously reported procedure,[195b] to a solution of ketone **551** (5.26 g, 25.77 mmol) in 20 mL of dichloromethane cooled to –78 ºC was added

dropwise of a solution of BBr_3 (1.0 M, 24 mL, 24 mmol). The mixture was warmed slowly to ambient temperature and stirred for 10 h. The mixture was then cooled to 0 ºC and carefully quenched by the slow addition of H_2O (15 mL). The mixture was extracted with dichloromethane (3 x 50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% EtOAc/Hexane) to afford the corresponding ketone **552** as a colourless oil (2.29 g, 47%). R_f = 0.46 (30% EtOAc/Hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.08-11.07 (1H, m, O**H**), 7.86-7.82 (1H, m, Ar**H**), 7.67-7.62 (1H, m, Ar**H**), 7.10 (1H, dd, *J* = 8.5, 0.8 Hz, Ar**H**), 7.02 (1H, ddd, *J* = 8.3, 7.2, 1.1 Hz, Ar**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 184.4 (q, *J* = 35.3 Hz, C), 164.6 (C), 139.0 (CH), 130.7 (q, *J* = 3.8 Hz, CH), 120.0 (CH), 119.1 (CH), 116.4 (q, *J* = 289.9 Hz, CF_3), 113.9 (C); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –70.3 ppm. The NMR data were in agreement with the literature.[195a]

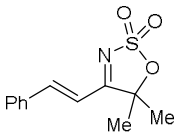


4-Trifluoromethyl-1,2,3-benzoxathiazine-2,2-dioxide (203). The title compound was prepared according to a slight modification of General Procedure A from 2-trifluoroacetylphenol (**552**) (2.03g, 10.68 mmol) to afford a yellow solid (1.72 g, 64%). R_f = 0.25 (30% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98-7.40 (1H, m, Ar**H**), 7.87 (1H, ddd, *J* = 8.9, 7.6, 1.5 Hz, Ar**H**), 7.54-7.49 (1H, m, Ar**H**), 7.44 (1H, dd, *J* = 8.4, 0.8 Hz, Ar**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 162.1 (dd, *J* = 75.3, 37.6 Hz, C), 155.1 (C), 138.8 (CH), 128.5 (q, *J* = 3.2 Hz, CH), 126.7 (CH), 119.6 (CH), 118.3 (q, *J* = 281.4 Hz, CF_3), 111.7 (C); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –67.0 ppm. The NMR data were in agreement with the literature.[195a]

1-(*E*)-4-Hydroxy-4-methyl-1-phenylpent-1-en-3-one (554)

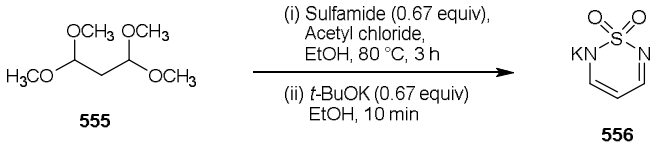


In a modification of a previously reported procedure,[197] a mixture of 3-hydroxy-3-methyl-2-butanone (**553**) (2.12 g, 20.75 mmol), benzaldehyde (**246**) (4.4 g, 41.52 mmol) and LiOH (96 mg, 4 mmol) in methanol (60 mL) and H_2O (20 mL) was stirred overnight at room temperature. Methanol was then removed under reduced pressure and H_2O (80 mL) was added. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (5% EtOAc/Hexane) to afford a yellow oil (2.83 g, 72%). R_f = 0.30 (30% EtOAc/Hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (1H, d, *J* = 15.7 Hz, C**H**=), 7.64-7.58 (2H, m, Ar**H**), 7.47-7.38 (3H, m, Ar**H**), 7.06 (1H, d, *J* = 15.7 Hz, C**H**=), 4.01 (1H, s, O**H**), 1.48 (6H, s, 2 x C**H**$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 202.4 (C), 145.5 (CH), 134.2 (C), 131.0 (CH), 129.0 (2 x CH), 128.6 (2 x CH), 118.4 (CH), 75.5 (C), 26.4 (2 x CH_3). The NMR data were in agreement with the literature.[197]



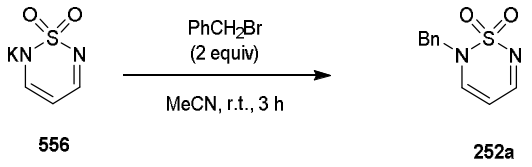
5,5-Dimethyl-4-[(*E*)-2-phenylethenyl]-5*H*-1,2λ^6,3-oxathiazole-2,2-dione (213f). The title compound was prepared according to a slight modification of General Procedure A (in that pyridine (4.5 equiv) was added and the solvent was acetonitrile instead of DMA) from **554** (515 mg, 2.7 mmol) and was purified by column chromatography (20% EtOAc/hexane) to give a white solid (162 mg, 24%). **m.p.** 146-148 ºC (EtOAc/Hexane); R_f = 0.34 (30% EtOAc/Hexane); **IR** (film) 2954, 1629, 1560, 1360, 1197, 1178, 1111, 966, 862, 656 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (1H, d, *J* = 15.7 Hz, C**H**=), 7.65-7.62 (2H, m, Ar**H**), 7.54-7.45 (3H, m, Ar**H**), 6.63 (1H, d, *J* = 15.7 Hz, C**H**=), 1.75 (6H, s, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 180.7 (C), 149.5 (CH), 133.5 (C), 132.2 (CH), 129.3 (2 x CH), 129.0 (2 x CH), 112.0 (CH), 93.8 (C), 25.0 (2 x CH_3); **HRMS** (ESI) Exact mass calcd. for $C_{12}H_{14}NO_3S$ $[M+H]^+$: 252.0689, found 252.0697.

1,2,6-Thiadiazine-1,1-dioxide potassium salt (556)



In a modification of a previously reported procedure,[198] to stirred ethanol (30 mL) was gently dropped acetyl chloride (0.5 mL) and the mixture was stirred for 30 min. To this solution, sulfamide (431 mg, 4.48 mmol) and 1,1,3,3-tetramethoxypropane (**555**) (1.1 g, 6.72 mmol) were added. The mixture was heated at reflux for 3 h. and then evaporated to dryness *in vacuo*. The residue was dissolved in ethanol (30 mL). Potassium *tert*-butoxide (502 mg, 4.50 mmol) was added at ambient temperature before the reaction mixture was heated at 80 ºC for 10 min, filtered whilst hot, cooled and partially evaporated. The solution was kept in refrigerator for 24 h and the precipitated product **556** was filtered and washed with diethyl ether (10 mL) to afford the salt product **556** as a pale yellow solid (494 mg, 65%). **^{1}H NMR** (500 MHz, CD_3OD) δ 7.56 (2H, d, *J* = 5.3 Hz, NC**H** and C**H**=N), 5.54 (1H, t, *J* = 5.3 Hz, NCH=C**H**); **^{13}C NMR** (125.8 MHz, CD_3OD) δ 159.0 (2 x CHN), 98.4 (CH). The NMR data were in agreement with the literature.[198]

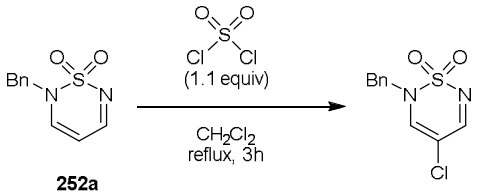
2-Benzyl-1,2,6-thiadiazine-1,1-dioxide (252a)



In a modification of a previously reported procedure,[198] benzyl bromide (1.14 g, 6.64 mmol) was added to the solution of 1,2,6-thiadiazine-1,1-dioxide potassium salt (**556**) (564 mg, 3.32 mmol) in acetonitrile 40 mL. The mixture was stirred at room temperature for 3 h and then the solvent was evaporated to give a crude product. The residue was purified by silica gel chromatography (40% EtOAc/hexane) to afford **252a** as a white

solid (544 mg, 74%). R_f = 0.21 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (1H, dd, *J* = 4.4, 2.5 Hz, C**H**=N), 7.44-7.37 (5H, m, Ar**H**), 7.13 (1H, dd, *J* = 7.2, 2.5 Hz, NC**H**=), 5.82 (1H, dd, *J* = 7.2, 4.4 Hz, NCH=C**H**), 4.95 (1H, s, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 162.4 (C=N), 147.7 (CH), 133.6 (C), 129.3 (2 x CH), 129.1 (CH), 128.8 (2 x CH), 100.2 (CH), 52.9 (CH_2). The NMR data were in agreement with the literature.[198]

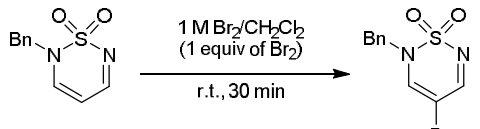
2-Benzyl-4-chloro-1,2,6-thiadiazine-1,1-dioxide (252b)



252a **252b**

In a modification of a previously reported procedure,[198] sulfuryl chloride (267 mg, 1.98 mmol) was added to a solution of 2-benzyl-1,2,6-thiadiazine-1,1-dioxide (**252a**) (398 mg, 1.80 mmol) in dichloromethane (8 mL). The mixture was heated at reflux for 3 h, and then the solvent was evaporated to give a crude product. The residue was purified by silica gel chromatography (40% EtOAc/hexane) to afford **252b** as a pale yellow solid (391 mg, 85%). R_f = 0.54 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (1H, d, *J* = 3.1 Hz, C**H**=N), 7.47-7.37 (5H, m, Ar**H**), 7.18 (1H, d, *J* = 3.1 Hz, NC**H**=), 4.93 (2H, s, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 161.8 (CH=N), 144.7 (CH), 133.0 (C), 129.5 (3 x CH), 128.8 (2 x CH), 107.5 (C), 53.6 (CH_2). The NMR data were in agreement with the literature.[198]

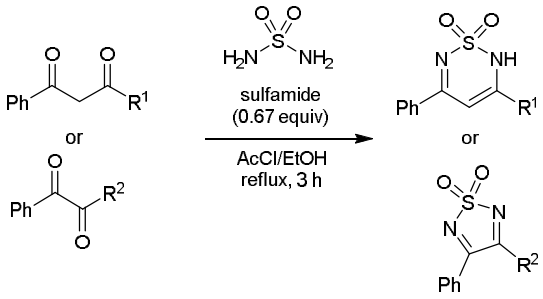
2-Benzyl-4-bromo-1,2,6-thiadiazine-1,1-dioxide (252c)



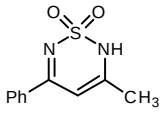
252a **252c**

In a modification of a previously reported procedure,[198] bromine in dichloromethane (1 M, 3.6 mL, 3.60 mmol) was added dropwise to a solution of 2-benzyl-1,2,6-thiadiazine-1,1-dioxide (**252a**) (800 mg, 3.56 mmol) in dry dichloromethane (10 mL). The mixture was stirred at ambient temperature for 30 min before the solvent was evaporated. The residue was purified by silica gel chromatography (40% EtOAc/hexane) to afford the pure product **252c** as a white solid (837 mg, 78%). R_f = 0.59 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 2.9 Hz, C**H**=N), 7.47-7.37 (5H, m, Ar**H**), 7.24 (1H, d, *J* = 2.9 Hz, NC**H**=), 4.93 (1H, s, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 163.1 (C=N), 146.9 (CH), 133.0 (C), 129.5 (2 x CH), 129.4 (CH), 128.8 (2 x CH), 92.3 (C), 53.6 (CH_2). The NMR data were in agreement with the literature.[198]

General Procedure B: Synthesis of 1,2,6-Thiadiazine 1,1-Dioxides and 1,2,5-Thiadiazole 1,1-Dioxides



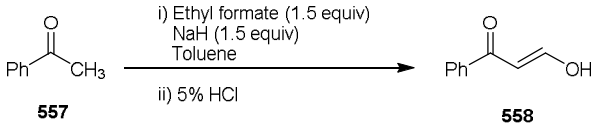
In a modification of a previously reported procedure,[191,199] to stirred ethanol (10 mL) was gently dropped acetyl chloride (0.50 mL). After stirring at room temperature for 10 min sulfamide (192 mg, 2.00 mmol) and dicarbonyl compound (3.00 mmol) were added. The mixture was heated at reflux for 3 h and then concentrated *in vacuo*. The residue was triturated with several portions of hexane and filtered to afford 1,2,6-thiadiazine 1,1-dioxides or 1,2,5-thiadiazole 1,1-dioxides.



5-Phenyl-3-methyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide (253c). The title compound was prepared according to General Procedure B from

1-phenyl-1,3-butanedione (485 mg, 3.00 mmol) to obtain a pale yellow solid (431 mg, 98%). **m.p.** (EtOH) 173-175 ºC (lit. 174 ºC); R_f = 0.28 (CH_2Cl_2; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.95 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.59 (1H, t, *J* = 7.3 Hz, Ar**H**), 7.52 (2H, t, *J* = 7.6 Hz, Ar**H**), 6.55 (1H, s, C**H**=), 3.85 (1H, s, N**H**), 2.55 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, DMSO-d_6) δ 166.0 (C=N), 161.4 (=CN), 135.0 (C), 132.8 (CH), 129.4 (2 x CH), 128.0 (2 x CH), 96.7 (CH), 21.2 (CH_3). The data were in agreement with the literature.[200]

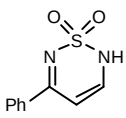
3-Oxo-3-phenylpropanol (558)



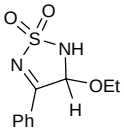
557 **558**

In a modification of a previously reported procedure,[201] acetophenone (**557**) (2.41 g, 0.02 mol) was dissolved in dry toluene 80 mL and the mixture was cooled to 0 ºC. Sodium hydride (1.20 g, 0.03 mol) was added to the solution and the mixture was stirred for 30 min. Ethyl formate (2.22 g, 0.03 mol) was then added dropwise to the reaction mixture which was maintained at <5 ºC, after the addition the reaction mixture was stirred for another 2 h then allowed to warm to room temperature, and stirred for 15 h. Water (100 mL) was added to the slurry, and the reaction was stirred for an additional 30 min and then partitioned between organic layer and aqueous. The aqueous layer was extracted with dichloromethane (2 x 50 mL). This organic extract was discarded. The aqueous phase was then acidified with 5% hydrochloric acid and extracted with dichloromethane (3 x 50 mL). This extract was washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give compound **558** as a yellow oil (1.61 g, 54 %). R_f = 0.49 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 15.33 (1H, br s, *J* = 1.8 Hz, O**H**), 8.29 (1H, d, *J* = 4.2 Hz, C**H**=), 7.93-7.90 (2H, m, Ar**H**), 7.58-7.54 (1H, m, Ar**H**), 7.49-7.45 (2H, m, Ar**H**), 6.23 (1H, d, *J* = 4.2 Hz, C**H**=). **^{13}C NMR** (125.8 MHz, $CDCl_3$): δ = 187.8 (C=O), 178.6 (CH), 134.9 (C), 132.8 (CH),

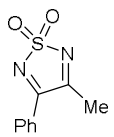
128.6 (2 x CH), 127.3 (2 x CH), 98.2 (CH). The NMR data were in agreement with the literature.[201]



5-Phenyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide (253a). The title compound was prepared according to a slight modification of General Procedure B from 3-oxo-3-phenylpropanol (**558**) (240 mg, 1.62 mmol) to obtain a yellow solid (145 mg, 64%). **m.p.** (EtOAc/hexane) 130-132 ºC; R_f = 0.18 (EtOAc); **IR** (film) 3132 (NH), 1600, 1506, 1489, 1433, 1398, 1328, 1172, 761, 740 cm^{-1}; **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.98-7.95 (2H, m, Ar**H**), 7.81 (1H, d, *J* = 7.0 Hz, NC**H**=), 7.63-7.58 (1H, m, Ar**H**), 7.55-7.51 (2H, m, Ar**H**), 6.57 (1H, d, *J* = 7.0 Hz, C**H**=), 3.76 (1H, s, N**H**); **^{13}C NMR** (125.8 MHz, DMSO-d_6) δ 167.3 (C=N), 149.3 (=CHN), δ 135.0 (C), 133.1 (CH), 129.5 (2 x CH), 128.1 (2 x CH), 96.6 (CH); **HRMS** (ESI) Exact mass calcd. for $C_9H_8N_2O_2SNa$ $[M+Na]^+$: 231.0199, found 231.0202.

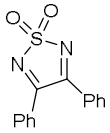


3-Ethoxy-4-phenyl-1,2,5-Δ^2-thiadiazolidine 1,1-dioxide (290).The title compound was prepared according to a slight modification of General Procedure B from phenylglyoxal monohydrate (484 mg, 3.18 mmol) to obtain a pale yellow solid (476 mg, 94%). **m.p.** (EtOAc/hexane) 106-108 ºC; R_f = 0.24 (40% EtOAc/hexane); **IR** (film) 3310 (NH), 1597, 1570, 1450, 1352, 1176, 1097, 982, 810, 739 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10-8.07 (2H, m, Ar**H**), 7.68-7.64 (1H, m, Ar**H**), 7.53-7.48 (2H, m, Ar**H**), 6.22 (1H, d, *J* = 5.2 Hz, N**H**), 5.95 (1H, d, *J* = 5.2 Hz, C**H**), 3.77-3.70 (1H, m, C**H**$_2$), 3.55-3.48 (1H, m, C**H**$_2$), 1.19 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 174.5 (C=N), 135.0 (CH), 130.4 (2 x CH), 129.1 (2 x CH), 127.9 (C), 88.4 (CH), 62.9 (CH_2), 14.7 (CH_3); **HRMS** (ESI) Exact mass calcd. for $C_{10}H_{13}N_2O_3SNa$ $[M+Na]^+$: 241.0641, found 241.0652.



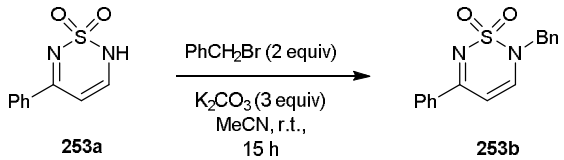
3-Phenyl-4-methyl-1,2,5-thiadiazole 1,1-dioxide (256b). The title compound was prepared according to a slight modification of General Procedure B from 1-phenyl 1,2-propanedione (208 mg, 1.40 mmol) to obtain a pale yellow solid (186 mg, 96%). **m.p.** (EtOAc/hexane)138-140 ºC (lit. 135 ºC); R_f =0.52 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 7.5 Hz,

Ar**H**), 7.73 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.61 (2H, t, *J* = 7.8 Hz, Ar**H**), 2.78 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 167.7 (C=N), 165.7 (C=N), 134.3 (CH), 130.2 (2 x CH), 129.4 (2 x CH), 127.3 (C), 18.8 (CH_3). The data were in agreement with the literature.[191,199]



3,4-Diphenyl-1,2,5-thiadiazole 1,1-dioxide (256c). The title compound was prepared according to a slight modification of General Procedure B from 1,2-diphenylethane 1,2-dione (710 mg, 3.38 mmol) to obtain a white solid (228 mg, 84%). **m.p.** (EtOH) 246-248 ºC (lit. 248 ºC) R_f = 0.58 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69-7.66 (2H, m, Ar**H**), 7.59-7.57 (4H, m, Ar**H**), 7.49-7.45 (4H, m, Ar**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.6 (2 x C=N), 134.0 (2 x CH), 130.8 (4 x CH), 128.7 (4 x CH), 128.0 (2 x C). The data were in agreement with the literature.[199,202]

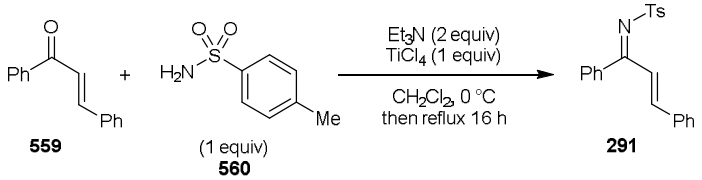
2-Benzyl-5-phenyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide (253b)



5-Phenyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide **(253a**) (41 mg, 0.20 mmol) and potassium carbonate (84 mg, 0.60 mmol) were dissolved in acetonitrile (12 mL) and the mixture was stirred at room temperature for 30 min. Benzyl bromide (68 mg, 0.40 mmol) was added to the solution and the mixture was stirred overnight and then concentrated *in vacuo*. The residue was recrystallised (hexane/EtOAc) to afford the pure product **253b** as a white solid (52 mg, 87%). **m.p.** 144-146 ºC (CH_2Cl_2); R_f = 0.27 (40% EtOAc/hexane); **IR** (film) 3095, 1599, 1575, 1508, 1485, 1337, 1277, 1227, 1173, 744 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.0-7.97 (2H, m, Ar**H**), 7.58-7.54 (1H, m, Ar**H**), 7.50-7.45 (2H, m, Ar**H**), 7.44-7.37 (5H, m, Ar**H**), 7.21 (1H, d, *J* = 7.6 Hz, NC**H**=), 6.38 (1H, d, *J* = 7.6 Hz, C**H**=CHN), 5.0 (2H, s, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 168.8 (C=N), 147.1 (CH), 134.5 (C), 133.9 (C), 132.9 (CH), 129.3 (2 x CH),

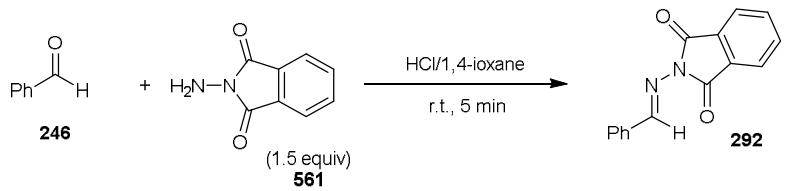
129.0 (CH), 128.8 (4 x CH), 128.2 (2 x CH), 97.9 (CH), 52.5 (CH_2); **HRMS** (ESI) Exact mass calcd. for $C_{16}H_{15}N_2O_7S$ $[M+H]^+$: 299.0849, found 299.0858.

(*E*)-*N*-(1,3-Diphenylallylidene)-4-methylbenzenesulfonamide (291)



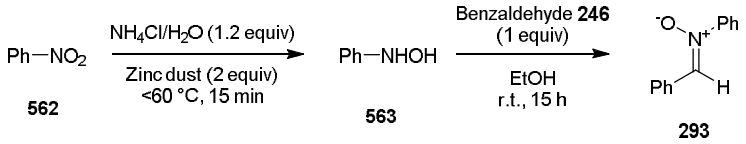
In a modification of a previously reported procedure,[203] to a solution of *trans*-chalcone (**559**) (4.16 g, 20 mmol) in dichloromethane (40 mL), was added *p*-toluene sulphonamide (**560**) (3.42 g, 20 mmol), triethylamine (5.6 mL, 40 mmol) and $TiCl_4$ (2.2 mL, 20 mmol) at 0 ºC under N_2 (g). The reaction mixture was heated at reflux for 16 h. Then it was cooled to room temperature and quenched with brine (20 mL). The aqueous phase was extracted with dichloromethane (3 x 40 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography on silica gel (20% EtOAc/hexane) to afford **291** as a white solid (4.44 g, 61%). R_f = 0.65 (40% EtOAc/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20-8.10 (1H, m, Ar**H**), 7.95 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.72-7.38 (10H, m, Ar**H** and C**H**=), 7.33 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.08 (1H, d, *J* = 16.1 Hz, C**H**=), 2.43 (3H, s, C$\mathbf{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.5 (C), 148.8 (CH), 143.4 (C), 138.7 (C), 137.2 (C), 134.5 (C), 131.9 (CH), 131.1 (CH), 130.2 (2 x CH), 129.4 (2 x CH), 129.0 (2 x CH), 128.7 (2 x CH), 128.3 (2 x CH), 127.2 (2 x CH), 122.5 (CH), 21.5 (CH_3). The NMR data were in agreement with the literature.[203b]

2-[(*E*)-(Phenylmethylidine)amino]-2,3-dihydro-1*H*-isoindole-1,3-dione (292)



In a modification of a previously reported procedure,[204] to a solution of benzaldehyde (**246**) (0.73g, 6.86 mmol) and *N*-aminophthalimide (**561**) (1.06 g, 6.54 mmol) in 1,4-dioxane (20 mL) was added conc. HCl (2 drops) at room temperature. After the mixture was stirred for 5 min, the solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography to afford the pure product **292** as a white solid (1.45 g, 88%). R_f = 0.53 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.41 (1H, s, C**H**=N), 7.95-7.89 (4H, m, Ar**H**), 7.79 (2H, dd, *J* = 5.5, 3.0 Hz, Ar**H**), 7.52-7.44 (3H, m, Ar**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.1 (2 x C), 158.6 (CH), 134.6 (2 x CH), 133.6 (C), 131.7 (CH), 130.3 (2 x C), 128.8 (2 x CH), 128.4 (2 x CH), 123.8 (2 x CH). The NMR data were in agreement with the literature.[204]

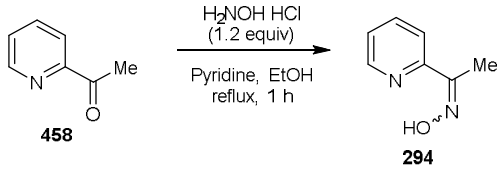
(*Z*)-*N*-Benzylidinebenzenamide oxide (293)



In a modification of a previously reported procedure,[205] to a stirred mixture of nitrobenzene (**562**) (6.2 mL, 60 mmol) and NH_4Cl (3.9 g, 72 mmol) in H_2O 60 mL was slowly added zinc dust (7.8 g, 120 mmol) while maintaining the temperature below 60 ºC. After stirring for 15 min, the reaction mixture was filtered while still warm and the solid was washed with hot water (20 mL). The filtrate was saturated with NaCl and cooled to 0 ºC and the resulting solid was collected and dried. This crude *N*-phenylhydroxylamine was recrystallised from hexane-diethyl ether to give the pure product **563** as a white solid (3.3 g, 30 mmol, 50%). To a stirred solution of *N*-phenylhydroxylamine (**563**) in EtOH was added benzaldehyde (**246**) (3.1 mL, 30 mmol). After overnight stirring at room temperature, the mixture was cooled in ice−water bath and filtered. The collected solid was recrystallised from EtOH to give the title compound **293** (3.1 g, 53 %). R_f = 0.34 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50-8.47 (2H, m, Ar**H**), 7.50-7.48 (2H, m, Ar**H**), 7.39 (1H, s, C**H**=N), 7.23-7.18 (2H, m, Ar**H**), 7.14-7.10 (1H, m, Ar**H**), 6.96-6.93 (3H, m, Ar**H**); **^{13}C NMR**

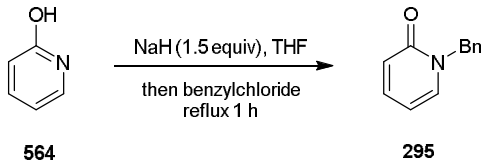
(125.8 MHz, $CDCl_3$) δ 149.9 (C), 133.0 (CH), 131.9 (C), 130.4 (CH), 129.5 (CH), 129.0 (2 x CH), 128.9 (2 x CH), 128.7 (2 x CH), 128.4 (CH), 122.1 (CH). The NMR data were in agreement with the literature.[205]

2-Acetylpyridyloxime (294)



In a modification of a previously reported procedure,[206] to a stirred solution of 2-acetylpyridine (**458**) (1.23 g, 10.15 mmol) and hydroxylamine hydrochloride (0.84 g, 12 mmol) in 60 mL of ethanol was added pyridine (2 g, 25 mmol). The reaction mixture was heated at reflux for 3 h and then cooled down to room temperature. The reaction mixture was evaporated to dryness. The residue was purified by silica gel chromatography (30% EtOAc/hexane) to afford the pure product **294** as a white solid (1.21 g, 90%). R_f = 0.46 (60% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.48 (1H, br s, NO**H**), 8.64 (1H, dd, *J* = 4.8, 0.6 Hz, Ar**H**), 7.85 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.70 (1H, dt, *J* = 7.9, 7.8, 1.8 Hz, Ar**H**), 7.3-7.26 (1H, m, Ar**H**), 2.42 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 156.7 (C=NOH), 154.3 (C=N), 148.9 (CH), 136.5 (CH), 123.7 (CH), 120.6 (CH), 10.8 (CH_3). The NMR data were in agreement with the literature.[206]

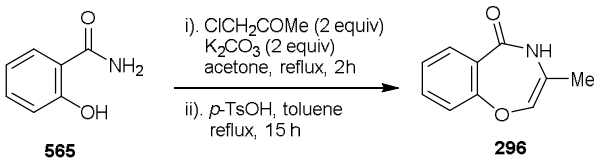
1-Benzyl-1,2-dihydropyridin-2-one (295)



In a modification of a previously reported procedure,[207] a solution of sodium salt of 2-hydroxypyridine in tetrahydrofuran (40 mL) was prepared by the use of 2-hydroxypyridine (**564**) (2.85 g, 30 mmol) and NaH (1.80 g, 45 mmol). To this

solution, benzyl bromide (7.70 g, 45 mmol) was added and the mixture was heated at reflux under N_2. After 1 h, the reaction mixture was cooled, poured into aq. NH_4Cl solution (30 mL), and then extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (pure EtOAc) to afford the product **295** as a white solid (4.48 g, 81%). R_f = 0.24 (EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36-7.21 (7H, m, Ar**H**, 2 x C**H**), 6.57 (1H, d, *J* = 9.1 Hz, C**H**), 6.10 (1H, td, *J* = 6.7, 1.3 Hz, C**H**), 5.11 (2H, s, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 162.4 (C), 139.2 (CH), 137.1 (CH), 136.2 (C), 128.6 (2 x CH), 127.9 (2 x CH), 127.8 (CH), 120.9 (CH), 106.0 (CH), 51.6 (CH_2). The NMR data were in agreement with the literature.[207]

3-Methyl-1,4-benzoxazepin-5(4*H*)-one (296)

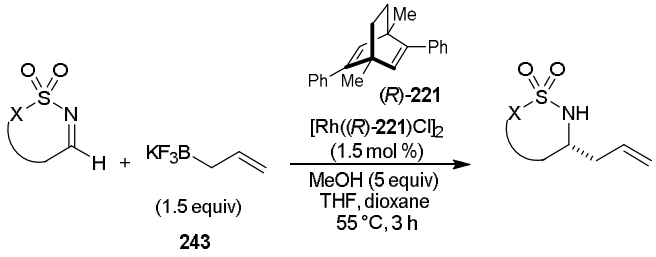


In a modification of a previously reported procedure,[208] to a stirred solution of salicylamide (**565**) (428 mg, 3.12 mmol) in acetone (25 mL) were added K_2CO_3 (862 mg, 6.24 mmol) and chloroacetone (0.5 mL, 6.24 mmol). The reaction mixture was heated at reflux for 2 h and then cooled down to room temperature. After the precipitate was removed by filtration, the filtrate was concentrated *in vacuo* and the residue was washed with Et_2O (15 mL) to give a white solid. A mixture of the white solid and *p*-toluenesulfonic acid monohydrate (8 mg, 0.04 mmol) in toluene (20 mL) was heated at reflux overnight with removal of water with a Dean-Stark trap. The reaction mixture was diluted with EtOAc (20 mL), washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then chromatographed over silica gel (40% EtOAc/hexane) to give the title compound **296** as a white solid (264 mg, 48%). R_f = 0.36 (40% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (1H, dd, *J* = 7.8, 1.7 Hz, Ar**H**), 7.80 (1H, br s, N**H**), 7.47 (1H, ddd, *J* = 8.1, 7.4, 1.8 Hz,

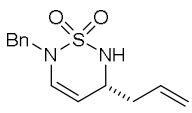
Ar**H**), 7.20 (1H, dt, *J* = 7.7, 1.1 Hz, Ar**H**), 7.00 (1H, dd, *J* = 8.1, 1.0 Hz, Ar**H**), 6.13-6.12 (1H, m, =C**H**O), 1.80 (3H, d, *J* = 1.4 Hz, 3 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 167.9 (C=O), 160.6 (=CN), 134.2 (CH), 132.1 (CH), 132.0 (CH), 125.5 (C), 124.5 (CH), 123.7 (C), 120.2 (CH), 15.9 (CH_3). The NMR data were in agreement with the literature.[208]

3.1.3 Enantioselective Allylation of imines

General Procedure C: Allylation of Imine Substrates

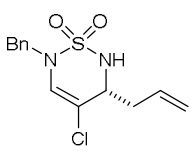


A Schlenk tube containing the appropriate cyclic imine substrate (0.30 mmol) and potassium allyltrifluoroborate (**243**) (0.45 mmol) was flushed with nitrogen before anhydrous THF (3 mL) was added. To this solution was added a stock solution of the rhodium–chiral diene complex (11.5 mM in anhydrous dioxane (Prepared by dissolving 270 mg of [Rh((*R*)-**221**)Cl]$_2$ in 27 mL of anhydrous dioxane) 0.39 mL, 0.0045 mmol = 3 mol % Rh), and MeOH (60 µL, 1.5 mmol), and the resulting mixture was heated to 55 ºC for 15 h. The reaction was cooled to room temperature, diluted with Et_2O (50 mL) and filtered through a silica plug. The resultant solution was concentrated to yield crude product and was purified using flash column chromatography to yield pure products.



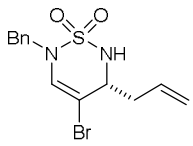
(*R*)-[Prop-2-en-1-yl]-5,6-dihydro-2-benzyl-1,2,6-thiadiazine-1,1-dioxide (254a). The title compound was prepared according to a slight modification of General Procedure C (in that the reaction time was 15 h) from 1,2,6-thiadiazine-1,1-dioxide **252a** (67 mg, 0.30 mmol) and was purified by column chromatography (2:40:58 Et_3N:EtOAc:hexane) to give a yellow oil (47 mg, 59%), which was not stable toward long term storage, and exhibited signs of

decomposition after *ca*. 2 h. R_f = 0.59 (40% EtOAc/hexane); **[α]** $^{20}_{D}$ –29.7 (*c* 0.94, $CHCl_3$); **IR** (film) 3250 (NH), 1641, 1402, 1334, 1217, 1174, 927, 769, 725, 700 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.31 (5H, m, Ar**H**), 5.95 (1H, dd, *J* = 8.5, 2.1 Hz, NC**H**=), 5.74-5.66 (1H, m, C**H**=CH_2), 5.20-5.15 (2H, m, =C**H**$_2$), 4.88 (1H, dd, *J* = 8.5, 1.8 Hz, NCH=C**H**), 4.66 (1H, d, *J* = 15.1 Hz, PhC**H**$_2$), 4.43 (1H, d, *J* = 15.1 Hz, PhC**H**$_2$), 4.36-4.31 (1H, m, NC**H**), 3.78 (1H, d, *J* = 10.4 Hz, N**H**), 2.50-2.44 (1H, m, C**H**$_2$CH=), 2.41-2.35 (1H, m, C**H**$_2$CH=); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 135.3 (C), 132.0 (CH), 130.0 (CH), 128.8 (2 x CH), 128.5 (2 x CH), 128.2 (CH), 120.0 (CH_2), 107.0 (CH), 55.2 (CH), 51.9 (CH_2), 37.7 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{13}H_{16}NO_2SNa$ [M+Na]+: 287.0825, found: 287.0820. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 ºC); t_r (major) = 18.9 min, t_r (minor) = 22.7 min; 95% ee.

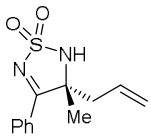


(*R*)-(Prop-2-en-1-yl)-5,6-dihydro-2-benzyl-4-chloro-1,2,6-thiadiazine-1,1-dioxide (254b).The title compound was prepared according to a slight modification of General Procedure C (in that the reaction time was 15 h) from 1,2,6-thiadiazine-1,1-dioxide **252b** (77 mg, 0.30 mmol) and was purified by column chromatography (20% EtOAc/hexane) to give a yellow oil (59 mg, 65%). R_f = 0.63 (40% EtOAc/hexane); **[α]** $^{20}_{D}$ +72.5 (*c* 0.80, $CHCl_3$); **IR** (film) 3250 (NH), 1640, 1454, 1408, 1350, 1292 1215, 1180, 923, 761 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.30 (5H, m, Ar**H**), 6.15 (1H, d, *J* = 1.6 Hz, NC**H**=), 5.61-5.49 (1H, m, C**H**=CH_2), 5.21-5.13 (2H, m, =C**H**$_2$), 4.65 (1H, d, *J* = 14.8 Hz, PhC**H**$_2$), 4.36 (1H, d, *J* = 14.8 Hz, PhC**H**$_2$), 4.26 (1H, br s, NC**H**), 4.00 (1H, br d, *J* = 6.6 Hz, N**H**), 2.82-2.72 (1H, m, C**H**$_2$CH=), 2.48-2.39 (1H, m, C**H**$_2$CH=); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 134.4 (C), 130.8 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 128.5 (CH), 128.4 (CH), 121.3 (CH_2), 114.6 (C), 57.6 (CH), 52.8 (CH_2), 34.4 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{13}H_{15}ClN_2O_2SClNa$ $[M+Na]^+$: 321.0435, found: 321.0437; Enantiomeric excess was determined by HPLC with a Chiralcel IC column (90:10

hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 ºC); t_r (minor) = 15.3 min, t_r (major) = 17.5 min; 94% ee.

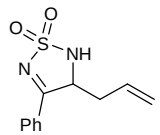


(*R*)-(Prop-2-en-1-yl)-5,6-dihydro-2-benzyl-4-bromo-1,2,6-thiadiazine-1,1-dioxide (254c). The title compound was prepared according to a slight modification of General Procedure C (in that the reaction time was 15 h) from 1,2,6-thiadiazine-1,1-dioxide **252c** (90 mg, 0.30 mmol) and was purified by column chromatography (20% EtOAc/hexane) to give a yellow oil (45 mg, 45%). R_f = 0.65 (40% EtOAc/hexane); **[α]** $^{20}_{D}$ +40.3 (*c* 0.74, $CHCl_3$); **IR** (film) 3250 (NH), 1640, 1406, 1352, 1292, 1213, 1180, 929, 761, 700, 617 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42-7.32 (5H, m, Ar**H**), 6.28 (1H, d, *J* = 1.7 Hz, NC**H**=), 5.64-5.55 (1H, m, C**H**=CH_2), 5.23-5.16 (2H, m, =C**H**$_2$), 4.66 (1H, d, *J* = 14.9 Hz, PhC**H**$_2$), 4.38 (1H, d, *J* = 14.9 Hz, PhC**H**$_2$), 4.33-4.28 (1H, m, NC**H**), 4.09 (1H, d, *J* = 10.0 Hz, N**H**), 2.86-2.78 (1H, m, C**H**$_2$CH=), 2.52-2.46 (1H, m, C**H**$_2$CH=); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 134.5 (CH), 131.0 (C), 130.8 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 128.5 (CH), 121.3 (CH_2), 103.5 (C), 58.4 (CH), 52.6 (CH_2), 35.6 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{13}H_{15}BrN_2O_2SNa$ $[M+Na]^+$: 364.9930, found: 364.9927. Enantiomeric excess was determined by HPLC with a Chiralcel IC column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 ºC); t_r (minor) = 14.0 min, t_r (major) = 16.2 min; 90% ee.

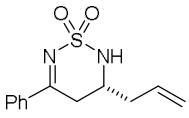


(*R*)-(Prop-2-en-1-yl)-3-methyl-4-phenyl-2,3-dihydro-[1,2,5] thiadiazole 1,1-dioxide (257b). The title compound was prepared according to a slight modification of General Procedure C (in that the reaction time was 12 h) from 1,2,5-thiadiazole 1,1-dioxide **256b** (62 mg, 0.30 mmol) and was purified by column chromatography (20% EtOAc/hexane) to give an orange oil (66 mg, 88%). R_f = 0.45 (40% EtOAc/hexane); **[α]** $^{20}_{D}$ −29.9 (*c* 0.74, $CHCl_3$); **IR** (film) 3244 (NH), 1557, 1315, 1158, 995, 818, 779, 700, 652, 561 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05-8.02 (2H, m, Ar**H**), 7.65 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.56-7.52 (2H, m, Ar**H**), 5.72-5.63 (1H, m, C**H**=CH_2), 5.28 (1H, d, *J* = 10.1 Hz, =C**H**$_2$), 5.21 (1H, dd,

J = 1.0, 17.0 Hz, =C**H**$_2$), 4.53 (1H, br s, N**H**), 2.91 (1H, dd, *J* = 14.6, 6.5 Hz, C**H**$_2$), 2.70 (1H, dd, *J* = 14.6, 8.0 Hz, C**H**$_2$), 1.82 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 181.6 (C), 133.8 (CH), 130.1 (CH), 130.0 (2 x CH), 129.2 (2 x CH), 128.8 (C), 122.4 (CH_2), 72.3 (C), 43.6 (CH_2), 26.3 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{12}H_{15}N_2O_2S$ $[M+H]^+$: 251.0849. found 251.0848; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min 280 nm, 25 ºC); t_r (minor) = 43.7 min, t_r (major) = 48.2 min; 97% ee.

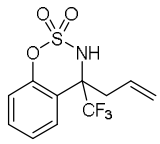


(*Rac*)-4-Phenyl-3-(prop-2-en-1-yl)-2,3-dihydro-[1,2,5]thiadiazole 1,1-dioxide (257d).The title compound was prepared according to a slight modification of General Procedure C (in that the reaction time was 2 h and potassium tertiarybutoxide (5 mg, 3 mol %) was added) from 3-ethoxy-4-phenyl-1,2,5-Δ^2-thiadiazolidine 1,1-dioxide (**290**) (73 mg, 0.30 mmol) and was purified by column chromatography (40% EtOAc/hexane) to give an colourless oil (57 mg, 80%); R_f = 0.62 (60% EtOAc/hexane); **IR** (film) 3245 (NH), 1597, 1566, 1448, 1341, 1306, 1173, 928, 812, 768 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88-7.86 (2H, m, Ar**H**), 7.67-763 (1H, m, Ar**H**), 7.54-7.50 (2H, m, Ar**H**), 5.83-5.74 (1H, m, C**H**=CH_2), 5.20 (1H, dd, *J* = 10.2, 1.1 Hz, =C**H**$_2$), 5.15-5.09 (3H, m, =C**H**$_2$, C**H**=N and N**H**), 2.69 (1H, dddd, *J* = 12.2, 6.1, 3.1, 1.4 Hz, C**H**$_2$), 2.43 (1H, ddd, *J* = 14.91, 8.3, 7.6 Hz, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 179.2 (C), 134.4 (CH), 131.5 (CH), 129.4 (2 x CH), 129.3 (2 x CH), 128.5 (C), 120.2 (CH_2), 64.0 (CH), 38.5 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{11}H_{12}N_2O_2S$ $[M+H]^+$: 237.0698. found 237.0696; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min 280 nm, 25 ºC); t_r = 39.5 min, 44.4 min; 0% ee.



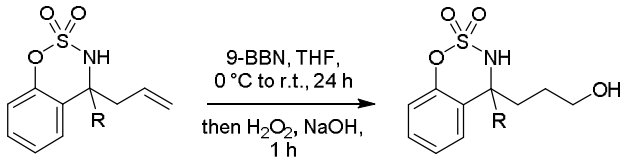
5-Phenyl-3-(prop-2-en-1-yl)-(2*H*)-1,2,6-dihydrothiadiazine 1,1-dioxide (255a).The title compound was prepared according to a slight modification of General Procedure C (in that the reaction time was 24 h) from 5-phenyl-(2*H*)-1,2,6-thiadiazine 1,1-dioxide (**253a**) (20 mg, 0.10 mmol) and was purified by preparative TLC (2:40:58 Et_3N:EtOAc:hexane) to give a colourless wax (8 mg, 33%), which was not stable toward long term storage, and exhibited signs of

decomposition after *ca* 2 h.; R_f = 0.78 (60% EtOAc/hexane); $[\alpha]_D^{20}$ −250 (*c* 0.04, $CHCl_3$); **IR** (film) 2924, 1597, 1572, 1448, 1348, 1329, 1265, 1170, 789, 744 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98-7.94 (2H, m, Ar**H**), 7.61-7.57 (1H, m, Ar**H**), 7.49-7.44 (2H, m, Ar**H**), 5.87-5.77 (1H, m, C**H**=), 5.31 (1H, br s, C$\mathbf{H}_2$=), 5.30-5.27 (1H, m, C$\mathbf{H}_2$=), 4.16 (1H, br s, *J* = 11.2 Hz, N**H**), 4.01-3.93 (1H, m, C**H**=N), 3.06 (1H, dd, *J* = 18.8, 4.0 Hz, C$\mathbf{H}_2$), 2.56 (1H, dd, *J* = 18.8, 11.2 Hz, C$\mathbf{H}_2$), 2.53-2.45 (2H, m, C$\mathbf{H}_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 175.4 (C=N), 135.3 (C), 133.7 (CH), 131.1 (CH), 128.9 (2 x CH), 127.9 (2 x CH), 120.8 (CH_2), 50.0 (CH), 39.0 (CH_2), 31.0(CH_2); **HRMS** (ESI) Exact mass calcd for $C_{11}H_{12}N_2O_2SNa$ $[M+Na]^+$: 273.0674. found 273.0676; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min 280 nm, 25 ºC); t_r (minor) = 66.0 min, t_r (major) = 59.6 min; 65% ee.

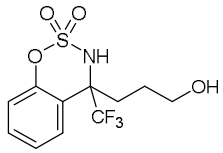


4-(Prop-2-en-l-yl)-4-(trifluoromethyl)-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dione (289). The title compound was prepared according to General Procedure C from imine **203** (75 mg, 0.30 mmol) and allyltrifluoroborate **243** (but chiral diene *ent*-**221** was used instead of (*R*)-**221**) and was purified by column chromatography (10% EtOAc/hexane) to give a yellow solid (75 mg, 86%). **m.p.** 76-77 ºC (CH_2Cl_2/hexane); R_f = 0.30 (10% EtOAc/hexane); **IR** (film) 3285 (NH), 1614, 1489, 1454, 1435, 1377, 1260, 1180, 856, 762 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.48 (1H, dt, *J* = 7.5, 5.4 Hz, Ar**H**), 7.34 (1H, td, *J* = 8.0, 1.2 Hz, Ar**H**), 7.16 (1H, dd, *J* = 8.2, 1.1 Hz, Ar**H**), 5.61-5.53 (1H, m, C**H**=), 5.41-5.36 (2H, m, =C$\mathbf{H}_2$), 5.13 (1H, s, N**H**), 3.05 (1H, dd, *J* = 14.5, 6.5 Hz, C$\mathbf{H}_2$), 2.85 (1H, dd, *J* = 14.5, 8.0 Hz, C$\mathbf{H}_2$), **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 150.8 (C), 131.5 (CH), 128.4 (CH), 127.0 (CH, q, *J* = 2.6 Hz), 126.5 (CH), 124.3 (C, q, *J* = 286.3 Hz), 124.2 (CH_2), 120.0 (CH), 117.9 (C), 65.8 (C, q, *J* = 29.1 Hz), 41.3 (CH_2); **^{19}F NMR** (376 MHz, $CDCl_3$) δ –74.7; **HRMS** (ESI) Exact mass calcd for $C_{11}H_{11}F_3NO_3S$ $[M+H]^+$: 294.0406, found: 294.0408. To facilitate determination of enantiomeric excess, **289** was converted into the primary alcohol **566**.

General Procedure D: Hydroboration of Terminal Alkenes



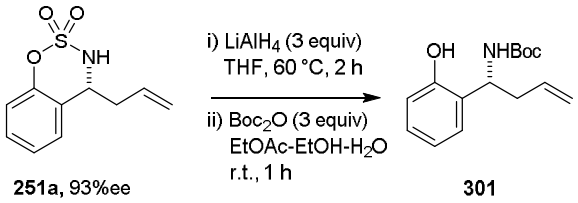
To a solution of the alkene (0.23 mmol) in THF (3 mL) at 0 ºC was added 9-BBN (0.5 M in THF, 1.37 mL, 0.68 mmol) over 2 min. The mixture was warmed to room temperature over 1 h and then stirred for a further 23 h. The reaction was cooled to 0 ºC and 3 M NaOH (1 mL) and H_2O_2 (30 wt.% in H_2O, 2 mL) were added successively. The resulting mixture was stirred for 1 h at room temperature, diluted with H_2O (20 mL), neutralised with 2 M HCl, and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography to afford the alcohol products.



4-(Trifluoromethyl)-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dione (566) The title compound was prepared according to General Procedure D from alkene **289** (66 mg, 0.23 mmol) and was purified by column chromatography (60% EtOAc/hexane) to obtain the alcohol **566** (61 mg, 86%) as a colourless gum. R_f = 0.41 (60% EtOAc/hexane); **IR** (film) 3288 (OH and NH), 2924, 1454, 1375, 1177, 1159, 1115, 1055, 856, 762 cm^{-1}; **^{1}H NMR** (CD_3OD, 500 MHz) δ 7.61 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.55-7.52 (1H, m, Ar**H**), 7.41-7.38 (1H, m, Ar**H**), 7.19 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 3.60-3.52 (2H, m, C**H**$_2$OH), 2.45-2.39 (1H, m, C**H**$_2$), 2.14-2.08 (1H, m, C**H**$_2$), 1.76-1.68 (1H, m, C**H**$_2$), 1.38-1.26 (1H, m, C**H**$_2$); **^{13}C NMR** (125.8 MHz, CD_3OD) δ 152.9 (C), 132.5 (CH), 125.0 (C, q, *J* = 286.0 Hz), 127.4 (CH), 126.4 (C, q, *J* = 286.0 Hz), 120.7 (CH), 119.9 (C), 68.1 (C, q, *J* = 28.6 Hz), 62.0 (CH_2), 33.1 (CH_2), 26.6 (CH_2); **^{19}F NMR** (CD_3OD) δ –78.0; **HRMS** (ESI) Exact mass calcd for $C_{11}H_{12}F_3NO_4SNa$ $[M+Na]^+$: 334.0331, found: 334.0331; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H

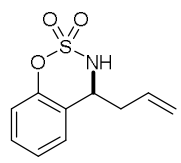
column (90:10 hexane:*i*-PrOH, 0.8 mL/min 280 nm, 25 ºC); t_r = 19.3 min, 29.0 min; 0% ee.

***tert*-Butyl *N*-[(*R*)-1-(2-hydroxyphenyl)but-3-en-1-yl]carbamate (301)**

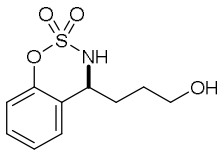


To a solution of allylation product **251a** in THF (1 mL) at room temperature was added $LiAlH_4$ (1.0 M in THF, 0.37 mL, 0.37 mmol) over 1 min at room temperature. The mixture was heated at 60 ºC for 15 h, allowed to cool to temperature, and then cooled with an ice bath. The reaction was quenched carefully with EtOAc (1 mL), followed by the addition of EtOH (1 mL) and H_2O (2 mL). To the resulting turbid mixture was added Boc_2O (81 mg, 0.37 mmol) in one portion and the resulting mixture was stirred at room temperature for 1 h. The reaction was diluted with EtOAc (20 mL) and acidified with 2 M HCl until the aqueous layer became clear. The aqueous layer was separated and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (6:1 hexane:Et_2O→2:1 hexane:Et_2O) gave the carbamate **301** as a colourless oil (28 mg, 85%). R_f = 0.54 (30% EtOAc/hexane); $[\alpha]_D^{20}$ +45.2 (*c* 1.15, $CHCl_3$); **IR** (film) 3310 (OH), 2925, 1680, 1502, 1456, 1367, 1170, 1043, 918, 860, 750 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50 (1H, br s, ArO**H**), 7.16-7.07 (2H, m, Ar**H**), 6.88-6.80 (2H, m, Ar**H**), 5.75 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, C**H**=CH_2), 5.27 (1H, br s, N**H**), 5.13 (1H, dd, *J* = 17.2, 1.0 Hz, =C**H**$_2$), 5.09 (1H, d, *J* = 10.4 Hz, =C**H**$_2$), 4.89 (1H, br s, C**H**N), 2.62 (2H, t, *J* = 7.0 Hz, C**H**$_2$), 1.47 (9H, s, C(C**H**$_3$)$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 157.0 (C), 154.7 (C), 134.6 (CH), 128.5 (CH), 127.9 (C), 126.6 (CH), 119.8 (CH), 117.8 (CH_2), 117.0 (CH), 80.7 (C), 48.9 (CH), 38.6 (CH_2), 28.4 (3 x CH_3); **HRMS** (EI) Exact mass calcd for $C_{15}H_{22}O_3N$ $[M]^+$: 264.1594, found: 264.1599; Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column

(98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 ºC); t_r (major) = 23.1 min, t_r (minor) = 30.6 min; 93% ee.



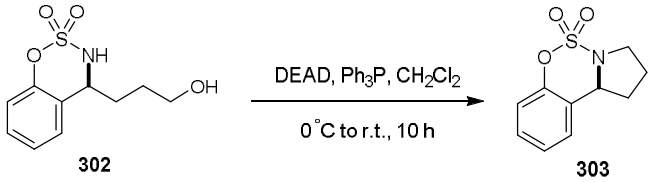
(*S*)-4-(Prop-2-en-1-yl)-3,4-dihydro[1,2,3]benzoxathiazine-2,2-dioxide (*ent*-251a). The title compound was prepared according to General Procedure C from benzoxathiazine-2,2-dioxide (**202a**) (55 mg, 0.30 mmol) (but chiral diene *ent*-**221** was used instead of (*R*)-**221**) and was purified by column chromatography (20% EtOAc/hexane) to give an orange oil (59 mg, 87%). R_f = 0.54 (40% EtOAc/hexane); $[\alpha]_D^{20}$ +177.9 (*c* 0.24, $CHCl_3$); **IR** (film) 3259 (NH), 1357, 1186, 1157, 1103, 900, 850, 831, 755, 680 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36-7.32 (1H, m, Ar**H**), 7.30-7.28 (1H, m, Ar**H**), 7.24-7.21 (1H, m, Ar**H**), 7.04 (1H, dd, *J* = 8.3, 1.1 Hz, Ar**H**), 5.69 (1H, dddd, *J* = 17.0, 10.1, 8.5, 5.8 Hz, C**H**=CH_2), 5.34-5.26 (2H, m, =C**H**$_2$), 4.93 (1H, ddd, *J* = 9.0, 7.0, 4.2 Hz, C**H**), 4.56 (1H, d, *J* = 9.0 Hz, N**H**), 3.01-2.94 (1H, m, C**H**$_2$), 2.82-2.75 (1H, m, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 151.5 (C), 131.2 (CH), 129.6 (CH), 126.1 (CH), 125.5 (CH), 121.4 (C), 121.4 (CH_2), 119.1 (CH), 55.8 (CH), 37.5 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{10}H_{10}NO_3S$ $[M–H]^-$: 224.0387, found: 224.0388. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 14.8 min, t_r (minor) = 18.0 min; 93% ee.



(*S*)-4-(3-Hydroxypropyl)-3,4-dihydro-[1,2,3]-benzoxathiazine-2,2-dioxide (302). The title compound was prepared according to General Procedure D from alkene *ent*-**251a** (225 mg, 1.00 mmol) and was purified by column chromatography (80% EtOAc/hexane) to obtain the alcohol **302** as a white solid (182 mg, 75%). **m.p.** 112-113 ºC (CH_2Cl_2); R_f = 0.36 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –36.7 (*c* 0.49, $CHCl_3$); **IR** (film) 3255 (OH), 2880, 1485, 1452, 1425, 1371, 1175, 1107, 883, 760 cm^{-1}; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.40 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.36 (1H, *J* = 8.3, 4.5, 1.1 Hz, Ar**H**), 7.24 (1H, td, *J* = 1.6, 1.2 Hz, Ar**H**), 7.02 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 4.70 (1H, dd, *J* = 10.9, 3.8 Hz, C**H**N), 3.70-3.61 (2H, m, C**H**$_2$OH), 2.26-2.18 (1H, m, C**H**$_2$$CH_2$$CH_2$OH), 2.03-1.95 (1H, m, C**H**$_2$$CH_2$$CH_2$OH), 1.90-1.82 (1H, m, C**H**$_2$$CH_2$OH), 1.76-1.67 (1H, m,

C**H**$_2$CH$_2$OH); **^{13}C NMR** (125.8 MHz, CD_3OD) δ 152.8 (C), 130.2 (CH), 127.9 (CH), 126.1 (CH), 125.0 (C), 119.3 (CH), 62.3 (CH), 57.9 (CH_2), 31.3 (CH_2), 29.6 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{10}H_{14}NO_4S$ $[M+H]^+$: 244.0638, found: 244.0640.

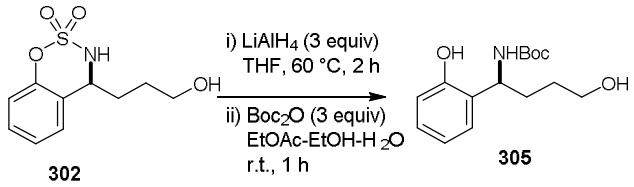
(*S*)-8-Oxa-7λ^6-thia-6-azatricyclo[7.4.0.0^{2,6}]trideca-1(9),10,12-triene-7,7-dioxide (303)



302 303

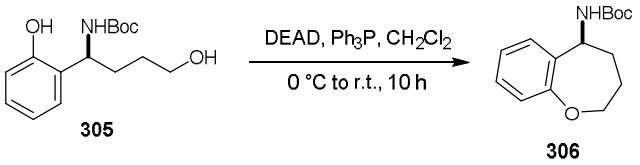
To a solution of the alcohol **302** (61 mg, 0.25 mmol) and PPh_3 (85 mg, 0.33 mmol) in dichloromethane (4 mL) at 0 ºC was added a solution of DEAD (53 mg, 0.30 mmol) in CH_2Cl_2 (1 mL). The mixture was allowed to warm to room temperature over 1 h and then stirred for an additional 9 h. The reaction was quenched with EtOH (1 mL) and concentrated *in vacuo*. Purification of the residue by column chromatography (60% EtOAc/hexane) gave the product **303** (56 mg, >95%) as a white solid. **m.p.** 85-86 ºC (CH_2Cl_2/hexane); R_f = 0.57 (30% EtOAc/hexane); **[α]**$_D^{20}$ –125.0 (*c* 0.40, $CHCl_3$); **IR** (film) 2982, 1485, 1450, 1392, 1206, 1175, 1103, 1005, 856, 758 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (1H, dddd, *J* = 8.1, 7.3, 1.7, 0.8 Hz, Ar**H**), 7.21 (1H, td, *J* = 7.5, 1.2 Hz, Ar**H**), 7.15 (1H, dt, *J* = 7.5, 1.0 Hz, Ar**H**), 7.01 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 5.20 (1H, dd, *J* = 7.4, 2.5 Hz, C**H**N), 3.61-3.56 (1H, m, C**H**$_2$N), 3.51 (1H, ddd, *J* = 10.1, 8.6, 5.8 Hz, C**H**$_2$N), 2.59 (1H, ddd, *J* = 16.5, 12.8, 7.7 Hz, CHC**H**$_2$C**H**$_2$), 2.30-2.24 (1H, m, CHC**H**$_2$C**H**$_2$), 2.07-1.99 (1H, m, CHC**H**$_2$C**H**$_2$), 1.92-1.83 (1H, m, CHC**H**$_2$C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 151.0 (C), 129.1 (CH), 126.6 (CH), 125.6 (CH), 122.5 (C), 118.8 (CH), 62.7 (CH), 49.7 (CH_2), 34.0 (CH_2), 23.4 (CH_2); **HRMS** (EI) Exact mass calcd for $C_{10}H_{12}NO_3S$ $[M+H]^+$: 226.0532, found: 226.0529; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min 280 nm 25 ºC); t_r (minor) = 18.6 min, t_r (major) = 20.2 min; 92% ee.

***tert*-Butyl-*N*-[(*S*)-4-hydroxy-1-(2-hydroxyphenyl)butyl] carbamate (305)**



To a solution of the cyclic sulfamate **302** (100 mg, 0.41 mmol) in THF (2 mL) at room temperature was added $LiAlH_4$ (2.0 M in THF, 0.62 mL, 1.24 mmol) dropwise over 4 min. The mixture was heated at 60 ºC for 2 h, allowed to cool to room temperature, and then cooled with an ice bath. The reaction was quenched carefully with EtOAc (2 mL), followed by the addition of EtOH (2 mL) and H_2O (2 mL). To the resulting turbid mixture was added Boc_2O (268 mg, 1.24 mmol) in one portion and the resulting mixture was stirred at room temperature for 1 h. The reaction was diluted with EtOAc (40 mL) and acidified with 2 M HCl until the aqueous layer became clear. The aqueous layer was separated and extracted with EtOAc (2 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (80% EtOAc/hexane) gave the carbamate **305** (87 mg, 75%) as a colourless gum. R_f = 0.42 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –33.6 (*c* 0.24, $CHCl_3$); **IR** (film) 3305 (OH and NH), 2980, 1680 (C=O), 1502, 1456, 1367, 1292, 1253, 1165, 752, 742 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 (1H, br s, O**H**), 7.18 (2H, dd, *J* = 12.1, 4.5 Hz, Ar**H**), 6.93 (1H, d, *J* = 7.8 Hz, Ar**H**), 6.90 (1H, dt, *J* = 7.5, 1.1 Hz, Ar**H**), 5.13 (1H, s, N**H**), 4.86 (1H, d, *J* = 6.9 Hz, C**H**N), 3.72 (2H, dt, *J* = 6.2, 0.9 Hz, C$\mathbf{H}_2$OH), 2.06-1.95 (2H, m, CHC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.73-1.58 (2H, m, CHC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.45 (9H, s, C(C$\mathbf{H}_3$)$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 157.3 (C), 154.9 (C), 128.8 (C), 128.4 (CH), 126.3 (CH), 120.3 (CH), 117.8 (CH), 80.8 (C), 62.3 (CH_2), 49.0 (CH), 30.6 (CH_2), 29.5 (CH_2), 28.3 (3 x CH_3); **HRMS** (ESI) Exact mass calcd for $C_{15}H_{24}NO_4$ $[M+H]^+$: 282.1700, found: 282.1696.

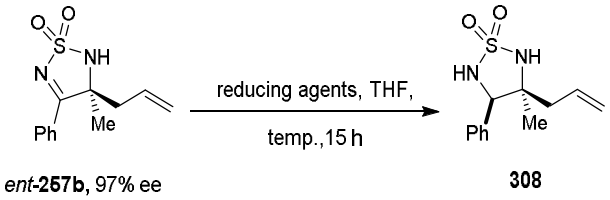
***tert*-Butyl *N*-[(*S*)-2,3,4,5-tetrahydro-1-benzoxepin-5-yl] carbamate (306)**



305 **306**

To a solution of the alcohol **305** (68 mg, 0.24 mmol) and PPh_3 (82 mg, 0.31 mmol) in dichloromethane (4 mL) at 0 ºC was added a solution of DEAD (51 mg, 0.29 mmol) in CH_2Cl_2 (1 mL). The mixture was allowed to warm to room temperature over 1 h and then stirred for an additional 9 h. The reaction was quenched with EtOH (1 mL) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane) gave the tetrahydrobenzoxepine **306** as a white solid (43 mg, 68%). **m.p.** 105-106 ºC (CH_2Cl_2/hexane); R_f = 0.40 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –40.0 (*c* 0.15, $CHCl_3$); **IR** (film) 3300 (NH), 2976, 2930, 1713(C=O), 1450, 1366, 1236, 1224, 1170, 760 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28-7.26 (1H, m, Ar**H**), 7.20 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.05 (1H, td, *J* = 7.5, 1.3 Hz, Ar**H**), 7.01 (1H, dd, *J* = 7.5, 1.3 Hz, Ar**H**), 5.29 (1H, d, *J* = 7.8 Hz, N**H**), 4.91 (1H, t, *J* = 7.1 Hz, C**H**N), 4.30 (1H, app d, *J* = 11.9 Hz, OC**H**$_2$), 3.75 (1H, app t, *J* = 11.2 Hz, OC**H**$_2$), 2.30-2.10 (2H, m, C**H**$_2$), 1.88-1.81 (1H, m, C**H**$_2$), 1.79-1.72 (1H, m, C**H**$_2$), 1.44 (9H, s, C(C**H**$_3$)$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 159.3 (C), 155.0 (C), 135.5 (C), 129.3 (CH), 128.9 (CH), 124.2 (CH), 122.0 (CH), 79.3 (C), 73.8 (CH_2), 53.9 (CH), 30.8 (CH_2), 28.4 (3 x CH_3), 26.7 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1594, found: 264.1595; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min 280 nm 25 ºC); t_r (major) = 12.5 min, t_r (minor) = 15.6 min; 90% ee.

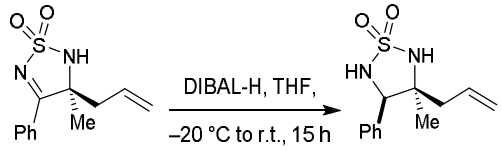
Screening and Optimisation for Compound 334 (Table 1.10)



ent-**257b**, 97% ee **308**

To a solution of the imine *ent*-**257b** (123 mg, 0.05 mmol, prepared as described in General procedure C by the reaction of imine **256b** with allyltrifluoroborate (**243**), but chiral diene *ent*-**221** was used instead of (*R*)-**221**) in THF (2 mL) at indicated temperature was slowly added reducing agents (0.2 mmol, 4 equiv). The mixture was stirred at that temperature for 15 h (in case of the reaction was set at 0 °C) or warmed gradually to room temperature over 2 h and stirred for a further 13 h (in case of the reaction was set at −5, −20 and −78 °C). The reaction was then quenched carefully with 1 M HCl solution until the pH value of the mixture reached 3. The mixture was diluted with H_2O (3 mL) and EtOAc (3 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 3 mL), and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The percent conversions were determined by ^{1}H NMR analysis of the unpurified reaction mixtures.

(3*S*,4*R*)-3-Methyl-4-phenyl-3-(prop-2-en-1-yl)-[1,2,5]-thiadiazolidine-1,1-dioxide (308)

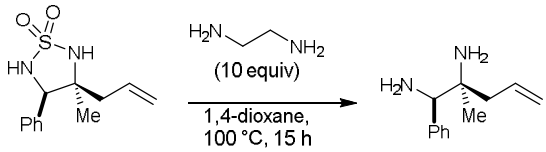


ent-**257b**, 97% ee **308**

To a solution of the imine *ent*-**257b** (200 mg, 0.80 mmol) in THF (32 mL) at –20 ºC was added DIBAL (1.0 M in THF, 3.2 mL, 3.2 mmol) over 2 min. The mixture was warmed

gradually to room temperature over 2 h and stirred for a further 13 h. The reaction was quenched carefully with 1 M HCl solution until the pH value of the mixture reached 3. The mixture was diluted with H_2O (20 mL) and EtOAc (30 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 30 mL), and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (33% EtOAc/hexane) gave the cyclic sulfamide **308** as a colourless amorphous solid (182 mg, 90%). R_f = 0.26 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –125.0 (*c* 0.42, CH_3OH); **IR** (film) 3271 (NH), 2980, 1454, 1381, 1312, 1265, 1157, 922, 741, 702 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43-7.36 (5H, m, Ar**H**), 5.67 (1H, dddd, *J* = 17.1, 10.2, 7.8, 7.0 Hz, C**H**=CH_2), 5.21-5.19 (1H, m, =C**H**$_2$), 5.14 (1H, ddd, *J* = 17.1, 3.0, 1.3 Hz, =C**H**$_2$), 4.90 (1H, d, *J* = 5.1 Hz, N**H**), 4.82 (1H, d, *J* = 5.1 Hz, C**H**N), 4.60 (1H, s, N**H**), 2.49 (1H, dd, *J* = 13.7, 7.9 Hz, C**H**$_2$), 1.59 (1H, dd, *J* = 13.7, 6.9 Hz, C**H**$_2$), 1.43 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 134.1 (C), 131.9 (CH), 128.9 (CH), 128.8 (2 x CH), 127.3 (2 x CH), 121.2 (CH_2), 70.0 (CH), 65.0 (C), 39.7 (CH_2), 24.2 (CH_3); **HRMS** (EI) Exact mass calcd for $C_{12}H_{16}N_2O_2S$ $[M]^+$: 252.0927, found: 252.0928.

(1*R*,2*S*)-2-Methyl-1-phenyl-4-butene-1,2-diamine (309)



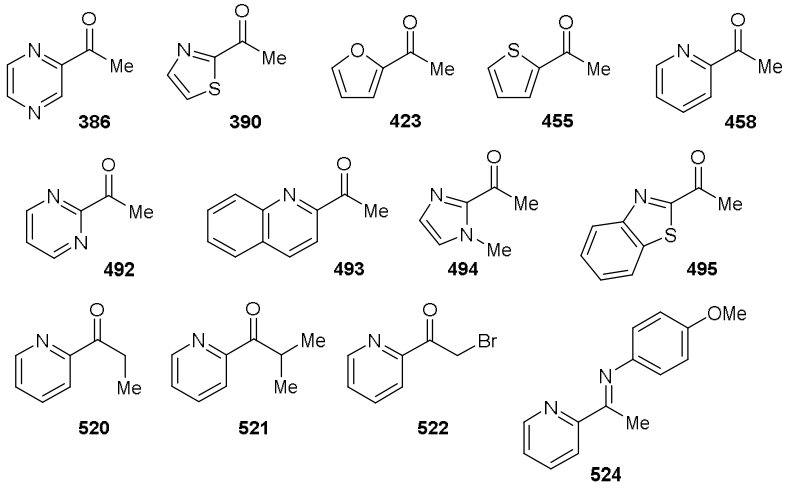
308 **309**

A solution of cyclic sulfamide **308** (101 mg, 0.40 mmol) and ethylenediamine (267 µL, 4.00 mmol) in dioxane (6 mL) was stirred at 100 ºC for 15 h. The reaction was cooled to room temperature and concentrated *in vacuo*. To the residue was added a 1.25 M solution of HCl in MeOH (2 mL) and the resulting solution was stirred at room temperature for 2 h before being concentrated *in vacuo*. The residue was dissolved in H_2O (10 mL) and washed with EtOAc (2 x 10 mL). The organic layers were discarded and the aqueous phase was basified with 3 M NaOH (2 mL) and extracted with EtOAc

(3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave the diamine **309** (67 mg, 88%) as a pale yellow oil. R_f = 0.15 (EtOAc); **[α]** $_D^{20}$ –30.0 (*c* 0.20, MeOH); **IR** (film) 3400 (NH), 2964, 1638, 1603, 1492, 1452, 1373, 999, 914, 704 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.31 (5H, m, Ar**H**), 5.89 (1H, ddt, *J* = 17.5, 10.2, 7.4 Hz, C**H**=CH_2), 5.12 (1H, ddt, *J* = 10.2, 2.0, 0.9 Hz, =C**H**$_2$), 5.08 (1H, ddt, *J* = 17.0, 2.3, 1.4 Hz, =C**H**$_2$), 3.82 (1H, s, C**H**N), 2.13-2.03 (2H, m, C**H**$_2$), 1.65 (4H, br s, 2 x N**H**$_2$), 1.09 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 142.6 (C), 134.3 (CH), 128.3 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 118.3 (CH_2), 64.2 (CH), 54.7 (C), 44.0 (CH_2), 24.7 (CH_3); **HRMS** (EI) Exact mass calcd for $C_{12}H_{18}N_2$ $[M]^+$: 190.1465, found: 190.1465.

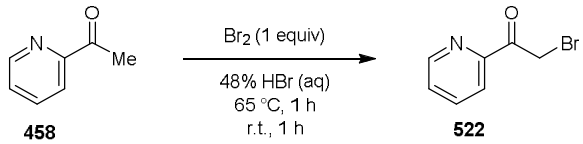
3.2 Enantioselective Nickel-Catalysed Michael Additions of 2-Acetylazaarenes to Nitroalkenes

3.2.1 Synthesis of 2-Acylheteroarenes



2-Acetylpyrazine (**386**), 2-acetylthiazole (**390**), 2-acetylthiophene (**455**) were purchased from Fluorochem. 2-Acetylfuran (**423**), 2-acetylpyridine (**458**) and were purchased from Acros. Compounds **492**,[209] **493**,[210] **494**,[211] **495**,[212] **520**,[213] and **521**[214] were prepared by Alain J. Simpson according to previously reported procedures. Yields and recation times reported in this Section are unoptimised.

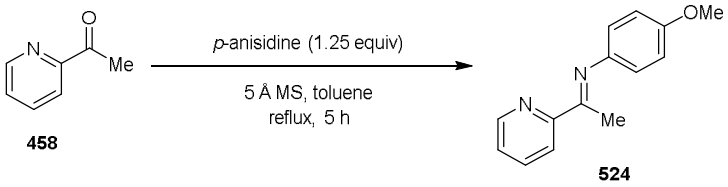
2-Bromo-1-(pyridine-2-yl) ethanone (522)



458 522

In a modification of a previously reported procedure,[215] to a solution of 2-acetylpyridine (**458**) (1.82 g, 15 mmol) in 48% HBr (3 mL) was added a solution of Br_2 (1.20 g, 15 mmol) in 48% HBr (3.2 mL). The mixture was stirred at 65 °C for 1 h, then at room temperature for 1 h. It was then quenched with ice (10 g) and the solvent was removed under reduced pressure. Ether (5 mL) was added and induced precipitation. The off-white solid was filtered and washed with cold ether to afford a white crystalline **522** (1.17 g, 39%). $R_f = 0.15$ (40% CH_2Cl_2/hexane); **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.6-8.71 (1H, m, Ar**H**), 8.08 (1H, td, J = 7.6, 1.6 Hz, Ar**H**), 8.06-8.02 (1H, m, Ar**H**), 7.73 (1H, ddd, J = 7.3, 4.8, 1.3 Hz, Ar**H**), 5.01 (2H, s, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 192.0 (C), 150.5 (C), 149.1 (CH), 138.5 (CH), 128.6 (CH), 122.6 (CH), 65.2 (CH_2). The NMR data were in agreement with the literature.[215]

(*E*)-4-Methoxy-*N*-[1'-(pyridin-2"-yl)ethylidene]aniline (524)

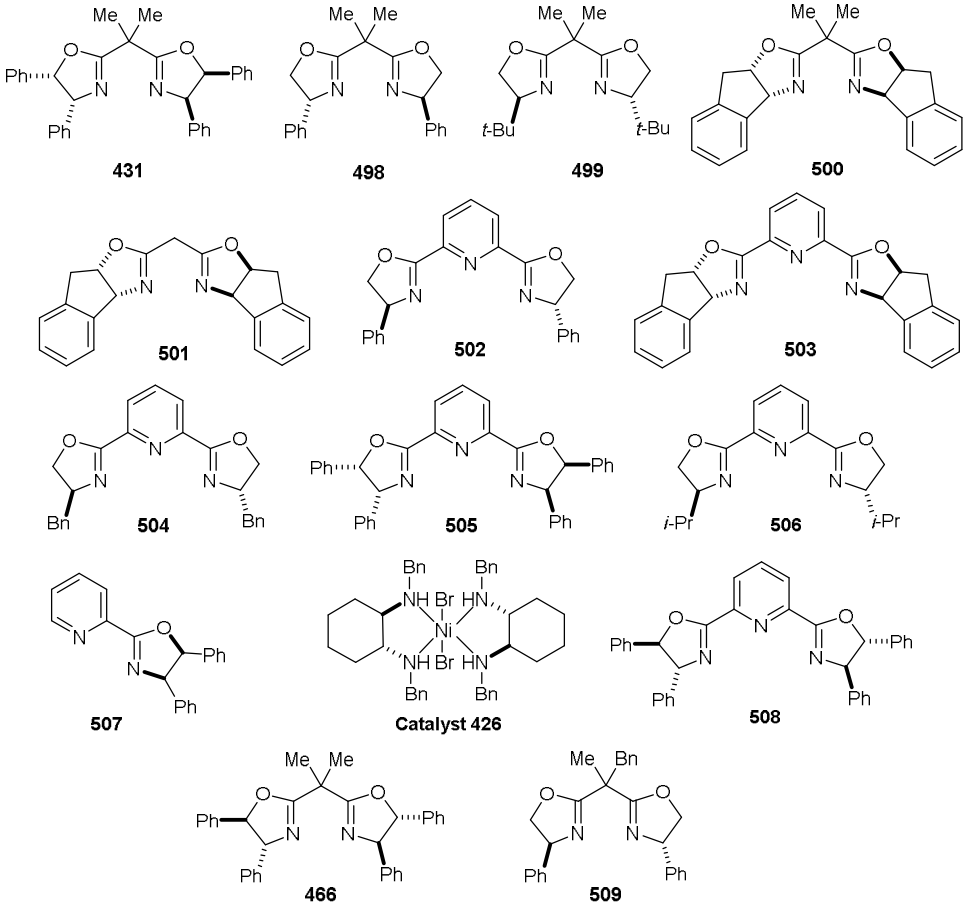


458 524

In a modification of a previously reported procedure,[216] 5 Å molecular sieves (12.5 g) were added to a solution of 2-acetylpyridine (**458**) (1.21 g, 10 mmol) and *p*-anisidine (1.54 g, 12.5 mmol) in dried toluene (100 mL) and the reaction mixture was heated at reflux for 5 h. The mixture was then cooled, the sieves were filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (pre-treated overnight with 10% Et_3N in diethyl ether) eluting with a 0→40% EtOAc/Et_2O to afford **524** (905 mg, 40%) as a yellow oil. $R_f = 0.29$ (40%

EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.66 (1H, ddd, *J* = 4.8, 1.6, 0.8 Hz, Ar**H**), 8.26 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.77 (1H, td, *J* = 7.7, 1.8 Hz, Ar**H**), 7.35 (1H, ddd, *J* = 7.5, 4.8, 1.2 Hz, Ar**H**), 6.95-6.91 (2H, m, Ar**H**), 6.83-6.79 (2H, m, Ar**H**), 3.83 (3H, s, OC**H**$_3$), 2.39 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 167.3 (C), 157.0 (C), 156.2 (C), 148.5 (CH), 144.3 (C), 136.3 (CH), 124.6 (CH), 121.3 (CH), 120.8 (2 x CH), 114.2 (2 x CH), 55.4 (CH_3), 16.3 (CH_3). The NMR data were in agreement with the literature.[216]

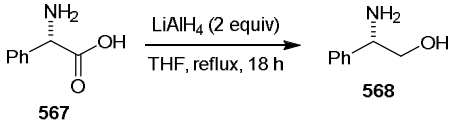
3.2.2 Synthesis of Chiral Ligands and Catalysts



Box **501** was purchased from Aldrich. PyBox **506** was purchased from Solvias and Box **509** was purchased from Strem. Catalyst **426**[149a] was prepared by Alain J. Simpson

according to previously reported procedure. Yields and reaction times reported in this Section are unoptimised.

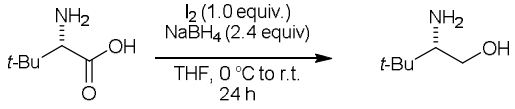
(2*S*)-(+)-2-Amino-2-phenylethanol (568).



567 **568**

In a modification of a previously reported procedure,[217] to a suspension of $LiAlH_4$ (3.5 g, 88.0 mmol) in THF (150 mL) at 0 °C was added (*S*)-(+)-2-phenylglycine (**567**) (6.05 g, 40.0 mmol) portionwise over 10 min. The reaction mixture was heated at reflux for 18 h, then allowed to cool to room temperature, quenched with saturated aqueous K_2CO_3 (10 mL), and filtered. The filter cake was washed with Et_2O (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Recrystallisation of the residue from 1:3 EtOAc/hexane afforded the title compound as a yellow solid (4.30 g, 78%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m, Ar**H**), 4.06 (1H, dd, *J* = 8.3, 4.4 Hz, C**H**NH_2), 3.75 (1H, dd, *J* = 10.7, 4.4 Hz, C**H**$_2$OH), 3.56 (1H, dd, *J* = 10.7, 8.3 Hz, C**H′**$_2$OH), 1.99 (3H, br s, N**H**$_2$, O**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 142.7 (C), 128.6 (2 x CH), 127.5 (CH), 126.4 (2 x CH), 68.0 (CH_2), 57.3 (CH). The NMR data were in agreement with the literature.[217]

(*S*)-2-Amino-3,3-dimethyl-1-butanol (570).

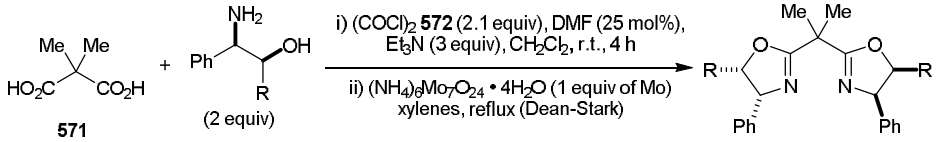


569 **570**

The title compound was prepared according the reported procedure.[218] To an ice-cooled solution of (*S*)-*tert*-leucine (**569**) (7.45 g, 57 mmol) and sodium borohydride (5.17 g, 136.8 mmol) in THF 300 mL was slowly added a solution of iodine (14.47 g, 57 mmol) in THF 50 mL over a period of 30 min (vigorous H_2 formation!). The reaction mixture

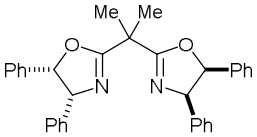
was warmed to room temperature and stirred for 30 min. The reaction mixture was subsequently heated at reflux for 24 h, cooled to 0 °C and then carefully treated with MeOH (20 mL). The solvents were removed under reduced pressure and the crude product was dissolved in 20% aqueous KOH (120 mL). After stirring for 6 h at room temperature, the reaction mixture was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford (*S*)-*tert*-leucinol (**570**) (5.30 g, 79%) as colourless oil that solidified upon cooling to room temperature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.71 (1H, dd, *J* = 10.2, 3.9 Hz, C**H**$_2$OH), 3.21 (1H, t, *J* = 10.2 Hz, C**H**NH$_2$), 2.51 (1H, dd, *J* = 10.1, 3.9 Hz, C**H**$_2$OH), 1.83 (3H, s, N**H**$_2$, O**H**), 0.9 (9H, s, 3 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 62.3 (CH), 61.8 (CH_2), 33.3 (C), 26.2 (3 x CH_3). The NMR data were in agreement with the literature.[218]

General Procedure E: Synthesis of *Bis*-Oxazoline (BOX) Ligands

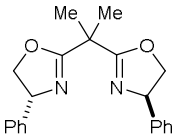


In a modification of a previously reported procedure,[150,219,220] a suspension of dimethylmalonic acid (**571**) (661 mg, 5.00 mmol) and DMF (0.1 mL, 1.3 mmol) in dichloromethane (10 mL) at 0 °C was treated with oxalyl chloride (**572**) (0.9 mL, 10.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h, then added by cannula transfer to a vigorously stirred mixture of the appropriate aminoalcohol (10 mmol) and Et_3N (4.2 mL, 30 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, then diluted with EtOAc (80 mL), washed with 1:1 brine/aqueous HCl (1 M) (3 x 50 mL) and brine (80 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the intermediate *bis*-amide in quantitative yield. The crude *bis*-amide (theoretically 4.4 mmol) was then suspended in xylenes (150 mL) and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (768 mg, 0.62 mmol) was added. The mixture was heated at reflux

using a Dean-Stark apparatus for 24 h. After cooling to room temperature, the mixture was concentrated *in vacuo* to *ca*. 25 mL, adsorbed onto silica (*ca*. 10 g) and concentrated *in vacuo*. Purification of the residue by column chromatography, followed by recrystallisation of necessary, afforded the desired *bis*-oxazolines.

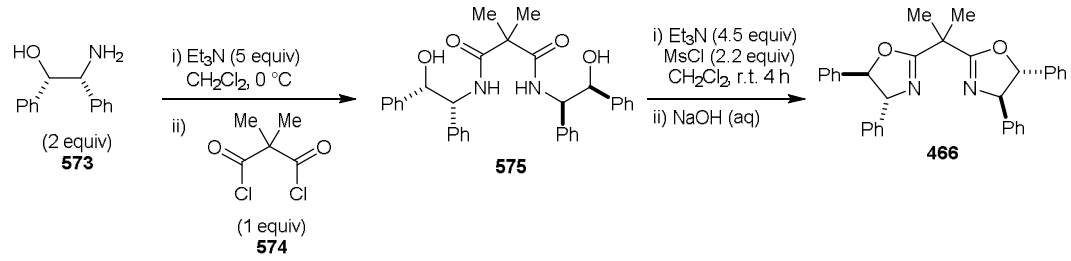


2,2-*Bis*[(4*R*,5*S*)-4,5-diphenyl-4,5-dihydro-1,3-oxazol-2-yl] propane (431). The title compound was prepared according to General Procedure E from (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**573**) (2.13 g, 10 mmol) and purified by column chromatography (20→80% EtOAc/hexane) followed by recrystallisation from heptane to afford a fine white needle (1.8 g, 78%). R_f = 0.38 (60% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.05-7.00 (10H, m, Ar**H**), 6.99-6.95 (10 H, m, Ar**H**), 5.97 (2H, d, *J* = 10.1 Hz, 2 x OC**H**), 5.60 (2H, d, *J* = 10.2 Hz, 2 x NC**H**), 1.93 (6H, s, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 170.4 (2 x C), 137.5 (2 x C), 136.2 (2 x C), 127.9 (4 x CH), 127.6 (4 x CH), 127.6 (4 x CH), 127.4 (2 x CH), 126.9 (2 x CH), 126.6 (4 x CH), 86.3 (2 x CH), 73.8 (2 x CH), 39.6 (C), 24.8 (2 x CH_3). The NMR data were in agreement with the literature.[219]



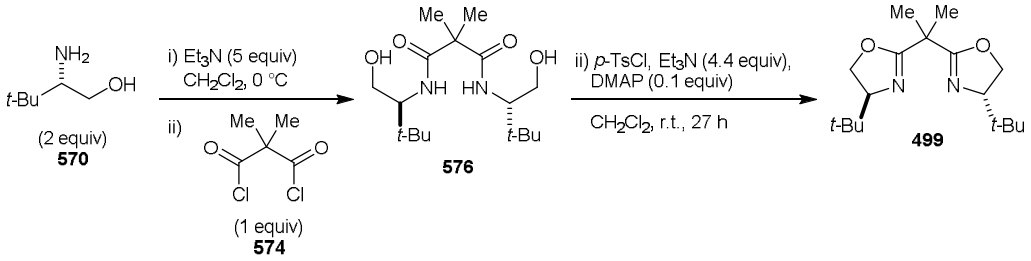
2,2-*Bis*[(*R*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]propane (498). The title compound was prepared according to General Procedure E from (*R*)-2-phenylglycinol (1.37 g, 10 mmol) and purified by column chromatography (40→80% EtOAc/hexane) to afford a yellow oil (563 mg, 35%). R_f = 0.43 (80% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.31 (4H, m, Ar**H**), 7.30-7.25 (6H, m, Ar**H**), 5.24 (2H, dd, *J* = 10.1, 7.6 Hz, 2 x OC**H**), 4.68 (2H, dd, *J* = 10.1, 8.4 Hz, 2 x OC**H′**), 4.17 (2H, dd, *J* = 8.3, 7.7 Hz, 2 x NC**H**), 1.70 (6H, s, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 170.3 (2 x C), 142.4 (2 x C), 128.6 (4 x CH), 127.5 (2 x CH), 126.6 (4 x CH), 75.5 (2 x CH), 69.4 (2 x CH_2), 38.9 (C), 24.5 (2 x CH_3). The NMR data were in agreement with the literature.[220,221]

2,2-*Bis*{2-[(4*R*,5*R*)-diphenyl-1,3-oxazolinyl]}propane (466).



In a modification of a previously reported procedure,[219] (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**573**) (213 mg, 1 mmol) and triethylamine (0.42 mL, 3 mmol) were dissolved in dichloromethane (10 mL) at 0 °C. Dimethylmalonyl chloride (**574)** (84 mg, 0.5 mmol) in dichloromethane (2 mL) was added dropwise under N_2, keeping the temperature below 0 °C. Stirring was continued overnight at room temperature, then the reaction mixture was quenched with H_2O (10 mL). A white solid was separated, filtered and then washed with aq. HCl (1 M, 10 mL) to afford crude **575** (>99%). To the crude *bis*-amide **575** (0.5 mmol) in dichloromethane (10 mL) and triethylamine (0.42 mL, 3 mmol), methanesulfonyl chloride (131 mg, 1.15 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. Then the solvent was distilled off and to the oily residue was added ethanol (10 mL) and aqueous NaOH (2 M, 4 mL). After 3 h reflux the residue was purified by column chromatography (7% EtOAc/hexane) to afford the product **466** as a white solid (37 mg, 15% yield). R_f = 0.19 (30% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35-7.25 (20H, m, Ar**H**), 5.31 (2H, d, *J* = 7.6 Hz, 2 x OC**H**), 5.10 (2H, d, *J* = 7.6 Hz, 2 x NC**H**), 1.87 (6H, s, 2 x C$\mathbf{H}_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 169.7 (2 x C), 142.0 (2 x C), 140.4 (2 x C), 128.9 (4 x CH), 128.8 (4 x CH), 128.4 (2 x CH), 127.7 (2 x CH), 126.7 (4 x CH), 125.9 (4 x CH), 89.8 (2 x CH), 78.6 (2 x CH), 39.4 (C), 24.9 (2 x CH_3). The NMR data were in agreement with the literature.[219]

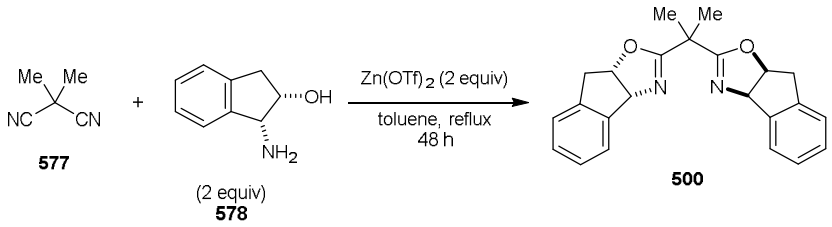
(4*S*)-4-*tert*-Butyl-2-{2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]propan-2-yl}-4,5-dihydro-1,3-oxazole (499)



The title compound was prepared according to a modification of the procedure reported by Evans and co-workers.[222a] A 100-mL two-necked flask with a magnetic stirrer was charged with a solution of (*S*)-*tert*-leucinol (**570**) (1.17 g, 10 mmol), in 15 mL of dichloromethane. The solution was cooled in an ice bath, and triethylamine (4.17 mL, 30 mmol) was added dropwise. A solution of dimethylmalonyl dichloride (**574**) (85 mg, 5 mmol) in dichloromethane (5 mL) was added to the vigorously stirred mixture over 10 min. The ice bath was removed, and the thick white suspension was stirred at room temperature for 35 min before dichloromethane (10 mL) was added. The reaction mixture was washed with 10 mL of aq. HCl (1 M), and the aqueous layer was back-extracted with dichloromethane (10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), and brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a crude *bis*-amide **576** as a white solid (1.31 g, 83%). A 150-mL round bottom flask with a magnetic stir bar was charged with the crude *bis*-amide **576** (1.28 g, 4.06 mmol), DMAP (50 mg, 0.41 mmol) and dichloromethane (20 mL) and triethylamine (2.5 mL, 17.86 mmol). The flask was placed in a water bath (room temperature), and a solution of *p*-toluenesulfonylchloride (1.55 g, 8.12 mmol) in dichloromethane (10 mL) was added *via* a cannula. The bright yellow solution was stirred at room temperature for 27 h, then diluted with dichloromethane (20 mL) and washed with saturated aqueous NH_4Cl (20 mL). Water (20 mL) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*.

Purification of the residue by column chromatography (20→80% EtOAc/hexane) afforded the title compound as a yellow gum (530 mg, 44% from *bis*-amide). R_f = 0.54 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.17-4.06 (4H, m, 2 x OC**H**$_2$), 3.85 (2H, dd, *J* = 10.0, 7.0 Hz, 2 x NC**H**), 1.52 (6H, s, 2 x C**H**$_3$), 0.88 (18H, s, 6 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 168.6 (2 x C), 75.3 (2 x CH), 69.0 (2 x CH_2), 38.6 (C), 34.0 (2 x C), 25.6 (6 x CH_3), 24.4 (2 x CH_3). The NMR data were in agreement with the literature.[222]

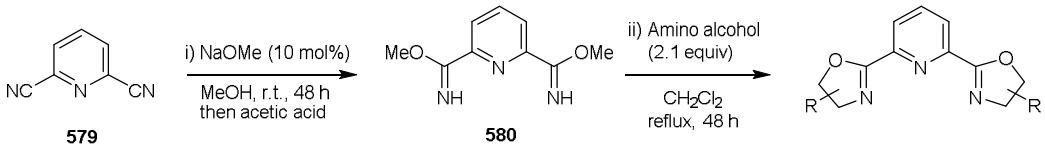
(3*aR*,8*aS*)-2{2-[(3*aR*,8*aS*)-3*aH*,8*H*,8*aH*-indeno-[1,2-d]-1,3-oxazol-2-yl]propan-2-yl}-3*aH*,8*H*,8*aH*-indeno[1, 2-d][1, 3]-oxazole (500).



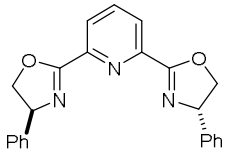
In a modification of a previously reported procedure,[223a] a 50 mL two-necked round-bottomed flask fitted with a reflux condenser was charged with 2,2-dimethylmalononitrile (**577**) (115 mg, 1.22 mmol), zinc triflate (885 mg, 2.43 mmol) and (*1R*,2*S*)-(+)-*cis*-1-amino-2-indanol (**578**) (115 mg, 2.43 mmol). The system was purged with nitrogen and anhydrous toluene (20 mL) was added. The solution was heated at reflux for 48 h. The system was allowed to cool and after diluting with more toluene (6 mL) was then washed with brine (3 x 40 mL) and $NaHCO_3$ (3 x 40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give almost pure product. It was further purified by recrystallisation (EtOAc/hexane) to give the desired product **500** as a white solid (314 mg, 72%). R_f = 0.16 (60% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52-7.48 (2H, m, Ar**H**), 7.30-7.22 (6H, m, Ar**H**), 5.53 (2H, d, *J* = 7.9 Hz, 2 x OC**H**), 5.24-5.29 (2H, m, 2 x NC**H**), 3.31 (2H, dd, *J* = 17.9, 7.1 Hz, C**H**$_2$), 2.96 (2H, d, *J* = 17.8 Hz, C**H′**$_2$), 1.43 (6H, s, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 169.1 (2 x C), 141.8 (2 x C), 139.7 (2 x C), 128.3 (2 x CH), 127.3 (2 x CH), 125.6 (2 x CH), 125.1 (2 x CH),

83.2 (2 x CH), 76.4 (2 x CH), 39.6 (2 x CH_2), 38.5 (C), 23.9 (2 x CH_3). The NMR data were in agreement with the literature.[223b]

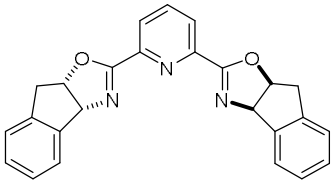
General Procedure F: Synthesis of PyBox Ligands



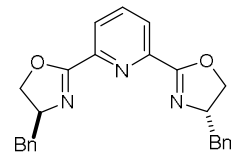
PyBox ligands were prepared according to a previously reported procedure.[224] Sodium methoxide (2 mg, 0.04 mmol) was dissolved in methanol (5 mL) and then treated with pyridine-2,6-dicarbonitrile (**579**) (47 mg, 0.36 mmol). The mixture was stirred at room temperature for 48 h, followed by addition of acetic acid (10 μL). The solvent was evaporated and the resulting solid, dimethyl pyridine-2,6-dicarboximidate (**580**), was dried under *vacuum* and used without further purification. A suspension of this compound (0.36 mmol) and amino alcohol (0.76 mmol) in dichloromethane (20 mL) was stirred at reflux for two days. After removal of the solvent, the residue was crystallised from methanol to give the desired PyBox ligands.



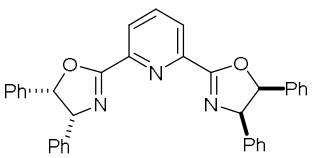
2,6-*Bis*[(*4S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine (502). The title compound was prepared according to General Procedure F from (*S*)-2-phenylglycinol (**568**) (104 mg, 0.76 mmol) and purified by recrystallisation in methanol to afford a white solid (84 mg, 63%). R_f = 0.14 (EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.36 (2H, d, *J* = 7.8 Hz, Ar**H**), 7.93 (1H, t, *J* = 7.9 Hz, Ar**H**), 7.40-7.29 (10H, m, Ar**H**), 5.47 (2H, dd, *J* = 10.2, 8.7 Hz, 2 x OC**H**), 4.94 (2H, dd, *J* = 10.9, 8.6 Hz, 2 x OC**H′**), 4.44 (2H, t, *J* = 8.6 Hz, 2 x NC**H**); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 163.5 (2 x C), 146.8 (2 x C), 141.7 (2 x C), 137.4 (CH), 128.8 (4 x CH), 127.8 (2 x CH), 126.8 (4 x CH), 126.3 (2 x CH), 75.5 (2 x CH), 70.4 (2 x CH_2). The NMR data were in agreement with the literature.[224]



2,6-*Bis*[(3*aR*,8*aS*)-3*aH*,8*H*,8*aH*-indeno[1,2-d][1,3] oxazol-2-yl]pyridine (503). The title compound was prepared according to General Procedure F from (1*R*,2*S*)-(+)-*cis*-aminoidal-ol (**578**) (313 mg, 2.1 mmol) and purified by recrystallisation in methanol to afford a white solid (387 mg, 98%). R_f = 0.15 (EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.78 (1H, t, *J* = 7.9 Hz, Ar**H**), 7.58-7.54 (2H, m, Ar**H**), 7.29-7.24 (6H, m, Ar**H**), 5.79 (2H, d, *J* = 8.0 Hz, 2 x OC**H**), 5.6 (2H, dt, *J* = 8.3, 4.3 Hz, 2 x NC**H**), 3.5 (4H, d, *J* = 4.03 Hz, 2 x C**H**$_2$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 162.8 (2 x C), 147.0 (2 x C), 141.4 (2 x C), 139.9 (2 x C), 137.1 (CH), 128.6 (2 x CH), 127.4 (2 x CH), 126.0 (2 x CH), 125.6 (2 x CH), 125.3 (2 x CH), 84.3 (2 x CH), 77.0 (2 x CH), 39.7 (2 x CH_2). The data is in agreement with the literature.[224]

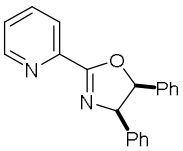


2,6-*Bis*[(*4S*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine (504). The title compound was prepared according to General Procedure F from (*S*)-(−)-2-amino-3-phenyl-1-propanol (159 mg, 1.05 mmol) and purified by recrystallisation in methanol to afford a white solid (152 mg, 77%). R_f = 0.26 (EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (2H, d, *J* = 7.8 Hz, Ar**H**), 7.9 (1H, t, *J* = 7.8 Hz, Ar**H**), 7.34-7.29 (4H, m, Ar**H**), 7.27-7.22 (6H, m, Ar**H**), 4.66 (2H, tdd, *J* = 9.1, 7.6, 5.2 Hz, 2 x NC**H**), 4.47 (2H, dd, *J* = 9.4, 8.7 Hz, 2 x OC**H**), 4.26 (2H, dd, *J* = 8.6, 7.6 Hz, 2 x OC**H′**), 3.28 (2H, dd, *J* = 13.8, 5.2 Hz, 2 x C**H**$_2$), 2.76 (2H, dd, *J* = 13.8, 9.0 Hz, 2 x C**H′**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 162.7 (2 x C), 146.8 (2 x C), 137.7 (2 x C), 137.4 (CH), 129.2 (4 x CH), 128.6 (4 x CH), 126.6 (2 x CH), 125.8 (2 x CH), 72.6 (2 x CH_2), 68.1 (2 x CH), 41.7 (2 x CH_2). The NMR data were in agreement with the literature.[225]



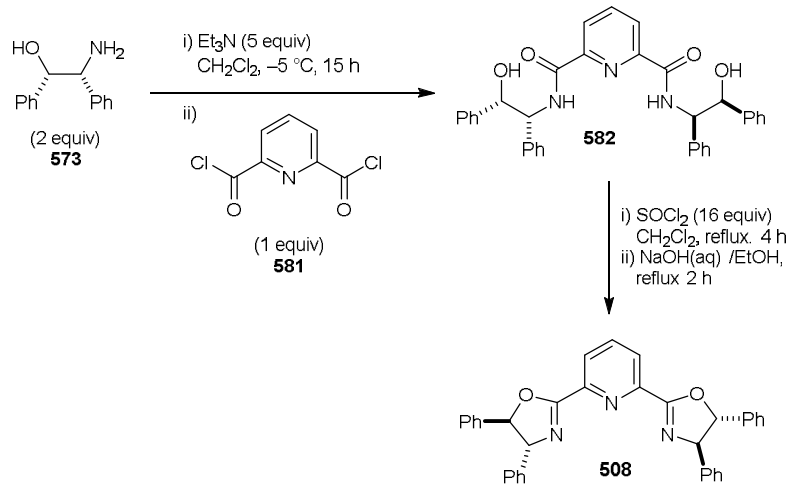
2,6-Bis[(*4R*,*5S*)-4,5-diphenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine (505). The title compound was prepared according to General Procedure F from (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**573**) (224 mg, 1.05 mmol) and purified by recrystalisation in methanol to afford a white solid (486 mg, 93%). R_f = 0.65 (EtOAc); **^{1}H NMR**

(600 MHz, $CDCl_3$) δ 8.46 (2H, d, *J* = 7.8 Hz, Ar**H**), 8.04 (1H, t, *J* = 7.9 Hz, Ar**H**), 7.09-7.02 (12H, m, Ar**H**), 7.01-6.97 (8H, m, Ar**H**), 6.15 (2H, d, *J* = 10.3 H, 2 x OC**H**), 5.84 (2H, d, *J* = 10.3 Hz, 2 x NC**H**); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 164.0 (2 x C), 147.2 (2 x C), 137.5 (CH), 137.3 (2 x C), 136.1 (2 x C), 127.9 (4 x CH), 127.7 (4 x CH), 127.6 (4 x CH), 127.5 (2 x CH), 127.1 (2 x CH), 126.6 (4 x CH), 126.4 (2 x CH), 86.3 (2 x CH), 74.5 (2 x CH). The NMR data were in agreement with the literature.[224]



2-[(4*R*,5*S*)-4,5-Diphenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine (507). The title compound was prepared according to General Procedure F from (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**573**) (224 mg, 1.05 mmol) and 2-cyanopyridine (52 mg, 0.5 mmol) and then purified by column chromatography (40→100% EtOAc/hexane) to afford a colourless gum (114.2 mg, 76%). R_f = 0.32 (EtOAc); $[\alpha]_D^{20}$ +46.4 (*c* 1.7, $CHCl_3$); **IR** (film) 2920, 1643, 1584, 1454, 1337, 1099, 966, 744, 696 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.83-8.81 (1H, m, Ar**H**), 8.27 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.86 (1H, td, *J* = 7.8, 1.7 Hz, Ar**H**), 7.47 (1H, ddd, *J* = 7.6, 4.8, 1.1, 1.0 Hz, Ar**H**), 7.08-7.01 (6H, m, Ar**H**), 7.00-6.95 (4H, m, Ar**H**), 6.12 (1H, d, *J* = 10.3 Hz, OC**H**), 5.83 (1H, d, *J* = 10.3 Hz, NC**H**); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 164.1 (C), 150.0 (CH), 146.6 (C), 137.3 (C), 136.7 (CH), 136.1 (C), 127.9 (2 x CH), 127.6 (4 x CH), 127.4 (CH), 127.0 (CH), 126.4 (2 x CH), 125.8 (CH), 124.3 (CH), 86.0 (CH), 74.6 (CH); **HRMS** (ESI) Exact mass calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$: 301.1335, found 301.1334.

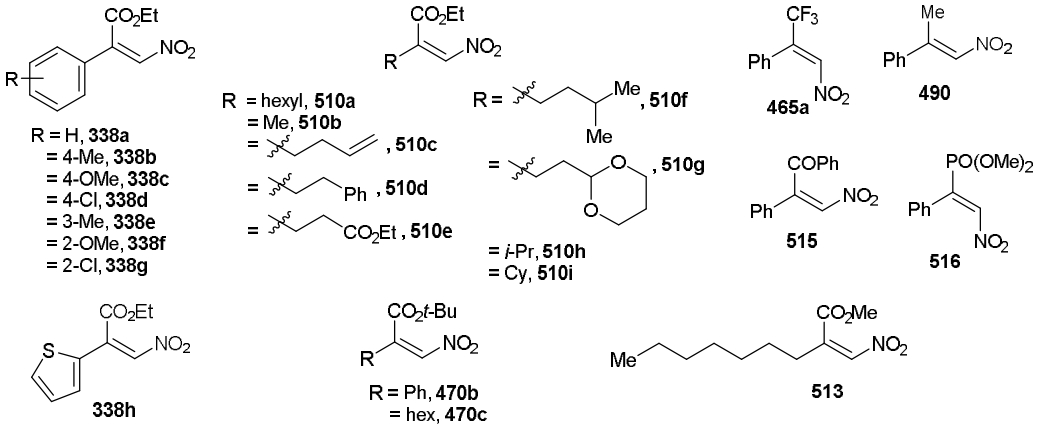
2,6-*Bis*[(*4R,5R*)-diphenyl-1,3-oxazolin-2-yl]pyridine (508)



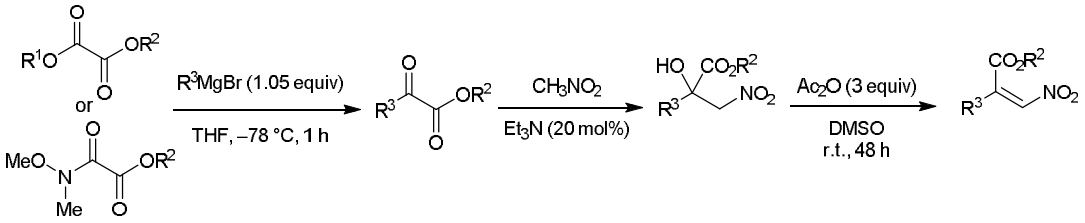
In a modification of a previously reported procedure,[226] a solution of pyridine 2,6-dicarbonylchloride (**581**) (102 mg, 0.5 mmol) in dried dichloromethane (10 mL), was added dropwise to a mixture of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**573**) (224 mg, 1.05 mmol) and trimethylamine (0.42 mL, 3 mmol) in dried dichloromethane (10 mL) at –5 °C. The reaction was stirred at room temperature overnight. The white precipitate was filtered and washed with water to give **2,6-*bis*[(1*R*,2*S*)*N,N*'-2-hydroxy-1,2-diphenylethyl]pyridinedicarboxamide** (**582**) as a pale yellow solid (231 mg, 83% yield). **^{1}H NMR** (600 MHz, DMSO-d_6) δ 9.03 (2H, d, *J* = 8.9 Hz, 2 x N**H**), 8.12-8.01 (3H, m, Ar**H**), 7.44-7.12 (20H, m, Ar**H**), 5.84 (2H, d, *J* = 4.7 Hz, 2 x O**H**), 5.24-5.14 (4H, m, 2 x NC**H**, 2 x OC**H**); **^{13}C NMR** (150.8 MHz, DMSO-d_6) δ 162.2 (2 x C), 148.9 (2 x C), 142.8 (2 x C), 139.7 (2 x C), 139.6 (CH), 128.5 (4 x CH), 127.7 (8 x CH), 127.1 (4 x CH), 126.7 (4 x CH), 124.7 (2 x CH), 74.3 (2 x CH), 58.9 (2 x CH); To a suspension of *bis*-amide (**581**) (200 mg, 0.36 mmol) in dried dichloromethane (5 mL), a solution of $SOCl_2$ (0.42 mL, 5.76 mmol) in the same solvent (1 mL) was added dropwise, and the mixture was heated at reflux for 3 h. The solvent and excess $SOCl_2$ were removed under *vacuum* and the mixture was washed with water (2 x 10 mL). This residue (0.36 mmol) was then suspended in ethanol (4 mL), an aqueous solution of NaOH (2M, 4 mL) was added and the mixture was heated at reflux for 3 h. The hot

suspension was filtered and the white solid was washed with water (10 mL) give **508** (20 mg, 12% from **582** as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.39 (2H, d, *J* = 7.8 Hz, Ar**H**), 7.98 (1H, t, *J* = 7.9 Hz, Ar**H**), 7.50-7.30 (20H, m, Ar**H**), 5.55 (2H, d, *J* = 8.4 H, 2 x OC**H**), 5.33 (2H, d, *J* = 8.4 Hz, 2 x NC**H**); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 163.0 (2 x C), 147.1 (2 x C), 141.3 (2 x C), 139.7 (2 x C), 137.5 (CH), 128.9 (4 x CH), 128.8 (4 x CH), 128.6 (2 x CH), 127.9 (2 x CH), 126.9 (4 x CH), 126.6 (2 x CH), 126.3 (4 x CH), 90.1 (2 x CH), 79.0 (2 x CH). The data is in agreement with the literature.[226]

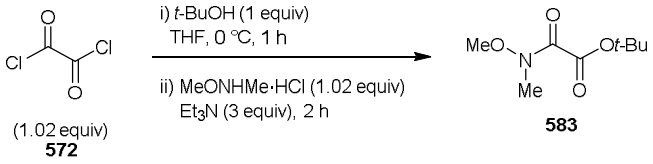
3.2.3 Synthesis of Nitroalkenes



Nitroalkene **490**[227] was prepared by Alain J. Simpson according to previously reported procedure. Nitrostyrenes **338a**,[172] **338c**,[172] **338d**,[172] **338f**, and **338h**[172] were prepared by Alain J. Simpson according to general procedure J. Yields and reaction times reported in this Section are unoptimised. A general pathway to obtain nitroacrylates is shown below.

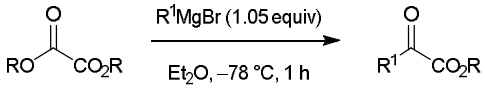


Mono-*tert*-butyloxalic acid-*N*-methoxy-*N*-methylamide (583)



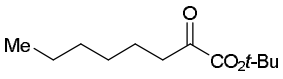
According to a previously reported procedure,[154] *tert*-butanol (7.4 g, 100 mmol) was slowly added in one charge to a solution of oxalyl chloride (**572**) (8.76 mL, 102 mmol) in THF (100 mL) at 0 °C under nitrogen. After 1 h, *N*,*O*-dimethylhydroxylamine hydrochloride (9.95 g, 102 mmol) and triethylamine (42 mL, 301 mmol) were added and the solution was stirred for 2 h. Water (200 mL) was added, and THF was evaporated under reduced pressure. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10% EtOAc/hexane) to give **583** as a pale yellow oil (14.85 g, 79%). R_f = 0.40 (40% EtOAc/hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.72 (3H, s, OC**H**$_3$), 3.17 (3H, s, NC**H**$_3$), 1.53 (9H, s, 3 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 162.3 (C), 161.8 (C), 84.1 (CH_3), 62.0 (CH_3), 31.1 (C), 27.8 (3 x CH_3). The NMR data were in agreement with the literature.[154]

General Procedure G: Synthesis of α-Ketoesters

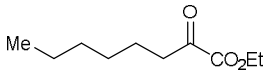


In a modification of a previously reported procedure,[173] to a solution of dialkyl oxalate or monoalkyloxalic acid-*N*-methoxy-*N*-methylamide (**583**) (40 mmol) in Et_2O (40 mL) at –78 °C was added a solution of the appropriate Grignard reagent (42.0 mmol) in THF dropwise over 1 h. The reaction mixture was stirred at –78 °C for 1 h, then allowed to warm to 10 °C and quenched with aqueous HCl (10% w/v, 10 mL). After stirring at room temperature for 5 min, the mixture was diluted with H_2O (10 mL) and the layers

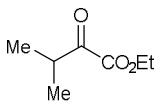
were separated. The aqueous phase was extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the α-ketoesters.



***tert*-Butyl 2-oxooctanoate (584a)**. The title compound was prepared according to General Procedure G from mono-*tert*-butyloxalic acid-*N*-methoxy-*N*-methylamide (**583**) (3.78 g, 20 mmol) and hexylmagnesium bromide (2.0 M in Et_2O, 10.5 mL, 21 mmol) and purified by column chromatography (1→4% EtOAc/hexane) to afford a colourless oil (1.42 g, 33%). R_f = 0.53 (10% EtOAc/hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.75 (2H, t, J = 7.4 Hz, C**H**$_2$), 1.30-1.58 (2H, m, C**H**$_2$), 1.54 (9H, s, 3 x C**H**$_3$), 1.35-1.25 (6H, m, 3 x C**H**$_2$), 0.88 (3H, t, J = 6.9 Hz, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 195.8 (C), 160.9 (C), 83.7 (C), 39.1 (CH_2), 31.4 (CH_2), 28.6 (CH_2), 27.8 (3 x CH_3), 23.0 (CH_2), 22.4 (CH_2), 13.9 (CH_3). The NMR data were in agreement with the literature.[156]

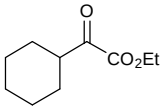


Ethyl 2-oxooctanoate (585a). The title compound was prepared according to General Procedure G from diethyl oxalate (5.85 g, 40 mmol) and hexylmagnesium bromide (2.0 M in Et_2O, 21 mL, 42 mmol) and purified by column chromatography (5→20% Et_2O/hexane) to afford a colourless oil (6.37 g, 85%). R_f = 0.54 (40% Et_2O/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.38-4.27 (2H, m, OC**H**$_2$), 2.83 (2H, t, J = 7.3 Hz, C**H**$_2$), 1.68-1.60 (2H, m, C**H**$_2$), 1.41-1.25 (9H, m, 3 x C**H**$_2$, C**H**$_3$), 0.89 (3H, t, J = 7.0 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 194.8 (C), 161.3 (C), 62.3 (CH_2), 39.3 (CH_2), 31.4 (CH_2), 28.6 (CH_2), 22.9 (CH_2), 22.4 (CH_2), 14.0 (2 x CH_3). The NMR data were in agreement with the literature.[228]

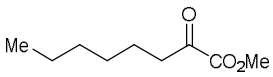


Ethyl 3-methyl-2-oxobutanoate (585b). The title compound was prepared according to General Procedure G from diethyl oxalate (5.85 g, 40 mmol) and *iso*propylmagnesium chloride (2.0 M in THF, 21 mL, 42 mmol) and purified by column chromatography (5→20% EtOAc/hexane) to afford a colourless oil (5.54 g, 96%). R_f = 0.53 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.26 (2H, q, J = 7.2 Hz, OC**H**$_2$), 3.24-3.15 (1H, m, C**H**), 1.31 (3H, t, J = 7.2

Hz, C**H**$_3$), 1.10 (6H, d, *J* = 7.0 Hz, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.1 (C), 161.7 (C), 62.0 (CH_2), 36.8 (CH), 17.0 (2 x CH_3), 13.8 (CH_3). The NMR data were in agreement with the literature.[229]

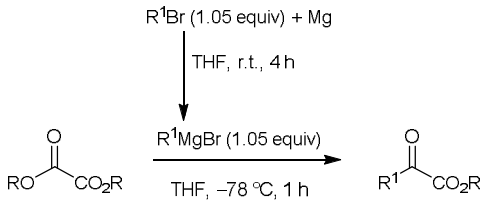


Ethyl 2-cyclohexyl-2-oxoacetate (585c). The title compound was prepared according to General Procedure G from diethyl oxalate (7.31 g, 50 mmol) and cyclohexylmagnesium chloride (2.0 M in Et_2O, 26.5 mL, 53 mmol) and purified by column chromatography (5% EtOAc/hexane) to afford a colourless oil (6.30 g, 85%). R_f = 0.59 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.32 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 3.06-3.01 (1H, m, C**H**), 1.93-1.89 (2H, m, C**H**$_2$), 1.83-1.79 (2H, m, C**H**$_2$), 1.73-1.66 (1H, m, C**H**$_2$), 1.40-1.31 (7H, m, 2 x C**H**$_2$, C**H**$_3$), 1.27-1.19 (1H, m, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 197.7 (C), 162.0 (C), 62.2 (CH_2), 46.3 (CH), 27.5 (2 x CH_2), 25.7 (CH_2), 25.3 (2 x CH_2), 14.0 (CH_3). The NMR data were in agreement with the literature.[229a]

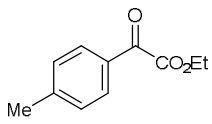


Methyl 2-oxooctanoate (586). The title compound was prepared according to General Procedure G from dimethyl oxalate (2.36 g, 20 mmol) and hexylmagnesium bromide (2.0 M in Et_2O, 10.5 mL, 21 mmol) and purified by column chromatography (2→8% EtOAc/hexane) to afford a colourless oil (585 mg, 17%). R_f = 0.59 (20% EtOAc/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.87 (3H, s, OC**H**$_3$), 2.84 (2H, t, *J* = 7.3 Hz, C**H**$_2$), 1.68-1.57 (2H, m, C**H**$_2$), 1.38-1.24 (6H, m, 3 x C**H**$_2$), 0.89 (3H, t, *J* = 6.9 Hz, C**H**$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 194.4 (C), 161.6 (C), 52.9 (CH_3), 39.3 (CH_2), 31.4 (CH_2), 28.6 (CH_2), 22.9 (CH_2), 22.4 (CH_2), 14 (CH_3). The data NMR were in agreement with the literature.[230]

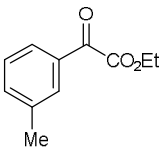
General procedure H: Synthesis of *α*-Ketoesters



In a modification of a previously reported procedure,[173] magnesium turning (2.56 g, 105 mmol) were heated (60 °C) at reduced pressure for 10 min in a three-necked round-bottomed flask with condenser. After cooling to room temperature, THF (90 mL) was added, followed by a solution of alkyl or aryl halide (105 mmol) in THF (10 mL) which was added dropwise.The reaction mixture was stirred at reflux for 10 min and then at room temperature for 4 h to afford the corresponding Grignard reagent. This was added to a solution of dialkyl oxalate or monoalkyloxalic acid-*N*-methoxy-*N*-methylamide (**583**) (100 mmol) in Et_2O (100 mL) at –78 °C dropwise over 1 h. The reaction mixture was stirred at –78 °C for 1 h, then allowed to warm to 10 °C and quenched with aqueous HCl (10% w/v, 20 mL). After stirring at room temperature for 5 min, the mixture was diluted with H_2O (20 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the α-ketoesters.

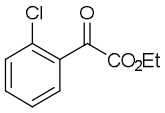


Ethyl 2-(4-methylphenyl)-2-oxoacetate (585d). The title compound was prepared according to General Procedure H from diethyl oxalate (14.6 g, 100 mmol), magnesium turning (2.67 g, 110 mmol) and 4-bromophenol (18.80 g, 110 mmol) and purified by column chromatography (40% Et_2O/hexane) to afford a colourless oil (9.02 g, 47%). R_f = 0.54 (30% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.31 (2H, d, *J* = 8.3 Hz, Ar**H**), 4.45 (2H, q, *J* = 7.2 Hz, OC**H**$_2$), 2.44 (3H, s, C**H**$_3$), 1.42 (3H, t, *J* = 7.2 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 186.1 (C), 164.0 (C), 146.2 (C), 130.1 (2 x CH), 130 (C), 129.6 (2 x CH), 62.2 (CH_2), 21.9 (CH_3), 14.1 (CH_3). The NMR data were in agreement with the literature.[231]

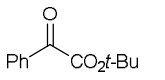


Ethyl 2-(3-methylphenyl)-2-oxoacetate (585e). The title compound was prepared according to General Procedure H from diethyl oxalate (7.3 g, 50 mmol), magnesium turning (1.46 g, 60 mmol) and 3-bromophenol (9.2 g, 53 mmol) and purified by column chromatography (2→6% EtOAc/hexane) to afford a colourless oil (6.41 g, 67%). R_f = 0.47 (20% EtOAc/hexane); **^{1}H NMR**

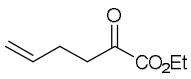
(400 MHz, $CDCl_3$) δ 7.83-7.79 (2H, m, Ar**H**), 7.50-7.46 (1H, m, Ar**H**), 7.43-7.38 (1H, m, Ar**H**), 4.46 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 2.43 (3H, s, C**H**$_3$), 1.43 (3H, t, *J* = 7.2 Hz, C**H**$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 186.7 (C), 164.0 (C), 138.8 (C), 135.7 (CH), 132.5 (C), 130.3 (CH), 128.8 (CH), 127.4 (CH), 62.3 (CH_2), 21.3 (CH_3), 14.1 (CH_3). The NMR data were in agreement with the literature.[231]



Ethyl 2-(2-chlorophenyl)-2-oxoacetate (585f). The title compound was prepared according to General Procedure H from diethyl oxalate (2.2 g, 15 mmol), magnesium turning (437 mg, 18 mmol) and 1-bromo-2-chlorobenzene (2.87 g, 15 mmol) and purified by column chromatography (2→6% EtOAc/hexane) to afford a colourless oil (1.74 g, 55%). R_f = 0.42 (10% EtOAc/hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (1H, dd, *J* = 7.7, 1.6 Hz, Ar**H**), 7.53-7.49 (1H, m, Ar**H**), 7.45-7.37 (2H, m, Ar**H**), 4.41 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 1.38 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 186.5 (C), 163.0 (C), 134.2 (CH), 133.7 (C), 133.3 (C), 131.5 (CH), 130.5 (CH), 127.2 (CH), 62.7 (CH_2), 13.8 (CH_3). The NMR data were in agreement with the literature.[232]

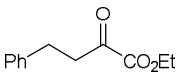


***tert*-Butyl 2-oxo-2-phenylacetate (584b)**. The title compound was prepared according to General Procedure H from mono-*tert*-butyloxalic acid-*N*-methoxy-*N*-methylamide (**583**) (3.78 g, 20 mmol), magnesium turning (583 mg, 24 mmol) and bromobenzene (3.14 g, 20 mmol) and purified by column chromatography (1→4% EtOAc/hexane) to afford a yellow oil (3.1 g, 75 %). R_f = 0.54 (10% EtOAc/hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 7.3 Hz, Ar**H**), 7.64 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.51 (2H, t, *J* = 7.8 Hz, Ar**H**), 1.63 (9H, s, 3 x C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 186.8 (C), 163.7 (C), 134.6 (CH), 132.5 (C), 129.8 (2 x CH), 128.8 (2 x CH), 84.7 (C), 28.0 (3 x CH_3). The NMR data were in agreement with the literature.[233]

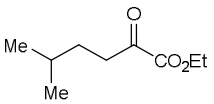


Ethyl 2-oxohex-5-enoate (585g). The title compound was prepared according to General Procedure H from diethyl oxalate (4.5 g, 30 mmol), magnesium turning (972 mg, 40 mmol) and 4-bromo-1-butene

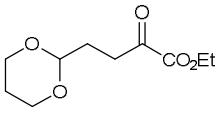
(5 g, 37 mmol) and purified by column chromatography (1→3% EtOAc/hexane) to afford a pale yellow oil (2.26 g, 39%). R_f = 0.42 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.88-5.77 (1H, m, C**H**=), 5.11-5.00 (2H, m, C**H**$_2$=), 4.33 (2H, qd, J = 7.1, 0.9 Hz, OC**H**$_2$), 2.98-2.93 (2H, m, C**H**$_2$), 2.44-2.37 (2H, m, C**H**$_2$), 1.38 (3H, td, J = 7.1, 0.8 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 193.8 (C), 161.1 (C), 136.1 (CH_2), 115.9 (CH), 62.4 (CH_2), 38.4 (CH_2), 26.9 (CH_2), 14.0 (CH_3). The NMR data were in agreement with the literature.[234]



Ethyl 2-oxo-4-phenylbutanoate (585h). The title compound was prepared according to General Procedure H from diethyl oxalate (5.85 g, 40 mmol), magnesium turning (972 mg, 40 mmol) and (2-bromoethyl) benzene (7.4 g, 40 mmol) and purified by column chromatography (5→20% EtOAc/hexane) to afford a pale yellow oil (1.98 g, 24%). R_f = 0.34 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32.7.28 (2H, m, Ar**H**), 7.24-7.20 (3H, m, Ar**H**), 4.32 (2H, q, J = 7.1 Hz, OC**H**$_2$), 3.19 (2H, t, J = 7.4 Hz, C**H**$_2$), 2.97 (2H, t, J = 7.5 Hz, C**H**$_2$), 1.37 (3H, t, J = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 193.6 (C), 160.9 (C), 140.1 (C), 128.6 (2 x CH), 128.4 (2 x CH), 126.4 (CH), 62.5 (CH_2), 40.9 (CH_2), 29.0 (CH_2), 14.0 (CH_3). The NMR data were in agreement with the literature.[232,235]

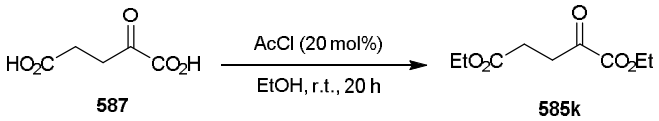


Ethyl 5-methyl-2-oxo-hexanoate (585i). The title compound was prepared according to General Procedure H from diethyl oxalate (14.6 g, 100 mmol), magnesium turning (2.92 g, 120 mmol) and 1-bromo-3-methyl butane (15.9 g, 100 mmol) and purified by column chromatography (2→5% EtOAc/hexane) to afford a colourless oil (5.0 g, 29%). R_f = 0.50 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.39-4.27 (2H, m, OC**H**$_2$), 2.83 (2H, dd, J = 8.0, 7.2 Hz, C**H**$_2$), 1.65-1.49 (3H, m, C**H**, C**H**$_2$), 1.41-1.32 (3H, m, C**H**$_3$), 0.92 (6H, d, J = 6.5 Hz, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 194.9 (C), 161.0 (C), 62.3 (CH_2), 37.3 (CH_2), 31.7 (CH_2), 27.6 (CH), 22.2 (2 x CH_3), 14.0 (CH_3). The NMR data were in agreement with the literature.[236]



Ethyl 4-(1,3-dioxan-2-yl)-2-oxobutanoate (585j). The title compound was prepared according to General Procedure H from diethyl oxalate (3.75 g, 25.6 mmol), magnesium turning (1.25 g, 51 mmol) and 2-(2-bromoethyl)-1,3-dioxane (5 g, 25.6 mmol) and purified by column chromatography (2→20% EtOAc/hexane) to afford a colourless oil (1.54 g, 28%). R_f = 0.20 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.61 (1H, t, *J* = 4.7 Hz, OC**H**), 4.31 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 4.09-4.03 (2H, m, OC**H**$_2$), 3.76-3.69 (2H, m, OC**H**$_2$), 2.94 (2H, t, *J* = 7.1 Hz, C**H**$_2$), 2.09-1.98 (1H, m, C**H**$_2$), 1.97 (2H, td, *J* = 7.1, 4.7 Hz, C**H**$_2$), 1.36 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 1.34-1.29 (1H, m, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 194.0 (C), 161.0 (C), 100.2 (CH), 66.7 (2 x CH_2), 62.2 (CH_2), 33.5 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 14.0 (CH_3). The NMR data were in agreement with the literature.[237]

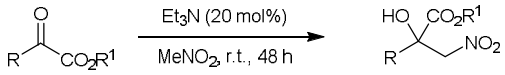
1,5-Diethyl 2-oxopentanedioate (585k)



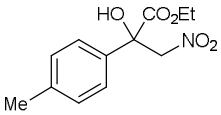
587 **585k**

In a modification of a previously reported procedure,[238] to a solution of *α*-oxo-glutaric acid (**587**) (5.88 g, 40 mmol) in ethanol (60 mL) was added acetyl chloride (550 µL, 8 mmol) dropwise. The reaction mixture was stirred at room temperature for 20 h and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (100 mL) and washed with water (2 x 50 mL). The organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **585k** as a colourless oil (7.24 g, 90%). R_f = 0.32 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.34 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 4.15 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 3.16 (2H, t, *J* = 6.5 Hz, C**H**$_2$), 2.67 (2H, t, *J* = 6.5 Hz, C**H**$_2$), 1.38 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 1.27 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 192.7 (C), 172.0 (C), 160.6 (C), 62.6 (CH_2), 60.9 (CH_2), 34.2 (CH_2), 27.7 (CH_2), 14.1 (CH_3), 14.0 (CH_3). The NMR data were in agreement with the literature.[238,239]

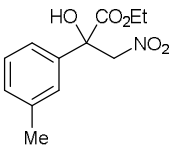
General Procedure I: Synthesis of *β*-Nitro-*α*-Hydroxyesters



In a modification of a procedure previously reported by List and co-workers.[173] In a dried two-necked round-bottomed flask, a solution of the *α*-ketoester (120 mmol) in nitromethane (100 mL) was treated with triethylamine (3.3 mL, 24 mmol). The mixture was then stirred at room temperature until complete conversion of the *α*-ketoester as indicated by TLC analysis. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography to give the *β*-nitro-*α*-hydroxyesters.

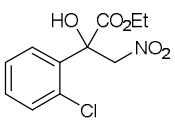


Ethyl 2-hydroxy-2-(4-methylphenyl)-3-nitropropanoate (588a). The title compound was prepared according to General Procedure I from ketoester **585d** (7.8 g, 40.6 mmol) and purified by column chromatography (20% Et_2O/hexane) to afford colourless oil (7.15 g, 70%). R_f = 0.35 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50-7.47 (2H, m, Ar**H**), 7.23-7.20 (2H, m, Ar**H**), 5.25 (1H, dd, *J* = 14.2, 1.0 Hz, C**H**$_2$NO$_2$), 4.67 (1H, d, *J* = 14.2 Hz, C**H**$_2$NO$_2$), 4.43-4.31 (2H, m, OC**H**$_2$), 4.19 (1H, d, *J* = 1.0 Hz, O**H**), 2.37 (3H, s, C**H**$_3$), 1.35 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 171.8 (C), 139.1 (C), 133.5 (C), 129.6 (2 x CH), 125.1 (2 x CH), 80.8 (CH_2), 75.9 (C), 63.5(CH_2), 21.0 (CH_3), 13.9 (CH_3). The NMR data were in agreement with the literature.[173]

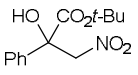


Ethyl 2-hydroxy-2-(3-methylphenyl)-3-nitropropanoate (588b). The title compound was prepared according to General Procedure I from ketoester **585e** (3.34 g, 17.35 mmol) and purified by column chromatography (2→10% EtOAc/hexane) to afford a colourless oil (4.15 g, 95%). R_f = 0.45 (20% EtOAc/hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (1H, s, Ar**H**), 7.38 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.29 (1H, t, *J* = 7.7 Hz, Ar**H**), 7.19 (1H, d, *J* = 7.5 Hz, Ar**H**), 5.26 (1H, d, *J* = 14.1 Hz, C**H**$_2$NO$_2$), 4.68 (1H, d, *J* = 14.1 Hz, C**H**$_2$NO$_2$), 4.43-4.33 (2H, m, OC**H**$_2$), 4.21 (1H, s, O**H**), 2.39 (3H, s, C**H**$_3$), 1.35 (3H, t, *J* =7.1 Hz, C**H**$_3$); **^{13}C NMR**

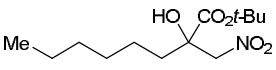
(150.8 MHz, $CDCl_3$) δ 171. (C), 138.8 (C), 136.4 (C), 129.8 (CH), 128.7 (CH), 125.8 (CH), 122.2 (CH), 80.8 (CH_2), 76.0 (C), 63.5 (CH_2), 21.5 (CH_3), 13.9 (CH_3). The NMR data were in agreement with the literature.[240]



Ethyl 2-(2-chlorophenyl)-2-hydroxy-3-nitropropanoate (588c). The title compound was prepared according to General Procedure I from ketoester **585f** (1.54 g, 7.24 mmol) and purified by column chromatography (10→40% EtOAc/hexane) to afford a colourless oil (1.38 g, 69%). R_f = 0.30 (20% EtOAc/hexane); **IR** (film) 3472 (OH), 2924, 1736 (C=O), 1555 (NO_2), 1468, 1377 (NO_2), 1225, 1119, 1036, 754 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68-7.64 (1H, m, Ar**H**), 7.43-7.39 (1H, m, Ar**H**), 7.38-7.32 (2H, m, Ar**H**), 5.43 (1H, d, J = 13.1 Hz, C**H**$_2$NO$_2$), 5.05 (1H, d, J = 13.1 Hz, C**H**$_2$NO$_2$), 4.7 (1H, s, O**H**), 4.40-4.26 (2H, m, OC**H**$_2$), 1.29 (3H, t, J = 7.1 Hz, C**H**$_3$), **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 170.0 (C), 134.5 (C), 131.6 (C), 131.3 (CH), 130.5 (CH), 128.0 (CH), 127.4 (CH), 78.7 (CH_2), 76.4 (C), 63.3 (CH_2), 13.7 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{11}H_{12}NO_5ClNa$ $[M+Na]^+$: 296.0296, found 296.0291.

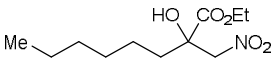


***tert*-Butyl 2-hydroxy-3-nitro-2-phenylpropanoate (589a)**. The title compound was prepared according to General Procedure I from ketoester **584b** (1.99 g, 9.65 mmol) and purified by column chromatography (10% EtOAc/hexane) to afford a colourless oil (1.63 g, 63 %). R_f = 0.24 (10% EtOAc/hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63-7.60 (2H, m, Ar**H**), 7.43-7.35 (3H, m, Ar**H**), 5.21 (1H, dd, J = 14.0, 0.9 Hz, C**H**$_2$NO$_2$), 4.66 (1H, d, J = 14.0 Hz, C**H**$_2$NO$_2$), 4.25 (1H, d, J = 1.0 Hz, O**H**), 1.53 (9H, s, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 170.5 (C), 137.0 (C), 128.9 (CH), 128.8 (2 x CH), 125.2 (2 x CH), 85.0 (C) 80.1 (CH_2), 75.9 (C), 27.7 (3 x CH_3). The NMR data were in agreement with the literature.[173]

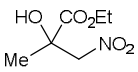


***tert*-Butyl 2-hydroxy-2-(nitromethyl)nonanoate (589b)**. The title compound was prepared according to General Procedure I from ketoester **584a** (1.2 g, 5.6 mmol) and purified by column chromatography (4→20% EtOAc/hexane) to afford a colourless oil (1.21 g, 79 %). R_f = 0.59 (20% EtOAc/hexane);

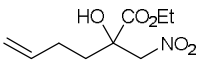
IR (film) 3495 (OH), 2924, 1730 (C=O), 1560 (NO_2), 1369 (NO_2), 1254, 1234, 1146, 1105, 843 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.76 (1H, d, *J* = 13.4 Hz, C**H**$_2$$NO_2$), 4.53 (1H, d, *J* = 13.4 Hz, C**H**$_2$$NO_2$), 3.71 (1H, s, O**H**), 1.62 (2H, dtd, *J* = 25.3, 13.3, 4.6 Hz, C**H**$_2$), 1.53-1.44 (1H, m, C**H**$_2$), 1.54 (9H, s, 3 x C**H**$_3$), 1.35-1.23 (6H, m, 3 x C**H**$_2$), 1.21-1.12 (1H, m, C**H**$_2$), 0.89 (3H, t, *J* = 6.8 Hz, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 171.8 (C), 84.2 (C), 81.1 (CH_2), 75.1 (C), 36.7 (CH_2), 31.5 (CH_2), 29.1 (CH_2), 27.8 (3 x CH_3), 22.5 (CH_2), 22.4 (CH_2), 14.0 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{13}H_{25}NO_5Na$ $[M+Na]^+$: 298.1625, found 298.1620.



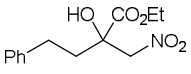
Ethyl 2-hydroxy-2-(nitromethyl)octanoate (588d). The title compound was prepared according to General Procedure I from ketoester **585a** (6 g, 32.22 mmol) and purified by column chromatography (20% Et_2O/hexane) to afford a colourless oil (5.85 g, 73.4%). R_f = 0.60 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.82 (1H, dd, *J* = 13.6, 0.4 Hz, C**H**$_2$$NO_2$), 4.57 (1H, d, *J* = 13.6 Hz, C**H**$_2$$NO_2$), 4.43-4.27 (2H, m, OC**H**$_2$), 3.70 (1H, s, O**H**), 1.73-1.58 (2H, m, C**H**$_2$), 1.54-1.41 (1H, m, C**H**$_2$), 1.34 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 1.33-1.22 (6H, m, 3 x C**H**$_2$), 1.20-1.10 (1H, m, C**H**$_2$), 0.89 (3H, t, *J* = 7.0 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.9 (C), 80.9 (CH_2), 75.3 (C), 63.0 (CH_2), 36.6 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 140.1 (CH_3), 14.0 (CH_3). The NMR data were in agreement with the literature.[239b]



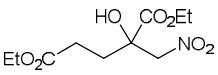
Ethyl 2-hydroxy-2-methyl-3-nitropropanoate (588e). The title compound was prepared according to General Procedure I from commercial available ethyl pyruvate (13.9 g, 120 mmol) and purified by column chromatography (Et_2O) to afford a colourless oil (19.5 g, 92 %). R_f = 0.23 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.84 (1H, d, *J* = 13.8 Hz, C**H**$_2$$NO_2$), 4.56 (1H, d, *J* = 13.8 Hz, C**H**$_2$$NO_2$), 4.40-4.28 (2H, m, OC**H**$_2$), 3.77 (1H, s, O**H**), 1.47-1.44 (3H, m, C**H**$_3$), 1.35-1.30 (3H, m, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 173.4 (C), 81.0 (C**H**$_2$), 72.4 (C), 63.0 C**H**$_2$), 23.8 (C**H**$_3$), 13.9 (C**H**$_3$). The NMR data were in agreement with the literature.[173]



Ethyl 2-hydroxy-2-(nitromethyl)hex-5-enoate (588f). The title compound was prepared according to General Procedure I from ketoester **585g** (1.73 g, 11.1 mmol) and purified by column chromatography (4→16% EtOAc/hexane) to afford a colourless oil (2.16 g, 89%). R_f = 0.30 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J* = 16.8, 10.2, 6.5 Hz, C**H**=), 5.07-4.98 (2H, m, C**H**$_2$=), 4.83 (1H, dd, *J* = 13.6, 0.7 Hz, C**H**$_2$NO$_2$), 4.58 (1H, d, *J* = 13.6 Hz, C**H**$_2$NO$_2$), 4.41-4.29 (2H, m, OC**H**$_2$), 3.76 (1H, s, O**H**), 2.30-2.20 (1H, m, C**H**$_2$), 2.01-1.92 (1H, m, C**H**$_2$), 1.84-1.71 (2H, m, C**H**$_2$), 1.34 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.7 (C), 136.5 (CH), 115.8 (CH_2), 80.8 (CH_2), 75.0 (C), 63.1 (CH_2), 35.6 (CH_2), 26.9 (CH_2), 14.0 (CH_3). The NMR data were in agreement with the literature.[241]

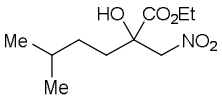


Ethyl 2-hydroxy-2-(nitromethyl)-4-phenylbutanoate (588g). The title compound was prepared according to General Procedure I from ketoester **585h** (1.71 g, 8.3 mmol) and purified by column chromatography (2→10% EtOAc/hexane) to afford a colourless oil (1.51 g, 68 %). R_f = 0.48 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m, Ar**H**), 7.24-7.20 (1H, m, Ar**H**), 7.18-7.15 (2H, m, Ar**H**), 4.84 (1H, dd, *J* = 13.6, 0.5 Hz, C**H**$_2$NO$_2$), 4.60 (1H, d, *J* = 13.6 Hz, C**H**$_2$NO$_2$), 4.40-4.27 (2H, m, OC**H**$_2$), 3.84 (1H, s, O**H**), 2.84 (1H, ddd, *J* = 13.7, 11.1, 5.4 Hz, C**H**$_2$), 2.51 (1H, ddd, *J* = 13.7, 11.4, 5.6 Hz, C**H**$_2$), 2.07-1.94 (2H, m, C**H**$_2$), 1.35 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.7 (C), 140.2 (C), 128.6 (2 x CH), 128.3 (2 x CH), 126.4 (CH), 80.9 (CH_2), 75.0 (C), 63.2 (CH_2), 38.2 (CH_2), 29.0 (CH_2), 14.1 (CH_3). The NMR data were in agreement with the literature.[241]

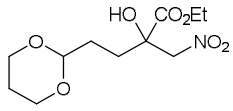


1,5-Diethyl 2-hydroxy-2-(nitromethyl)pentanedioate (588h). The title compound was prepared according to General Procedure I from ketoester **585k** (2.02 g, 10 mmol) and purified by column chromatography (5→20% EtOAc/hexane) to afford a colourless oil (2.33 g, 88 %). R_f = 0.36 (30% EtOAc/hexane); **IR** (film) 3485 (OH), 2984, 1728 (C=O), 1557 (NO_2), 1377 (NO_2), 1221, 1184, 1132, 1097, 1014 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.86 (1H, d, *J* = 13.7 Hz, C**H**$_2$NO$_2$), 4.58 (1H, d, *J* = 13.7 Hz, C**H**$_2$NO$_2$), 4.42-4.28 (2H, m, OC**H**$_2$), 4.14 (2H, q, *J* = 7.1 Hz,

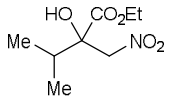
OC**H**$_2$), 3.81 (1H, s, O**H**), 2.55-2.47 (1H, m, C**H**$_2$), 2.32-2.23 (1H, m, C**H**$_2$), 2.10-1.98 (2H, m, C**H**$_2$), 1.34 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 1.26 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.4 (C), 172.3 (C), 80.6 (CH_2), 74.4 (C), 63.3 (CH_2), 60.9 (CH_2), 31.3 (CH_2), 27.8 (CH_2), 14.2 (CH_3), 14.0 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{10}H_{18}NO_7$ $[M+H]^+$: 264.1078, found 264.1080.



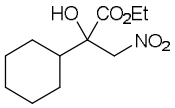
Ethyl 2-hydroxy-5-methyl-2-(nitromethyl)hexanoate (588i). The title compound was prepared according to General Procedure I from ketoester **585i** (3.69 g, 21.4 mmol) and purified by column chromatography (4→12% EtOAc/hexane) to afford a colourless oil (4.60 g, 92%). R_f = 0.46 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.83 (1H, d, *J* = 13.6 Hz, C**H**$_2$NO$_2$), 4.58 (1H, d, *J* = 13.6 Hz, C**H**$_2$NO$_2$), 4.41-4.31 (2H, m, OC**H**$_2$), 3.69 (1H, s, O**H**), 1.74-1.60 (2H, m, C**H**$_2$), 1.57-1.46 (1H, m, C**H**), 1.44-1.36 (1H, m, C**H**$_2$), 1.35 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 1.06-0.96 (1H, m, C**H**$_2$), 0.89 (6H, dd, *J* = 6.6, 5.23 Hz, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.9 (C), 80.9 (CH_2), 75.3 (C), 63.0 (CH_2), 34.5 (CH_2), 31.4 (CH_2), 27.9 (CH), 22.4 (CH_3), 22.3 (CH_3), 14.1 (CH_3). The NMR data were in agreement with the literature.[241]



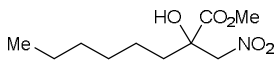
Ethyl 4-(1,3-dionan-2-yl)-2-hydroxy-2-(nitromethyl) butanoate (588j). The title compound was prepared according to General Procedure I from ketoester **585j** (1.33 g, 5.14 mmol) and purified by column chromatography (10→30% EtOAc/hexane) to afford a colourless oil (1.04 g, 73%). R_f = 0.29 (40% EtOAc/hexane); **IR** (film) 3435 (OH), 2853, 2363, 1736 (C=O), 1558 (NO_2), 1377 (NO_2), 1263, 1219, 1144, 1010 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.83 (1H, d, *J* = 13.5 Hz, C**H**$_2$NO$_2$), 4.59-4.54 (2H, m, C**H**$_2$NO$_2$, O$_2$C**H**), 4.41-4.27 (2H, m, OC**H**$_2$), 4.12-4.06 (2H, m, OC**H**$_2$), 3.93 (1H, s, O**H**), 3.79-3.71 (2H, m, OC**H**$_2$), 2.11-2.00 (1H, m, C**H**$_2$), 1.90-1.72 (3H, m, 2 x C**H**$_2$), 1.59-1.51 (1H, m, C**H**$_2$), 1.37-1.31 (4H, m, C**H**$_2$, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.7 (C), 100.9 (CH), 80.9 (CH_2), 74.9 (C), 66.9 (2 x CH_2), 63.0 (CH_2), 30.6 (CH_2), 28.5 (CH_2), 25.6 (CH_2), 14.0 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{11}H_{20}NO_7$ $[M+H]^+$: 278.1234, found 278.1242.



Ethyl 2-hydroxy-3-methyl-2-(nitromethyl)butanoate (588k). The title compound was prepared according to General Procedure I from ketoester **585b** (5 g, 34.68 mmol) and purified by column chromatography (20% Et_2O/hexane) to afford a colourless oil (6.47 g, 91%). R_f = 0.44 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.82 (1H, d, *J* = 13.5 Hz, C**H**$_2$NO$_2$), 4.67 (1H, d, *J* = 13.5 Hz, C**H**$_2$NO$_2$), 4.40-4.30 (2H, m, OC**H**$_2$), 3.62 (1H, s, O**H**), 1.98 (1H, hept, *J* = 6.8 Hz, C**H**), 1.34 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 0.99 (3H, d, *J* = 6.8 Hz, C**H**$_3$), 0.90 (3H, d, *J* = 6.8 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 173.0 (C), 80.1 (CH_2), 77.5 (C), 62.9 (CH_2), 34.1 (CH), 16.8 (CH_3), 16.2 (CH_3), 14.0 (CH_3). The NMR data were in agreement with the literature.[173]

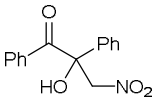


Ethyl 2-cyclohexyl-2-hydroxy-3-nitropropanoate (588l). The title compound was prepared according to General Procedure I from ketoester **585c** (5.2 g, 28 mmol) and purified by column chromatography (5→15%EtOAc/hexane) to afford a colourless oil (6.41 g, 93%). R_f = 0.43 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.81 (1H, dd, *J* = 13.5, 0.8 Hz, C**H**$_2$NO$_2$), 4.68 (1H, d, *J* = 13.5 Hz, C**H**$_2$NO$_2$), 4.39-4.28 (2H, m, OC**H**$_2$), 3.64 (1H, s, O**H**), 1.84-1.74 (2H, m, C**H**$_2$), 1.73-1.60 (2H, m, C**H**$_2$), 1.43-1.37 (1H, m, C**H**), 1.33 (3H, td, *J* = 7.1, 0.6 Hz, C**H**$_3$), 1.30-1.05 (6H, m, 3 x C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.9 (C), 79.9 (CH_2), 77.6 (C), 62.8 (CH_2), 43.8 (CH), 26.7 (CH_3), 26.1 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 14.0 (CH_3). The NMR data were in agreement with the literature.[239b]



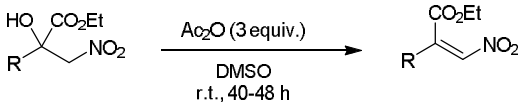
Methyl 2-hydroxy-2-(nitromethyl)octanoate (590). The title compound was prepared according to General Procedure I from ketoester **586** (500 mg, 2.9 mmol) and purified by column chromatography (2→10% EtOAc/hexane) to afford a colourless oil (633 mg, 94 %). R_f = 0.50 (20% EtOAc/hexane); **IR** (film) 3510 (OH), 2924, 1742 (C=O), 1558 (NO_2), 1445, 1379 (NO_2), 1223, 1153, 1103, 968 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.82 (1H, d, *J* = 13.6 Hz, C**H**$_2$NO$_2$), 4.57 (1H, d, *J* = 13.6 Hz, C**H**$_2$NO$_2$), 3.89 (3H, s, C**H**$_3$), 3.69 (1H, s, O**H**), 1.72-1.60 (2H, m, C**H**$_2$), 1.52-1.43 (1H, m, C**H**$_2$), 1.33-1.22 (6H, m, 3 x C**H**$_2$), 1.18-1.10

(1H, m, C**H**$_2$), 0.88 (3H, t, *J* = 7.0 Hz, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 173.5 (C), 80.9 (CH_2), 75.4 (C), 53.6 (CH_3), 36.6 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 13.9 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{10}H_{20}NO_5$ $[M+H]^+$: 234.1336, found 234.1382.



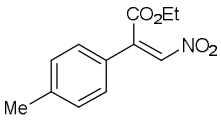
2-Hydroxy-3-nitro-1,2-diphenylpropan-1-one (591). The title compound was prepared according to General Procedure I (with a reaction time of 7 days) from commercially available benzyl (6.3 g, 30 mmol) and purified by column chromatography (5→15% Et_2O/hexane) to afford a colourless gum (2.95 g, 36%). R_f = 0.26 (10% EtOAc/hexane); **IR** (film) 3516 (OH), 3061, 2358, 1678 (C=O), 1552 (NO_2), 1448, 1371 (NO_2), 1265, 1240, 1169 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.96-7.92 (2H, m, Ar**H**), 7.62-7.59 (2H, m, Ar**H**), 7.52-7.47 (1H, m, Ar**H**), 7.47-7.42 (2H, m, Ar**H**), 7.41-7.37 (1H, m, Ar**H**), 7.37-7.32 (2H, m, Ar**H**), 5.11 (1H, s, O**H**), 5.35 (1H, d, *J* = 14.9 Hz, C**H**$_2$NO$_2$), 4.55 (1H, d, 14.9 Hz, C**H**$_2$NO$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 197.8 (C), 135.8 (C), 133.4 (CH), 133.3 (C), 130.7 (2 x CH), 129.3 (2 x CH), 129.1 (CH), 128.2 (2 x CH), 124.9 (2 x CH), 81.9 (C), 81.5 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{15}H_{14}NO_4$ $[M+H]^+$: 272.0917, found 272.0929.

General Procedure J: Synthesis of *β*-Acylnitroalkenes

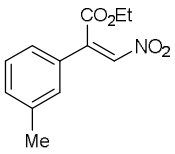


In a modification of a previously reported procedure by List and co-workers,[173] to a solution of the appropriate *β*-nitro-*α*-hydroxyester (22.6 mmol) in DMSO (40 mL) was added Ac_2O (6.4 mL, 67.7 mmol). The reaction was then stirred at room temperature. After complete consumption of the starting material as indicated by TLC analysis, the mixture was poured into water (50 mL). The two phases were separated and the aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated

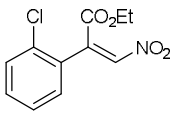
in vacuo. The residue was purified by flash chromatography to afford the pure *β*-acylnitroalkenes.



Ethyl (2*Z*)-2-(4-methylphenyl)-3-nitroprop-2-enoate (338b). The title compound was prepared according to General Procedure J from nitroalcohol **588a** (6.65 g, 26.26 mmol) and purified by column chromatography (10→20% EtOAc/hexane) to afford a yellow oil (4.96 g, 80%). R_f = 0.31 (20% EtOAc/hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.39 (2H, m, Ar**H**), 7.36 (1H, s, C**H**NO_2), 7.30-7.26 (2H, m, Ar**H**), 4.49 (2H, q, *J* = 7.2 Hz, OC**H**$_2$), 2.42 (3H, s, C**H**$_3$), 1.41 (3H, t, *J* = 7.2 Hz, C**H**$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 165.0 (C), 143.4 (C), 143.1 (C), 133.6 (CH), 130.3 (2 x CH), 127.5 (2 x CH), 126.6 (C), 62.7 (CH_2), 21.5 (CH_3), 13.9 (CH_3). The NMR data were in agreement with the literature.[173]

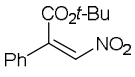


Ethyl (2*Z*)-2-(3-methylphenyl)-3-nitroprop-2-enoate (338e). The title compound was prepared according to General Procedure J from nitroalcohol **588b** (3.11 g, 12.28 mmol) and purified by column chromatography (2→10%EtOAc/hexane) to afford a colourless oil (2.29 g, 80%). R_f = 0.51 (20% EtOAc/hexane); **IR** (film) 2984, 1732 (C=O), 1622, 1518 (NO_2), 1346 (NO_2), 1327, 1265, 1213, 1180, 789 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37-7.32 (3H, m, Ar**H**), 7.32-7.30 (2H, m, Ar**H**, C**H**NO_2), 4.48 (2H, q, *J* = 7.2 Hz, OC**H**$_2$), 2.40 (3H, s, C**H**$_3$), 1.40 (3H, t, *J* = 7.2 Hz, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 164.8 (C), 143.5 (C), 139.4 (C), 134.3 (CH), 132.9 (CH), 129.4 (C), 129.3 (CH), 127.9 (CH), 124.6 (CH), 62.7 (CH_2), 21.3 (CH_3), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0917, found 236.0926.

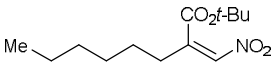


Ethyl (2*Z*)-2-(2-chlorophenyl)-3-nitroprop-2-enoate (338g). The title compound was prepared according to General Procedure J from nitroalcohol **588c** (1.27 g, 4.63 mmol) and purified by column chromatography (2→10%Et_2O/hexane) to afford a pale yellow oil (131 mg, 11%). R_f = 0.34 (20% EtOAc/hexane); **IR** (film) 2984, 1730 (C=O), 1531 (NO_2), 1470, 1348 (NO_2), 1325, 1205, 1069, 1022, 752 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52-7.48

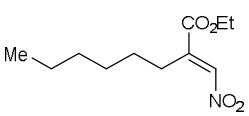
(1H, m, Ar**H**), 7.46 (1H, dd, *J* = 7.6, 1.6 Hz, Ar**H**), 7.42 (1H, td, *J* = 7.7, 1.8, Ar**H**), 7.36 (1H, td, *J* = 7.5, 1.3 Hz, Ar**H**), 7.23 (1H, s, C**H**NO_2), 4.39 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 1.36 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 163.7 (C), 139.5 (CH), 138.8 (C), 133.2 (C), 131.8 (CH), 130.8 (CH), 130.6 (CH), 129.6 (C), 127.4 (CH), 62.9 (CH_2), 13.7 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{11}H_{10}NO_4ClNa$ $[M+Na]^+$: 278.0191, found 278.0188.



***tert*-Butyl (2*Z*)-3-nitro-2-phenylprop-2-enoate (470b)**. The title compound was prepared according to General Procedure J from nitroalcohol **589a** (1.51 g, 5.66 mmol) and purified by column chromatography (2→8% EtOAc/hexane) to afford a yellow solid (1.16 g, 83%). **m.p.** 75-76 °C (CH_2Cl_2); R_f = 0.39 (10% EtOAc/hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55-7.51 (3H, m, Ar**H**), 7.49-7.45 (2H, m, Ar**H**), 7.31 (1H, s, C**H**NO_2), 1.63 (9H, s, 3 x C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 163.5 (C), 143.6 (C), 133.7 (CH), 131.8 (CH), 130.0 (C), 129.4 (2 x CH), 127.4 (2 x CH), 84.8 (C), 27.9 (3 x CH_3). The data is in agreement with the literature.[173]

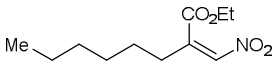


***tert*-Butyl (2*Z*)-2-(nitromethylidene)octanoate (470c)**. The title compound was prepared according to General Procedure J from nitroalcohol **589b** (1.05 g, 3.8 mmol) and purified by column chromatography (1→4% EtOAc/hexane) to afford a colourless oil (421 mg, 43%). R_f = 0.62 (20% EtOAc/hexane); **IR** (film) 2932, 1728 (C=O), 1647, 1530 (NO_2), 1352 (NO_2), 1236, 1159, 1140, 841, 737 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.78 (1H, s, C**H**NO_2), 2.37 (2H, t, *J* = 7.6 Hz, C**H**$_2$), 1.54 (9H, s, 3 x C**H**$_3$), 1.54-1.51 (1H, m, C**H**$_2$), 1.39-1.25 (7H, m, 4 x C**H**$_2$), 0.89 (3H, t, *J* = 6.7 Hz, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 164.8 (C), 146.0 (C), 134.4 (CH), 84.0 (C), 31.9 (CH_2), 31.3 (CH_2), 28.4 (CH_2), 27.8 (3 x CH_3), 26.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{13}H_{23}NO_4Na[M+Na]^+$: 280.1519, found 280.1510.

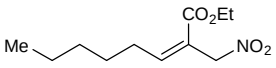


Ethyl (2*E*)-2-(nitromethylidene)octanoate (*E*-510a). The title compound was prepared according to General Procedure J from

nitroalcohol **588d** (5.2 g, 21 mmol) and purified by column chromatography (1→3%Et_2O/hexane) to afford a pale yellow oil (100 mg, 2%). R_f = 0.58 (10% EtOAc/hexane); **IR** (film) 2931, 1726 (C=O), 1637, 1529 (NO_2), 1354 (NO_2), 1244, 1188, 1140, 1067, 860 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67-7.65 (1H, m, C**H**NO_2), 4.32 (2H, qd, *J* = 7.1, 0.2 Hz, OC**H**$_2$), 2.77-2.72 (2H, m, C**H**$_2$), 1.57-1.49 (2H, m, C**H**$_2$), 1.42-1.26 (9H, m, C**H**$_3$ and 3 x C**H**$_2$), 0.93-0.87 (3H, m, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.2 (C), 143.3 (CH), 141.2 (C), 62.4 (CH_2), 31.3 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 27.3 (CH_2), 22.4 (CH_2), 14.0 (2 x CH_3); **^{1}H-^{1}H NOESY** showed no cross peaks between proton C**H**NO_2 and protons =CC**H**$_2$; **HRMS** (ESI) Exact mass calcd for $C_{11}H_{20}NO_4$ $[M+H]^+$: 230.1387, found 230.1396.

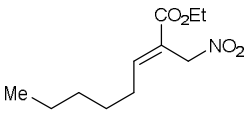


Ethyl (2*Z*)-2-(nitromethylidene)octanoate (*Z*-510a). The title compound was isolated from the same reaction mixture as above to afford a pale yellow oil (2.56 g, 53%). R_f = 0.52 (10% EtOAc/hexane); **IR** (film) 2932, 1732 (C=O), 1649, 1530 (NO_2), 1466, 1350 (NO_2), 1217, 1140, 1015, 856 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.85 (1H, t, *J* = 1.5 Hz, C**H**NO_2), 4.37 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 2.43-2.39 (2H, m, C**H**$_2$), 1.58-1.50 (2H, m, C**H**$_2$), 1.40-1.25 (9H, m, C**H**$_3$ and 3 x C**H**$_2$), 0.93-0.87 (3H, m, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 166.0 (C), 145.5 (C), 135.3 (CH), 62.3 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 28.5 (CH_2), 26.5 (CH_2), 22.4 (CH_2), 14.0 (CH_3), 13.8 (CH_3); **^{1}H-^{1}H NOESY**, proton C**H**NO_2 showed cross peaks with protons =CC**H**$_2$; **HRMS** (ESI) Exact mass calcd for $C_{11}H_{20}NO_4$ $[M+H]^+$: 230.1387, found 230.1423.

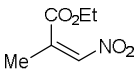


Ethyl (2*Z*)-2-(nitromethyl)oct-2-enoate (*Z*-512). The title compound was isolated from the same reaction mixture as above to afford a pale yellow oil (60 mg, 1.2 %). R_f = 0.39 (10% EtOAc/hexane); **IR** (film) 2926, 1707 (C=O), 1653, 1558 (NO_2), 1373 (NO_2), 1219, 1198, 1151, 1020, 804 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.42 (1H, t, *J* = 7.5 Hz, C**H**=), 5.08 (2H, d, *J* = 0.5 Hz, C**H**$_2$$NO_2$), 4.25 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 2.71 (2H, q, *J* = 7.5 Hz, C**H**$_2$), 1.54-1.47 (2H, m, C**H**$_2$), 1.38-1.26 (7H, m, C**H**$_3$ and 2 x C**H**$_2$), 0.94-0.85 (3H, m, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 164.7 (C), 155.2 (CH), 122.4 (C), 78.3 (CH_2), 61.0 (CH_2), 31.5

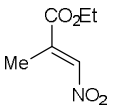
(CH_2), 29.8 (CH_2), 28.4 (CH_2), 22.4 (CH_2), 14.0 (CH_3), 13.9 (CH_3); **^{1}H-^{1}H NOESY**, protons C**H**$_2$NO$_2$ showed cross peaks with proton C**H**=; **HRMS** (ESI) Exact mass calcd for $C_{11}H_{20}NO_4$ $[M+H]^+$: 230.1387, found 230.1400.



Ethyl (2*E*)-2-(nitromethyl)oct-2-enoate (*E*-512). The title compound was isolated from the same reaction mixture as above to afford a pale yellow oil (300 mg, 6.2%). R_f = 0.27 (10% EtOAc/hexane); **IR** (film) 2931, 1708 (C=O), 1653, 1557 (NO_2), 1466, 1387 (NO_2), 1294, 1219, 1094, 777 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (1H, t, *J* = 7.9 Hz, C**H**=), 5.24 (2H, s, C**H**$_2$NO$_2$), 4.26 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 2.29 (2H, dd, *J* = 15.1, 7.6 Hz, C**H**$_2$), 1.55-1.48 (2H, m, C**H**$_2$), 1.37-1.28 (7H, m, C**H**$_3$ and 2 x C**H**$_2$), 0.90 (3H, t, *J* = 7.0 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.3 (C), 152.1 (CH), 122.5 (C), 70.2 (CH_2), 61.4 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 27.9 (CH_2), 22.3 (CH_2), 14.1 (CH_3), 13.9 (CH_3); **^{1}H-^{1}H NOESY**, protons C**H**$_2$NO$_2$ showed cross peaks with protons =CHC**H**$_2$; **HRMS** (ESI) Exact mass calcd for $C_{11}H_{20}NO_4$ $[M+H]^+$: 230.1387, found 230.1405.

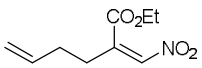


(*Z*)-Ethyl 2-methyl-3-nitroacrylate (*Z*-510b). The title compounds were prepared according to General Procedure J from nitroalcohol **588e** (4.0 g, 22.58 mmol) and purified by column chromatography (4→20% EtOAc/hexane) to afford **(*Z*)-ethyl 2-methyl-3-nitroacrylate** as a colourless oil (551 mg, 15 %). R_f = 0.45 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (1H, q, *J* = 1.7 Hz, C**H**NO$_2$), 4.33 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 2.33 (3H, d, *J* = 1.7 Hz, C**H**$_3$), 1.36 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.2 (C), 144.0 (C), 136.9 (CH), 62.6 (CH_2), 14.0 (CH_3), 13.7 (CH_3).[173]

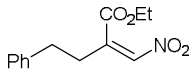


(*E*)-Ethyl 2-methyl-3-nitroacrylate (*E*-510b). The title compound was isolated from the same reaction mixture as above to afford a colourless oil (1.53 g, 43%). R_f = 0.30 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.88 (1H, dd, *J* = 3.2, 1.6 Hz, C**H**NO$_2$), 4.35 (2H, qd, *J* = 7.1, 1.3 Hz, OC**H**$_2$), 2.11 (3H, d, *J* = 1.6 Hz, C**H**$_3$), 1.34 (3H, td, *J* = 7.2, 1.2 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz,

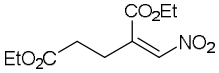
$CDCl_3$) δ 166.1 (C), 140.9 (C), 135.6 (CH), 62.4 (CH_2), 17.5 (CH_3), 13.7 (CH_3). The NMR data were in agreement with the literature.[173]



Ethyl (2*Z*)-2-(nitromethylidene)hex-5-enoate (510c). The title compound was prepared according to General Procedure J from nitroalcohol **588f** (1.73 g, 2.96 mmol) and purified by column chromatography (1→2% EtOAc/hexane) to afford a pale yellow oil (777 mg, 82%). R_f = 0.41 (20% EtOAc/hexane); **IR** (film) 2984, 1732 (C=O), 1530 (NO_2), 1447, 1352 (NO_2), 1219, 1134, 1013, 918, 856 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.86 (1H, s, C**H**NO_2), 5.83-5.71 (1H, m, C**H**=), 5.15-5.06 (2H, m, C**H**$_2$=), 4.37 (2H, qd, *J* = 7.1, 1.7 Hz, OC**H**$_2$), 2.51 (2H, t, *J* = 7.5 Hz, C**H**$_2$), 2.35-2.28 (2H, m, C**H**$_2$), 1.36 (3H, td, *J* = 7.1, 1.6 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.7 (C), 144.2 (C), 135.7 (CH), 135.2 (CH), 117.0 (CH_2), 62.4 (CH_2), 31.1 (CH_2), 30.5 (CH_2), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_9H_{13}NO_4Na$ $[M+Na]^+$: 222.0737, found 222.0747.

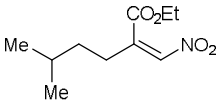


Ethyl (2*Z*)-2-(nitromethylidene)-4-phenylbutanoate (510d). The title compound was prepared according to General Procedure J from nitroalcohol **588g** (573 mg, 2.15 mmol) and purified by column chromatography (2% EtOAc/hexane) to afford a colourless oil (212 mg, 39%). R_f = 0.38 (20% EtOAc/hexane); **IR** (film) 2982, 1730 (C=O), 1647, 1528 (NO_2), 1454, 1352 (NO_2), 1221, 1109, 1015, 700 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35-7.30 (2H, m, Ar**H**), 7.27-7.23 (1H, m, Ar**H**), 7.21-7.18 (2H, m, Ar**H**), 6.74 (1H, t, *J* = 1.4 Hz, C**H**NO_2), 4.38 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 2.88 (2H, t, *J* = 7.7 Hz, C**H**$_2$), 2.73-2.69 (2H, m, C**H**$_2$), 1.37 (3H, t, *J* = 7.2 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.7 (C), 143.7 (C), 138.9 (C), 135.9 (CH), 128.7 (2 x CH), 128.4 (2 x CH), 126.8 (CH), 62.5 (CH_2), 33.6 (CH_2), 32.8 (CH_2), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{13}H_{16}NO_4$ $[M+H]^+$: 250.1074, found 250.1077.

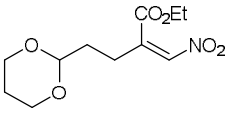


1,5-Diethyl (2*Z*)-2-(nitromethylidene)pentanedioate (510e). The title compound was prepared according to General Procedure J from nitroalcohol **588h** (1.35 g, 5.1 mmol) and purified by column chromatography (4→10%

EtOAc/hexane) to afford a light yellow oil (551 mg, 44%). R_f = 0.26 (20% EtOAc/hexane); **IR** (film) 2984, 1730 (C=O), 1651, 1531 (NO_2), 1352 (NO_2), 1221, 1178, 1123, 1016, 735 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.93 (1H, t, *J* = 1.3 C**H**NO_2), 4.36 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 4.17 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 2.76-2.70 (2H, m, C**H**$_2$), 2.61-2.56 (2H, m, C**H**$_2$), 1.35 (3H, t, *J* = 7.2 Hz, C**H**$_3$), 1.27 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 171.0 (C), 165.3 (C), 142.7 (C), 136.4 (CH), 62.5 (CH_2), 61.1 (CH_2), 31.0 (CH_2), 26.7 (CH_2), 14.1 (CH_3), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{10}H_{16}NO_6$ $[M+H]^+$: 246.0972, found 246.0981.

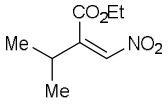


Ethyl (2*Z*)-5-methyl-2-(nitromethylidene)hexanoate (510f). The title compound was prepared according to General Procedure J from nitroalcohol **588i** (4.38 g, 18.79 mmol) and purified by column chromatography (1→3% EtOAc/hexane) to afford a pale yellow oil (2.44 g, 60%). R_f = 0.30 (10% EtOAc/hexane); **IR** (film) 2959, 1732 (C=O), 1649, 1530 (NO_2), 1467, 1352 (NO_2), 1219, 1097, 1013, 736 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.85 (1H, t, *J* = 1.5 Hz, C**H**NO_2), 4.36 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 2.43-2.39 (2H, m, C**H**$_2$), 1.69-1.57 (1H, m, C**H**$(CH_3)_2$), 1.45-1.39 (2H, m, C**H**$_2$), 1.35 (3H, t, *J* = 7.2 Hz, C**H**$_3$), 0.92 (6H, d, *J* = 6.6 Hz, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 166.0 (C), 145.7 (C), 135.2 (CH), 62.3 (CH_2), 35.4 (CH_2), 29.8 (CH_2), 27.5 (CH), 22.1 (2 x CH_3), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{10}H_{18}NO_4$ $[M+H]^+$: 216.1230, found 216.1234.

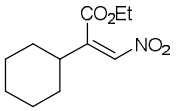


Ethyl (2*Z*)-4-(1,3-dioxan-2-yl)-2-(nitromethylidene) butanoate (510g). The title compound was prepared according to General Procedure J from nitroalcohol **588j** (978 mg, 3.53 mmol) and purified by column chromatography (3→15% EtOAc/hexane) to afford a pale yellow oil (293 mg, 32%). R_f = 0.21 (30% EtOAc/hexane); **IR** (film) 2852, 1724 (C=O), 1638, 1530 (NO_2), 1447, 1367 (NO_2), 1246, 1140, 1018, 851 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (1H, s, C**H**NO_2), 4.57 (1H, t, *J* = 4.9 Hz, OC**H**), 4.31 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 4.08-4.03 (2H, m, OC**H**$_2$), 3.75-3.67 (2H, m, OC**H**$_2$), 2.89 (2H, t, *J* = 7.2 Hz, C**H**$_2$), 2.11-1.99 (1H, m, C**H**$_2$), 1.88 (2H, td, *J* = 7.2, 4.9 Hz, C**H**$_2$), 1.36 (3H, t, *J* = 7.1

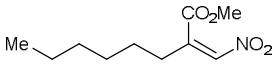
Hz, C**H**$_3$), 1.34-1.29 (1H, m, C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.0 (C), 143.5 (CH), 140.6 (C), 101.2 (CH), 66.7 (2 x CH_2), 62.4 (CH_2), 33.3 (CH_2), 25.5 (CH_2), 21.9 (CH_2), 14.1 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{11}H_{18}NO_6$ $[M+H]^+$: 260.1129, found 260.1144.



Ethyl (2*Z*)-3-methyl-2-(nitromethylidene)butanoate (510h). The title compound was prepared according to General Procedure J from nitroalcohol **588k** (4.88 g, 23.8 mmol) and purified by column chromatography (10% Et_2O/hexane) to afford a colourless oil (1.52 g, 35%). R_f = 0.45 (30% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.85-6.83 (1H, m, C**H**NO_2), 4.37 (2H, qd, *J* = 7.1, 1.7 Hz, OC**H**$_2$), 2.80-2.70 (1H, m, C**H**), 1.36 (3H, td, *J* = 7.1, 1.7 Hz, C**H**$_3$), 1.21 (6H, dd, *J* = 6.9, 1.6 Hz, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.6 (C), 150.7 (C), 134.8 (CH), 62.2 (CH_2), 31.5 (CH), 20.3 (2 x CH_3), 13.9 (CH_3); The data is in agreement with the literature.[173]

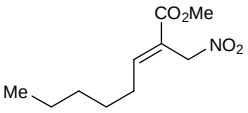


Ethyl (2*Z*)-2-cyclohexyl-3-nitroprop-2-enoate (510i). The title compound was prepared according to General Procedure J from nitroalcohol **588l** (4.8 g, 19.6 mmol) and purified by column chromatography (2→6% EtOAc/hexane) to afford a colourless oil (3.3 g, 74%). R_f = 0.45 (10% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.81 (1H, dd, *J* = 6.6, 1.3 Hz, C**H**NO_2), 4.36 (2H, q, *J* = 7.2 Hz, OC**H**$_2$), 2.43-2.35 (1H, m, C**H**), 1.92-1.82 (4H, m, 2 x C**H**$_2$), 1.76-1.60 (1H, m, C**H**$_2$), 1.35 (3H, t, *J* = 7.2 Hz, C**H**$_3$), 1.35-1.15 (5H, m, 3 x C**H**$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.8 (C), 150.1 (C), 134.9 (CH), 62.2 (CH_2), 40.8 (CH), 30.8 (2 x CH_2), 25.8 (2 x CH_2), 25.4 (CH_2), 13.9 (CH_3). The NMR data were in agreement with the literature.[242]

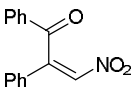


Methyl (2*Z*)-2-(nitromethylidene)octanoate (514). The title compound was prepared according to General Procedure J from nitroalcohol **590** (563 g, 2.41 mmol) and purified by column chromatography (2→10%EtOAc/hexane) to afford a colourless oil (61 mg, 12%). R_f = 0.35 (10% EtOAc/hexane); **IR** (film) 2932, 1738 (C=O), 1649, 1529 (NO_2), 1437, 1354 (NO_2),

1265, 1225, 964, 735 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.85 (1H, t, *J* = 1.4 Hz, C**H**NO_2), 3.88 (3H, s, OC**H**$_3$), 2.42-2.38 (2H, m, C**H**$_2$), 1.56-1.48 (2H, m, C**H**$_2$), 1.39-1.24 (6H, m, 3 x C**H**$_2$), 0.90-0.87 (3H, m, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 166.4 (C), 145.1 (CH), 135.5 (C), 53.0 (CH_3), 31.8 (CH_2), 31.3 (CH_2), 28.5 (CH_2), 26.5 (CH_2), 22.3 (CH_2), 13.9 (CH_3); **^{1}H-^{1}H NOESY**, proton C**H**NO_2 shows cross peaks with protons =CC**H**$_2$; **HRMS** (ESI) Exact mass calcd for $C_{10}H_{17}NO_4Na$ $[M+Na]^+$: 238.1050, found 238.1059.

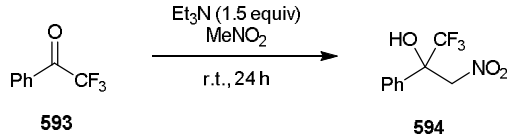


Methyl (2*E*)-2-(nitromethyl)oct-2-enoate (592). The title compound was isolated from the same reaction mixture as above to afford a colourless oil (127 mg, 25%). R_f = 0.28 (10% EtOAc/hexane); **IR** (film) 2930, 1691 (C=O), 1557 (NO_2), 1424, 1379 (NO_2), 1221, 1186, 1157, 963, 743 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.28 (1H, t, *J* = 7.8 Hz, C**H**=), 5.23 (2H, s, C**H**$_2$$NO_2$), 3.78 (3H, s, OC**H**$_3$), 2.28 (2H, dd, *J* = 15.1, 7.6 Hz, C**H**$_2$), 1.53-1.46 (2H, m, C**H**$_2$), 1.34-1.26 (4H, m, 2 x C**H**$_2$), 0.88 (3H, t, *J* = 7.0 Hz, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 165.8 (C), 152.5 (CH), 122.3 (C), 70.2 (CH_2), 52.3 (CH_3), 31.3 (CH_2), 29.1 (CH_2), 27.8 (CH_2), 22.3 (CH_2), 13.8 (CH_3); **^{1}H-^{1}H NOESY**, protons C**H**$_2$$NO_2$ showed cross peaks with protons =CHC**H**$_2$; **HRMS** (ESI) Exact mass calcd for $C_{10}H_{17}NO_4Na$ $[M+Na]^+$: 238.1050, found 238.1043.



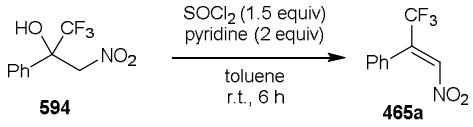
(2*Z*)-3-Nitro-1,2-diphenylprop-2-en-1-one (515). The title compound was prepared according to General Procedure J from nitroalcohol **591** (2.96 g, 10.3 mmol) and purified by column chromatography (5→30% Et_2O/hexane) to afford a yellow amorphous solid (2.10 g, 81%). **m.p.** 104-105 °C (CH_2Cl_2); R_f = 0.17 (10% EtOAc/hexane); **IR** (film) 3101, 1676 (C=O), 1597, 1514 (NO_2), 1447, 1344 (NO_2), 1246, 1219, 1177, 770 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97-7.93 (2H, m, Ar**H**), 7.63-7.58 (1H, m, Ar**H**), 7.58 (1H, s, C**H**NO_2), 7.54-7.41 (7H, m, Ar**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 192.2 (C), 150.3 (C), 134.9 (CH), 134.8 (C), 134.3 (CH), 132.1 (CH), 130.3 (C), 129.6 (2 x CH), 129.0 (2 x CH), 128.8 (2 x CH), 127.6 (2 x CH); **HRMS** (ESI) Exact mass calcd for $C_{15}H_{12}NO_3$ $[M+H]^+$: 254.0812, found 254.0838.

1,1,1-Trifluoro-3-nitro-2-phenylpropan-2-ol (594)



In a modification of a previously reported procedure,[163] to a solution of the trifluoromethyl ketone (**593**) (3.5 g, 20 mmol) in $MeNO_2$ (40 mL) was added Et_3N (3.04 g, 30 mmol). The mixture was stirred overnight at room temperature, then diluted with ethyl acetate (40 mL) and washed successively with aq. HCl (1 M), water (40 mL), and brine (40 mL). The organic phase was separated and dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5→10% EtOAc/hexane) to afford the corresponding nitroalcohol **594** as a colourless oil (1.44 g, 31%). R_f = 0.15 (10% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63-7.58 (2H, m, Ar**H**), 7.49-7.44 (3H, m, Ar**H**), 5.10 (1H, d, *J* = 13.7 Hz, C**H**$_2$NO$_2$), 5.02 (1H, d, *J* = 13.7 Hz, C**H**$_2$NO$_2$), 4.63 (1H, s, O**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 133.0 (C), 130.0 (CH), 129.0 (2 x CH), 126.1 (2 x CH), 123.4 (q, *J* = 285.6 Hz, C), 77.5 (CH_2), 76.2 (dd, *J* = 59.7, 29.8 Hz, C); **^{19}F NMR** (400 MHz, $CDCl_3$) δ –78.67 (s, 3F). The NMR data were in agreement with the literature.[243]

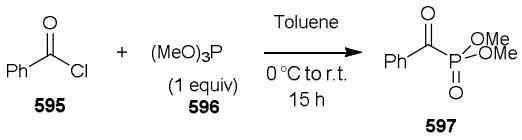
[(1*E*)-3, 3, 3-Trifluoro-1-nitroprop-1-en-2-yl]benzene (465a)



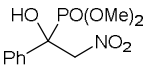
In the modification of a previously reported procedure, [163] to a solution of nitroalcohol **594** (730 mg, 3.1 mmol) in toluene (20 mL) were added $SOCl_2$ (340 µL, 4.7 mol) and pyridine (501 µL, 6.2 mmol) at 0 °C. The mixture was stirred at room temperature for 6 h, then diluted with ethyl acetate (20 mL), washed with water (30 mL), and brine (20 mL). The organic phase was separated and dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5→10%

EtOAc/hexane) (2% EtOAc/hexane) to afford the corresponding nitroalkene **465a** as a pale yellow oil (347 mg, 52%). R_f = 0.51 (20% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55-7.53 (1H, m, Ar**H**), 7.53-7.44 (3H, C**H**NO_2, Ar**H**), 7.34-7.30 (2H, m, Ar**H**); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 140.0 (CH), 136.0 (q, *J* = 32.0 Hz, C), 130.5 (CH), 128.9 (2 x CH), 128.2 (2 x CH), 126.8 (C), 121.9 (q, *J* = 275.7 Hz, C); **^{19}F NMR** (400 MHz, $CDCl_3$) δ –66.78 (s, 3F). The NMR data were in agreement with the literature.[163]

Dimethyl benzoylphosphonate (597)



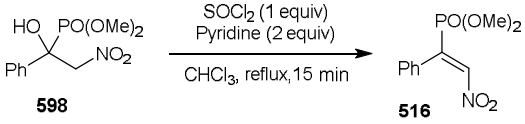
In a modification of a previously reported procedure,[244] benzoyl chloride (**595**) (28 g, 200 mmol) was added to a solution of trimethyl phosphite **596** (25 g, 200 mmol) in dry toluene (200 mL). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and a residue was distilled (120 °C) under vacuum to afford a colourless oil (35.4 g, 91%). R_f = 0.30 (30% EtOAc/hexane); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.18 (2H, dt, *J* = 8.5, 1.5 Hz, Ar**H**), 7.58 (1H, ddt, *J* = 7.1, 2.6, 1.6 Hz, Ar**H**), 2.47-2.42 (2H, m, Ar**H**), 3.85 (6H, d, *J* = 10.9 Hz, 2 x O**C**$\mathbf{H}_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.1 (d, *J* = 174.7 Hz, C), 135.3 (d, *J* = 63.7 Hz, C), 134.8 (s, CH), 129.7 (d, *J* = 1.6 Hz, 2 x CH), 128.7 (s, 2 x CH), 53.9 (d, *J* = 7.4 Hz, 2 x CH_3); **^{31}P NMR** (400 MHz, $CDCl_3$) δ 0.7 (s). The NMR data were in agreement with the literature.[244]



Dimethyl (1-hydroxy-2-nitro-1-phenylethyl)phosphonate (598). The title compound was prepared according to General Procedure I from dimethyl benzoylphosphonate (**597**) (8.57 g, 40 mmol) and purified by recrystallisation (6:4 EtOAc/hexane) to afford a yellow crystalline (8 g, 73%). R_f = 0.26 (80% EtOAc/hexane); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.65-7.61 (2H, m, Ar**H**), 7.45-7.41 (2H, m, Ar**H**), 7.39-7.35 (1H, m, Ar**H**), 5.13 (2H, ddd, *J* = 17.9, 13.5, 6.1 Hz, C$\mathbf{H}_2NO_2$), 3.81

(3H, d, *J* = 10.5 Hz, OC**H**$_3$), 3.55 (3H, d, *J* = 10.5 Hz, OC**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 135.0 (d, *J* = 2.7 Hz, C), 128.9 (d, *J* = 3.0 Hz, CH), 128.7 (d, *J* = 2.7 Hz, 2 x CH), 125.9 (d, *J* = 4.2 Hz, 2 x CH), 79.7 (d, *J* = 9.7 Hz, CH_2), 75.7 (d, *J* = 165.5 Hz, C), 55.1 (d, *J* = 7.3 Hz, CH_3), 54.6 (d, *J* = 7.6 Hz, CH_3); **^{31}P NMR** (400 MHz, $CDCl_3$) δ 18.7 (s). The NMR data were in agreement with the literature.[174,245]

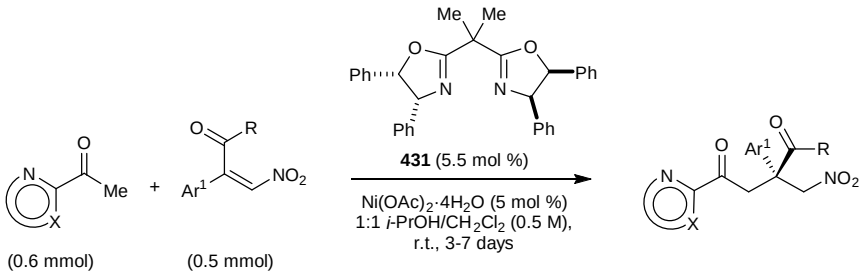
Dimethyl [(*E*)-2-nitro-1-phenylethenyl]phosphonate (516)



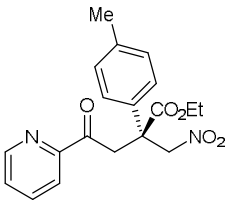
The title compound was prepared according to the procedure reported by Yuan and co-workers.[174] A solution of dimethyl (1-hydroxy-2-nitro-1-phenylethyl) phosphonate (**598**) (7.61 g, 27.65 mmol) in $CHCl_3$ (100 ml) was heated at reflux under nitrogen. Under vigorous stirring, thionyl chloride (2.02 mL, 27.65 mmol) was added slowly, followed by dropwise addition of pyridine (4.47 ml, 55.3 mmol). After being stirred for 15 min, the mixture was cooled to room temperature and then washed with brine (4 x 50 mL) until pH 7. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (20→60% EtOAc/hexane) to afford a yellow solid (3.19 g, 45%). **m.p.** 59-60 °C (CH_2Cl_2); R_f = 0.39 (80% EtOAc/hexane); **IR** (film) 2957, 1533 (NO_2), 1445, 1357 (NO_2), 1260 (P=O), 1177, 1015 (P-O-C), 933, 835, 744 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* = 15.3 Hz, Ar**H**), 7.43-7.38 (3H, m, Ar**H**, C**H**NO_2), 7.29-7.25 (2H, m, Ar**H**), 3.77 (6H, d, *J* = 11.2 Hz, 2 x OC**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 144.8 (d, *J* = 20.5 Hz, CH), 135.6 (d, *J* = 171.6 Hz, C), 129.7 (d, *J* = 3.0 Hz, C), 129.4 (d, *J* = 2.3 Hz, CH), 128.7 (d, *J* = 1.6 Hz, 2 x CH), 127.6 (d, *J* = 5.2 Hz, 2 x CH), 53.8 (d, *J* = 6.2 Hz, 2 x CH_3); **^{31}P NMR** (400 MHz, $CDCl_3$) δ 13.9 (s). **HRMS** (ESI) Exact mass calcd for $C_{10}H_{13}NO_5P$ $[M+H]^+$: 258.0531, found 358.0533.

3.2.4 Michael Addition of 2-Acetylazaarenes to *β*,*β*-Disubstituted Nitroalkenes

General Procedure K: Michael Addition of 2-Acetylazaarenes to Aromatic Substituted Nitroalkenes

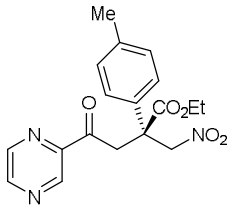


A suspension of $Ni(OAc)_2 \cdot 4H_2O$ (6.2 mg, 0.025 mmol) and ligand **431** (13.4 mg, 0.0275 mmol) in 1:1 *i*-PrOH/CH_2Cl_2 (0.5 mL) was stirred at room temperature for 30 min. To the resulting solution was added a solution of the appropriate 2-acetylazaarene (0.60 mmol) and the appropriate nitroalkene (0.50 mmol) in 1:1 *i*-PrOH/CH_2Cl_2 (0.5 mL), and the reaction mixture was stirred until complete consumption of the nitroalkene as indicated by TLC analysis. The reaction mixture was filtered through a short pad of silica gel (washed several times with EtOAc) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the nitroalkane products.

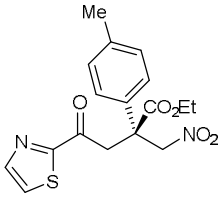


Ethyl 2-(4-methylphenyl)-2-(nitromethyl)-4-oxo-4-(pyridin-2-yl)butanoate (496h). The title compound was prepared according to General Procedure K from 2-acetylpyridine (**458**) (73 mg, 0.60 mmol) and nitroalkene **338b** (118 mg, 0.50 mmol) for a reaction time of 72 h and purified by column chromatography (5→20% EtOAc/hexane) to afford a pale yellow solid (145 mg, 81%). **m.p.** 65-66 °C (CH_2Cl_2); R_f = 0.32 (30% Et_2O/hexane); $[\alpha]_D^{20}$ –52.5 (*c* 1.4, $CHCl_3$); **IR** (film) 2982, 1730 (C=O), 1699 (C=O), 1549 (NO_2), 1437, 1356 (NO_2), 1211, 1192, 995, 771 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.74 (1H, ddd, *J* = 4.7, 1.7, 0.9 Hz, Ar**H**), 8.05 (1H, dt, *J* = 7.9, 1.1 Hz, Ar**H**), 7.86 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.53 (1H, ddd, *J* = 7.6, 4.7,

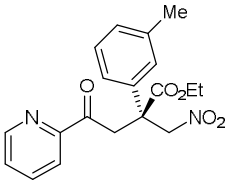
1.2 Hz, Ar**H**), 7.37-7.33 (2H, m, Ar**H**), 7.22-7.18 (2H, m, Ar**H**), 5.40-5.32 (2H, m, C**H**$_2$NO$_2$), 4.63 (1H, d, *J* =19.3 Hz, C**H**$_2$C=O), 4.26 (1H, dd, *J* = 19.2, 0.7 Hz, C**H**$_2$C=O), 4.26-4.12 (2H, m, OC**H**$_2$), 2.35 (3H, s, C**H**$_3$), 1.16 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.9 (C), 171.7 (C), 152.8 (C), 149.1 (CH), 138.2 (C), 136.9 (CH), 134.0 (C), 129.8 (2 x CH), 127.6 (CH), 125.8 (2 x CH), 121.8 (CH), 79.7 (CH_2), 62.0 (CH_2), 50.5 (C), 40.3 (CH_2), 21.0 (CH_3), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{19}H_{21}N_2O_5$ $[M+H]^+$: 357.1445, found 357.1457; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 16.6 min, t_r (minor) = 27.5 min; 98% ee.



Ethyl 2-(4-methylphenyl)-2-(nitromethyl)-4-oxo-4-(pyrazin-2-yl) butanoate (496i). The title compound was prepared according to General Procedure K from 2-acetylpyrazine (**386**) (73, 0.60 mmol) and nitroalkene **338b** (118 mg, 0.50 mmol) for a reaction time of 72 h and purified by column chromatography (5→30% Et_2O/hexane) to afford a white solid (145 mg, 81%). **m.p.** 114-115 °C (CH_2Cl_2); R_f = 0.27 (30% Et_2O/hexane); $[\alpha]_D^{20}$ –44.2 (*c* 0.97, $CHCl_3$); **IR** (film) 2982, 1730 (C=O), 1703 (C=O), 1548 (NO_2), 1375 (NO_2), 1354, 1265, 1194, 1018, 734 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.24 (1H, d, *J* = 1.3 Hz, Ar**H**), 8.82 (1H, d, *J* = 2.4 Hz, Ar**H**), 8.70 (1H, dd, *J* = 2.4, 1.5 Hz, Ar**H**), 7.34-7.30 (2H, m, Ar**H**), 7.22-7.18 (2H, m, Ar**H**), 5.36 (2H, q, *J* = 12.4 Hz, C**H**$_2$NO$_2$), 4.60 (1H, d, *J* = 19.3 Hz, C**H**$_2$C=O), 4.28-4.15 (3H, m, C**H**$_2$C=O and OC**H**$_2$), 2.35 (3H, s, C**H**$_3$), 1.19 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.4 (C), 171.4 (C), 148.4 (CH), 147.1 (C), 143.6 (CH), 143.5 (CH), 138.4 (C), 133.7 (C), 129.8 (2 x CH), 125.7 (2 x CH), 79.4 (CH_2), 62.2 (CH_2), 50.4 (C), 40.3 (CH_2), 21.0 (CH_3), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{18}H_{20}N_3O_5$ $[M+H]^+$: 358.1397, found 398.1412; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 19.1 min, t_r (minor) = 23.9 min; 98% ee.

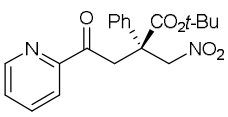


Ethyl 2-(4-methylphenyl)-2-(nitromethyl)-4-oxo-4-(1,3-thiazol-2-yl)butanoate (496j). The title compound was prepared according to General Procedure K from 2-acetylthiazole (**390**) (76, 0.60 mmol) and nitroalkene **338b** (118 mg, 0.50 mmol) for a reaction time of 72 h and purified by column chromatography (20% Et_2O/hexane) to afford a white solid (158 mg, 87%). **m.p.** 66-67 °C (CH_2Cl_2); R_f = 0.35 (30% Et_2O/hexane); $[\alpha]_D^{20}$ –41.1 (*c* 1.36, $CHCl_3$); **IR** (film) 2982, 1730 (C=O), 1686 (C=O), 1549 (NO_2), 1377 (NO_2), 1265, 1205, 1194, 960, 823 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.73 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.32-7.29 (2H, m, Ar**H**), 7.21-7.17 (2H, m, Ar**H**), 5.38 (2H, dt, *J* = 25.8, 6.6 Hz, C**H**$_2$NO$_2$), 4.56 (1H, d, *J* = 19.0 Hz, C**H**$_2$C=O), 4.27-4.14 (3H, m, C**H**$_2$C=O and OC**H**$_2$), 2.34 (3H, s, C**H**$_3$), 1.18 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 190.9 (C), 171.2 (C), 166.1 (C), 145.0 (CH), 138.4 (C), 133.5 (C), 129.8 (2 x CH), 126.8 (CH), 125.7 (2 x CH), 79.4 (CH_2), 62.2 (CH_2), 50.5 (C), 40.8 (CH_2), 21.0 (CH_3), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{17}H_{19}N_2O_5S$ $[M+H]^+$: 363.1009, found 363.1027; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 20.6 min, t_r (minor) = 23.4 min; 99% ee.

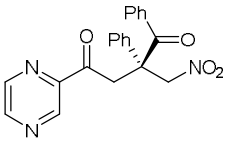


Ethyl 2-(3-methylphenyl)-2-(nitromethyl)-4-oxo-4-(pyridin-2-yl) butanoate (496p). The title compound was prepared according to General Procedure K from 2-acetylpyridine (**458**) (73 mg, 0.60 mmol) and nitroalkene **338b** (118 mg, 0.50 mmol) for a reaction time of 72 h and purified by column chromatography (5→20% EtOAc/hexane) to afford a white solid (166 mg, 93%). **m.p.** 101-102 °C (CH_2Cl_2); R_f = 0.35 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –95.8 (*c* 1.0, $CHCl_3$); **IR** (film) 2982, 1732 (C=O), 1699 (C=O), 1549 (NO_2), 1439, 1377 (NO_2), 1267, 1211, 995, 770 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (1H, ddd, *J* = 4.7, 1.7, 0.9 Hz, Ar**H**), 8.04 (1H, dt, *J* = 7.9, 1.0 Hz, Ar**H**), 7.86 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.52 (1H, ddd, *J* = 7.6, 4.7, 1.2 Hz, Ar**H**), 7.29-7.22 (3H, m, Ar**H**), 7.15-7.11 (21H, m, Ar**H**), 5.40-5.32 (2H, m, C**H**$_2$NO$_2$), 4.63 (1H, d, *J* =19.3 Hz, C**H**$_2$C=O), 4.28-4.11 (3H, m, C**H**$_2$C=O, OC**H**$_2$), 2.37 (3H, s, C**H**$_3$), 1.15

(3H, t, J = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 198.9 (C), 171.7 (C), 152.8 (C), 149.1 (CH), 138.7 (C), 137.0 (CH), 136.9 (C), 129.2 (CH), 128.9 (CH), 127.6 (CH), 126.6 (CH), 123.0 (CH), 121.8 (CH), 79.7 (CH_2), 62.0 (CH_2), 50.7 (C), 40.3 (CH_2), 21.6 (CH_3), 13.8 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{19}H_{21}N_2O_5$ $[M+H]^+$: 357.1445, found 357.1460; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 12.1 min, t_r (minor) = 19.9 min; 96% ee.

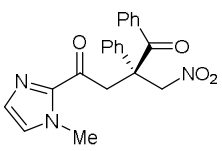


***tert*-Butyl 2-(nitromethyl)-4-oxo-2-phenyl-4-(pyridin-2-yl) butanoate (497a).** The title compound was prepared according to General Procedure K from 2-acetylpyridine (**548**) (73, 0.60 mmol) and nitroalkene **470b** (125 mg, 0.50 mmol) for a reaction time of 72 h and purified by column chromatography (5% EtOAc/hexane) to afford a white solid (161 mg, 87%). **m.p.** 79-80 °C (CH_2Cl_2); R_f = 0.14 (10% EtOAc/hexane); **$[\alpha]_D^{20}$** –88.0 (*c* 0.64, $CHCl_3$); **IR** (film) 2983, 1728 (C=O), 1701 (C=O), 1549 (NO_2), 1369 (NO_2), 1279, 1215, 1155, 995, 771 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.73 (1H, ddd, J = 4.7, 1.5, 0.8 Hz, Ar**H**), 8.06 (1H, d, J = 7.8 Hz, Ar**H**), 7.86 (1H, td, J = 7.7, 1.7 Hz, Ar**H**), 7.51 (1H, ddd, J = 7.5, 4.7, 1.2 Hz, Ar**H**), 7.49-7.46 (2H, m, Ar**H**), 7.41-7.37 (2H, m, Ar**H**), 7.35-7.31 (1H, m, Ar**H**), 5.35 (2H, dt, J = 12.4, 6.5 Hz, C**H**$_2$NO$_2$), 4.55 (1H, d, J =19.1 Hz, C**H**$_2$C=O), 4.26 (1H, dd, J = 19.1, 0.7 Hz, C**H**$_2$C=O), 1.38 (9H, s, C**H**$_3$); **^{13}C NMR** (150.8 MHz, $CDCl_3$) δ 198.9 (C), 170.2 (C), 153.0 (C), 149.1 (CH), 137.6 (C), 136.9 (CH), 128.9 (2 x CH), 128.2 (CH), 127.5 (CH), 125.9 (2 x CH), 121.7 (CH), 82.7 (C), 79.7 (CH_2), 51.4 (C), 40.3 (CH_2), 27.5 (3 x CH_3); **HRMS** (ESI) Exact mass calcd for $C_{20}H_{23}N_2O_5$ $[M+H]^+$: 371.1601, found 371.1615; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 11.1 min, t_r (minor) = 13.4 min; 98% ee.



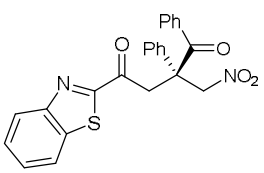
2-(Nitrophenyl)-1,2-diphenyl-4-(pyrazin-2-yl)butane-1,4-dione (517a). The title compound was prepared according to General Procedure K from 2-acetylpyrazine (**386**) (73 mg, 0.60 mmol) and

nitroalkene **515** (127 mg, 0.50 mmol) for a reaction time of 7 days and purified by column chromatography (4→12% EtOAc/hexane) to afford a yellow amorphous solid (125 mg, 67%). **m.p.** 94-95 °C (CH_2Cl_2); R_f = 0.29 (40% EtOAc/hexane); $[\alpha]_D^{20}$ –107.9 (*c* 0.63, $CHCl_3$); **IR** (film) 2918, 1701 (C=O), 1680 (C=O), 1545 (NO_2), 1446 (NO_2), 1375, 1354, 1265, 997, 700 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.12 (1H, s, Ar**H**), 8.75 (1H, d, *J* = 2.3 Hz, Ar**H**), 8.60 (1H, dd, *J* = 2.2, 1.6 Hz, Ar**H**), 7.55-7.47 (4H, m, Ar**H**), 7.46-7.42 (1H, m, Ar**H**), 7.35-7.29 (3H, m, Ar**H**), 7.22-7.17 (2H, m, Ar**H**), 5.41 (1H, dd, *J* = 11.8, 1.2 Hz, C**H**$_2$NO$_2$), 5.30 (1H, d, *J* = 11.8 Hz, C**H**$_2$NO$_2$), 4.81 (1H, d, *J* = 19.4 Hz, C**H**$_2$C=O), 4.26 (1H, dd, *J* = 19.4, 1.2 Hz, C**H**$_2$C=O); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.9 (C), 197.6 (C), 148.4 (CH), 146.7 (C), 143.5 (2 x CH), 136.3 (C), 136.1 (C), 132.0 (CH), 129.8 (2 x CH), 129.0 (CH), 128.8 (2 x CH), 128.2 (2 x CH), 126.6 (2 x CH), 81.6 (CH_2), 55.1 (C), 40.6 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{21}H_{18}N_3O_4$ $[M+H]^+$: 376.1292, found 376.1293; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (10:90, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 21.2 min, t_r (major) = 28.9 min; 97% ee.



4-(1-Methyl-1H-imidazol-2-yl)-2-(nitromethyl)-1,2-diphenylbutane-1,4-dione (517b). The title compound was prepared according to General Procedure K from 1-methyl-2-acetylimidazole (**494**) (75 mg, 0.60 mmol) and nitroalkene **515** (127 mg, 0.50 mmol) for a reaction time of 7 days and purified by column chromatography (60→100% Et_2O/hexane) to afford a white solid (155.1 mg, 82%). **m.p.** 146-147 °C (EtOAc/hextane); R_f = 0.26 (40% EtOAc/hexane); $[\alpha]_D^{20}$ –264.3 (*c* 0.96, $CHCl_3$); **IR** (film) 2918, 1681 (C=O), 1547 (NO_2), 1447 (NO_2), 1410, 1375, 1354, 1221, 993, 700 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (2H, dt, *J* = 8.6, 2.4 Hz, Ar**H**), 7.49-7.44 (2H, m, Ar**H**), 7.44-7.39 (1H, m, Ar**H**), 7.35-7.30 (3H, m, Ar**H**), 7.21-7.16 (2H, m, Ar**H**), 7.11 (1H, d, *J* = 0.7 Hz, Ar**H**), 6.98 (1H, s, Ar**H**), 5.38 (1H, dd, *J* = 11.7, 1.3 Hz, C**H**$_2$NO$_2$), 5.29 (1H, d, *J* = 11.7 Hz, C**H**$_2$NO$_2$), 4.76 (1H, d, *J* = 19.1 Hz, C**H**$_2$C=O), 4.28 (1H, dd, *J* = 19.1, 1.3 Hz, C**H**$_2$C=O), 3.89 (3H, s, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 199.1 (C), 198.4 (C), 142.1 (C), 136.3 (C), 136.2 (C), 131.9 (CH), 129.7 (2 x CH),

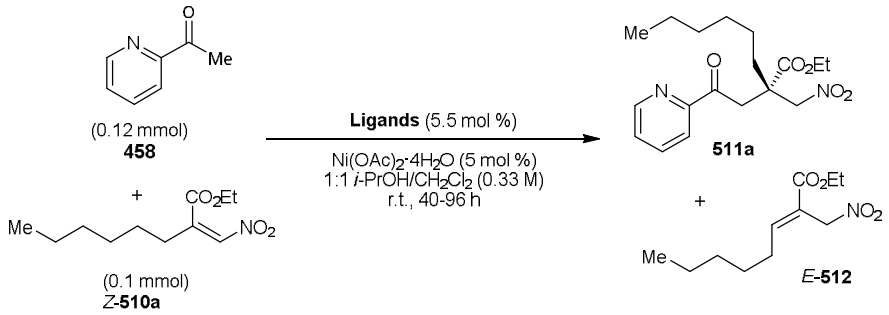
129.4 (CH), 129.0 (2 x CH), 128.9 (CH), 128.2 (2 x CH), 127.4 (CH), 126.7 (2 x CH), 81.9 (CH_2), 55.1 (C), 41.6 (CH_2), 36.1 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{21}H_{20}N_3O_4$ $[M+H]^+$: 378.1448, found 378.1447; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (10:90, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 18.8 min, t_r (minor) = 23.3 min; 99% ee.



4-(1,3-Benzothiazol-2-yl)-2-(nitromethyl)-1,2-diphenylbutane-1,4-dione (517c). The title compound was prepared according to General Procedure K from 2-acetylbenzothiazole (**495**) (106 mg, 0.60 mmol) and nitroalkene **515** (127 mg, 0.50 mmol) for a reaction time of 7 days and purified by column chromatography (2→6% EtOAc/hexane) to afford a yellow solid (170 mg, 79%). **m.p.** 64-65 °C (CH_2Cl_2); R_f = 0.15 (20% EtOAc/hexane); $[\alpha]_D^{20}$ –152.4 (*c* 0.89, $CHCl_3$); **IR** (film) 3063, 1693 (C=O), 1547 (NO_2), 1483 (NO_2), 1447, 1375, 1204, 948, 758, 700 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.19-8.16 (1H, m, Ar**H**), 7.96-7.93 (1H, m, Ar**H**), 7.61-7.49 (6H, m, Ar**H**), 7.47-7.43 (1H, m, Ar**H**), 3.35-3.30 (3H, m, Ar**H**), 7.22-7.17 (2H, m, Ar**H**), 5.45 (1H, dd, *J* = 12.0, 1.2 Hz, C**H**$_2$NO$_2$), 5.33 (1H, d, *J* = 12.0 Hz, C**H**$_2$NO$_2$), 4.91 (1H, d, *J* = 19.2 Hz, C**H**$_2$C=O), 4.37 (1H, dd, *J* = 19.2, 1.2 Hz, C**H**$_2$C=O); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.7 (C), 191.7 (C), 164.9 (C), 153.3 (C), 137.4 (C), 136.2 (C), 135.9 (C), 132.1 (CH), 129.8 (2 x CH), 129.1 (CH), 128.9 (2 x CH), 128.3 (2 x CH), 128.0 (CH), 127.2 (CH), 126.6 (2 x CH), 125.6 (CH), 122.4 (CH), 81.4 (CH_2), 55.3 (C), 41.4 (CH_2); **HRMS** (ESI) Exact mass calcd for $C_{24}H_{19}N_2O_4S$ $[M+H]^+$: 431.1060, found 431.1056; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (10:90, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 15.8 min, t_r (minor) = 19.6 min; >99% ee.

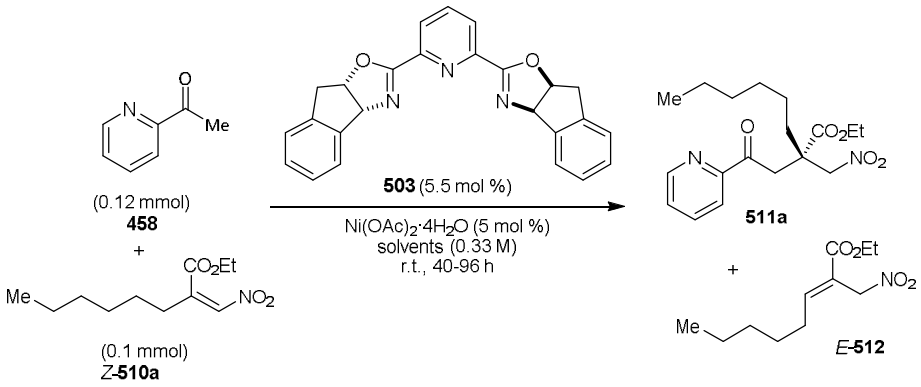
Screening and Optimisation for Aliphatic Substituted Nitroalkenes

Catalyst Screening (Table 2.5)



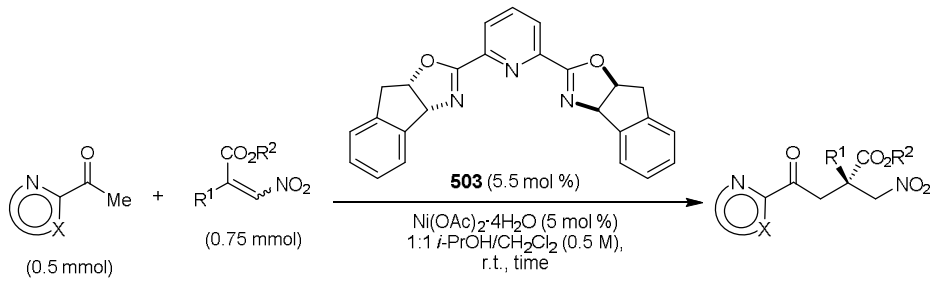
A suspension of $Ni(OAc)_2 \cdot 4H_2O$ (1.2 mg, 0.005 mmol) and ligand (0.0055 mmol) in 1:1 *i*-PrOH/CH_2Cl_2 (0.3 mL) was stirred at room temperature for 30 min. This resulting solution was then added to a 1 mL vial containing 2-acetylpyridine (**458**) (0.12 mmol) and nitroalkene *Z*-**510a** (0.1 mmol), and the reaction mixture was stirred until complete consumption of the nitroalkene as indicated by TLC analysis. The reaction mixture was then filtered through a short pad of silica gel (washed several times with EtOAc) and concentrated *in vacuo*. The percent conversions were determined by ^{1}H NMR analysis of crude mixture using 1,3,5-tetramethoxybenzene as internal standard.

Solvent screening (Table 2.6 and Table 2.7)

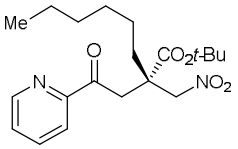


A suspension of $Ni(OAc)_2 \cdot 4H_2O$ (1.2 mg, 0.005 mmol) and ligand **503** (2.2 mg, 0.0055 mmol) in pure solvent or mixed solvent (0.3 mL) was stirred at room temperature for 30 min. This resulting solution was then added to a 1 mL vial containing 2-acetylpyridine (**458**) (0.12 mmol) and nitroalkene *Z*-**510a** (0.1 mmol), and the reaction mixture was stirred until complete consumption of the nitroalkene as indicated by TLC analysis. The reaction mixture was then filtered through a short pad of silica gel (washed several times with EtOAc) and concentrated *in vacuo*. The percent conversions were determined by ^1H NMR analysis of crude mixtures using 1,3,5-tetramethoxybenzene as internal standard.

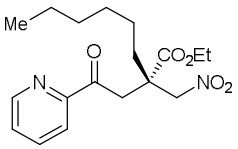
General Procedure L: Michael Addition of 2-Acetylazaarenes to Aliphatic Substituted Nitroalkenes



A suspension of $Ni(OAc)_2 \cdot 4H_2O$ (6.2 mg, 0.025 mmol) and ligand **503** (10.8 mg, 0.0275 mmol) in 1:1 *i*-PrOH/CH_2Cl_2 (0.5 mL) was stirred at room temperature for 30 min. To the resulting solution was added a solution of the appropriate 2-acetylazaarene (0.50 mmol) and the appropriate nitroalkene (0.75 mmol) in 1:1 *i*-PrOH/CH_2Cl_2 (0.5 mL), and the reaction mixture was stirred until complete consumption of 2-acetylazaarene as indicated by TLC analysis. The reaction mixture was filtered through a short pad of silica gel (washed several times with EtOAc) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the nitroalkane products.

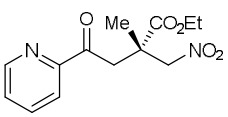


***tert*-Butyl 2-(nitromethyl)-2-[2-oxo-2-(pyridin-2-yl)ethyl] octanoate (497b).** The title compound was prepared according to General Procedure L from 2-acetylpyridine (**458**) (61, 0.50 mmol) and *Z*-nitroalkene **470c** (193 mg, 0.75 mmol) for a reaction time of 40 h and purified by column chromatography (2→6% EtOAc/hexane) to afford a white solid (171 mg, 90%). **m.p.** 42-43 °C (CH_2Cl_2); R_f = 0.24 (20% EtOAc/hexane); $[\alpha]_D^{20}$ –9.9 (*c* 1.0, $CHCl_3$); **IR** (film) 2930, 1726 (C=O), 1701 (C=O), 1549 (NO_2), 1369 (NO_2), 1252, 1213, 1155, 845, 766 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.68 (1H, ddd, *J* = 4.7, 1.5, 0.8 Hz, Ar**H**), 8.05-8.01 (1H, m, Ar**H**), 7.85 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.49 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar**H**), 5.01 (1H, d, *J* = 11.9 Hz, C**H**$_2$NO$_2$), 4.93 (1H, d, *J* = 11.9 Hz, C**H**$_2$NO$_2$), 3.74 (2H, q, *J* = 19.3 Hz, C**H**$_2$C=O), 1.78-1.68 (2H, m, C**H**$_2$), 1.49-1.41 (1H, m, C**H**$_2$), 1.45 (9H, s, 3 x C**H**$_3$), 1.34-1.23 (7H, m, 4 x C**H**$_2$), 0.88 (3H, t, *J* = 6.7 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.9 (C), 171.4 (C), 152.9 (C), 148.9 (CH), 137.0 (CH), 127.4 (CH), 121.7 (CH), 82.2 (C), 77.0 (CH_2), 47.6 (C), 41.6 (CH_2), 35.7 (CH_2), 31.4 (CH_2), 29.3 (CH_2), 27.8 (3 x CH_3), 23.5 (CH_2), 22.4 (CH_2), 14.0 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{20}H_{31}N_2O_5$ $[M+H]^+$: 379.2228, found 379.2248; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 5.9 min, t_r (major) = 6.8 min; 52% ee.

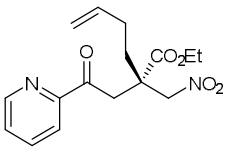


Ethyl 2-(nitromethyl)-2-[2-oxo-2-(pyridin-2-yl)ethyl] octanoate (511a). The title compound was prepared according to General Procedure L from 2-acetylpyridine (**458**) (60.6, 0.50 mmol) and *Z*-nitroalkene (**510a**) (172 mg, 0.75 mmol) for a reaction time of 40 h and purified by column chromatography (5→20% Et_2O/hexane) to afford a colourless oil (172 mg, 98%). R_f = 0.39 (20% EtOAc/hexane); $[\alpha]_D^{20}$ –17.7 (*c* 0.96, $CHCl_3$); **IR** (film) 2928, 1732 (C=O), 1699 (C=O), 1549 (NO_2), 1439, 1377 (NO_2), 1211, 1196, 995, 764 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.67 (1H, ddd, *J* = 4.8, 1.7, 0.9 Hz, Ar**H**), 8.01 (1H, dt, *J* = 7.9, 1.1 Hz, Ar**H**), 7.83 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.48 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar**H**), 5.01 (2H, dd, *J* = 26.5, 12.0 Hz, C**H**$_2$NO$_2$), 4.26-4.16 (2H, m, OC**H**$_2$),

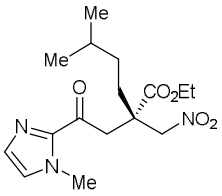
3.85 (1H, d, *J* = 19.2 Hz, C**H**$_2$C=O), 3.74 (1H, d, *J* = 19.2 Hz, C**H**$_2$C=O), 1.80-1.70 (2H, m, C**H**$_2$), 1.49-1.39 (1H, m, C**H**$_2$), 1.34-1.18 (10H, 4 x C**H**$_2$, C**H**$_3$), 0.86 (3H, t, *J* = 6.9 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.9 (C), 172.5 (C), 152.8 (C), 149.0 (CH), 136.9 (CH), 127.5 (CH), 121.7 (CH), 76.9 (CH_2), 61.5 (CH_2), 47.2 (C), 41.4 (CH_2), 35.5 (CH_2), 31.3 (CH_2), 29.2 (CH_2), 23.5 (CH_2), 22.4 (CH_2), 14.0 (CH_3), 13.9 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{18}H_{27}N_2O_5$ $[M+H]^+$: 351.1915, found 351.1928; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 8.6 min, t_r (major) = 10.4 min; 78% ee.



Ethyl 2-methyl-2-(nitromethyl)-4-oxo-4-(pyridin-2-yl) butanoate (511b). The title compound was prepared according to General Procedure L from 2-acetylpyridine (**458**) (61, 0.50 mmol) and *E*-nitroalkene **510b** (119 mg, 0.75 mmol) for a reaction time of 40 h and purified by column chromatography (4→12% EtOAc/hexane) to afford a colourless oil (106 mg, 76%). **m.p.** 51-52 °C (CH_2Cl_2); R_f = 0.28 (20% EtOAc/hexane); $[\alpha]_D^{20}$ –11.7 (*c* 1.02, $CHCl_3$); **IR** (film) 2982, 1730 (C=O), 1697 (C=O), 1549 (NO_2), 1464, 1358 (NO_2), 1211, 1111, 1016, 764 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.70-8.67 (1H, ddd, m, Ar**H**), 8.03 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.86 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.51 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar**H**), 5.00 (1H, d, *J* = 12.0 Hz, C**H**$_2$NO$_2$), 4.91 (1H, d, *J* = 12.0 Hz, C**H**$_2$NO$_2$), 4.22 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 3.83-3.73 (2H, m, C**H**$_2$C=O), 1.49 (3H, s, C**H**$_3$), 1.25 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.6 (C), 173.3 (C), 152.8 (C), 149.0 (CH), 137.0 (CH), 127.6 (CH), 121.8 (CH), 79.7 (CH_2), 61.7 (CH_2), 43.7 (C), 42.4 (CH_2), 22.2 (CH_3), 13.9 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{13}H_{17}N_2O_5$ $[M+H]^+$: 281.1132, found 281.1142; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 12.4 min, t_r (major) = 14.4 min; 74% ee.

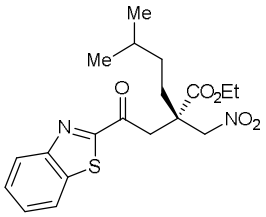


Ethyl 2-(nitomethly)-2-[2-oxo-2-(pyridin-2-yl)ethyl]hex-5-enoate (511c). The title compound was prepared according to General Procedure L from 2-acetylpyridine (**458**) (61 mg, 0.50 mmol) and *Z*-nitroalkene **510c** (149 mg, 0.75 mmol) for a reaction time of 40 h and purified by column chromatography (3→12% EtOAc/hexane) to afford a colourless gum (150 mg, 94%). R_f = 0.38 (20% EtOAc/hexane); $[\alpha]_D^{20}$ –13.6 (*c* 1.32, $CHCl_3$); **IR** (film) 2980, 1730 (C=O), 1699 (C=O), 1549 (NO_2), 1439, 1377 (NO_2), 1211, 1096, 995, 914, 764 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.66 (1H, ddd, *J* = 4.8, 1.7, 0.9 Hz, Ar**H**), 8.00 (1H, dt, *J* = 7.9, 1.1 Hz, Ar**H**), 7.83 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.48 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar**H**), 5.74 (1H, ddt, *J* = 16.8, 10.2, 6.5 Hz, C**H=**), 5.07-4.95 (4H, m, C**H**$_2$=, **CH**$_2$$NO_2$), 4.27-4.16 (2H, m, OC**H**$_2$), 3.79 (2H, dt, *J* = 19.3, 9.8 Hz, C**H**$_2$C=O), 2.26-2.17 (1H, m, C**H**$_2$), 2.09-1.97 (1H, m, C**H**$_2$), 1.92-1.82 (2H, m, C**H**$_2$), 1.24 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.7 (C), 172.2 (C), 152.7 (C), 149.0 (CH), 136.9 (CH), 136.6 (CH), 127.5 (CH), 121.6 (CH), 115.6 (CH_2), 76.8 (CH_2), 61.6 (CH_2), 46.9 (C), 41.2 (CH_2), 34.5 (CH_2), 28.0 (CH_2), 14.0 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{16}H_{21}N_2O_5$ $[M+H]^+$: 321.1445, found 321.1447; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 9.8 min, t_r (major) = 15.3 min; 73% ee.

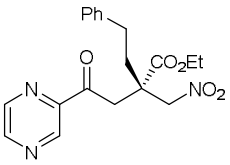


Ethyl 5-methyl-2-[2-(1-methyl-1H-imidazol-2-yl)-2-oxoethyl]-2-(nitromethyl)hexanoate (511d). The title compound was prepared according to General Procedure L from 1-methyl-2-acetylimidazole (**494**) (62 mg, 0.50 mmol) and *Z*-nitroalkene **510f** (161 mg, 0.75 mmol) for a reaction time of 96 h and purified by column chromatography (10→30% EtOAc/hexane) to afford a colourless oil (115 mg, 68%). R_f = 0.35 (40% EtOAc/hexane); $[\alpha]_D^{20}$ –25.3 (*c* 0.91, $CHCl_3$); **IR** (film) 2957, 1732 (C=O), 1676 (C=O), 1549 (NO_2), 1468, 1414, 1379 (NO_2), 1211, 999, 776 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.14 (1H, d, *J* = 0.9 Hz, Ar**H**), 7.04 (1H, s, Ar**H**), 4.98 (2H, dd, *J* = 30.1, 12.0 Hz, C**H**$_2$$NO_2$), 4.27-4.16 (2H, m, OC**H**$_2$), 3.98 (3H, s, C**H**$_3$), 3.76-3.65 (2H, m,

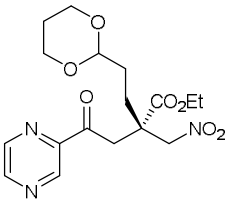
C**H**$_2$C=O), 1.77-1.69 (2H, m, C**H**$_2$), 1.55-1.43 (1H, m, C**H**), 1.36-1.27 (1H, m, C**H**$_2$), 1.25 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 1.17-1.06 (1H, m, C**H**$_2$), 0.88-0.84 (6H, m, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 189.3 (C), 172.4 (C), 142.3 (C), 129.1 (CH), 127.2 (CH), 76.9 (CH_2), 61.5 (CH_2), 47.1 (C), 42.5 (CH_2), 36.1 (CH_3), 33.3 (CH_2), 32.4 (CH_2), 28.1 (CH), 22.4 (CH_3), 22.3 (CH_3), 14.1 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{16}H_{26}N_3O_5$ $[M+H]^+$: 340.1867, found 340.1873; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 8.9 min, t_r (major) = 14.2 min; 92% ee.



Ethyl 2-[2-(1,3-benzothiazol-2-yl)-2-oxoethyl]-5-methyl-2-(nitromethyl)hexanoate (511e). The title compound was prepared according to General Procedure L from 2-acetylbenzothiazole (**495**) (89 mg, 0.50 mmol) and *Z*-nitroalkene **510f** (161 mg, 0.75 mmol) for a reaction time of 96 h and purified by column chromatography (1→3% EtOAc/hexane) to afford a white solid (105 mg, 54%). **m.p.** 78-79 °C (hextane); R_f = 0.29 (10% EtOAc/hexane); $[\alpha]_D^{20}$ −35.9 (*c* 0.72, $CHCl_3$); **IR** (film) 2957, 2928, 1731 (C=O), 1693 (C=O), 1551 (NO_2), 1485 (NO_2), 1377, 1206, 1015, 764 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (1H, dd, *J* = 7.5, 0.7 Hz, Ar**H**), 8.01-7.98 (1H, m, Ar**H**), 7.62-7.53 (2H, m, Ar**H**), 5.03 (2H, q, *J* = 12.3 Hz, C**H**$_2$NO$_2$), 4.30-4.20 (2H, m, OC**H**$_2$), 3.88 (2H, dd, *J* = 43.0, 19.0 Hz, C**H**$_2$C=O), 1.84-1.76 (2H, m, C**H**$_2$), 1.57-1.48 (1H, m, C**H**), 1.39-1.31 (1H, m, C**H**$_2$), 1.28 (3H, t, *J* = 7.1 Hz, C**H**$_3$), 1.21-1.12 (1H, m, C**H**$_2$), 0.89 (6H, t, *J* = 6.4 Hz, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 192.5 (C), 172.0 (C), 165.3 (C), 153.4 (C), 137.3 (C), 128.0 (CH), 127.2 (CH), 125.6 (CH), 122.4 (CH), 76.8 (CH_2), 61.8 (CH_2), 47.3 (C), 41.9 (CH_2), 33.3 (CH_2), 32.4 (CH_2), 28.1 (CH), 22.4 (CH_3), 22.3 (CH_3), 14.1 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{19}H_{24}N_2O_5SNa$ $[M+Na]^+$: 415.1298, found 415.1313; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 8.9 min, t_r (major) = 10.1 min; 80% ee.

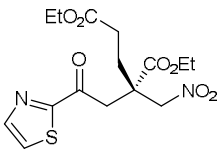


Ethyl 2-(nitromethyl)-4-oxo-2-(2-phenylethyl)-4-(pyrazin-2-yl) butanoate (511f). The title compound was prepared according to General Procedure L from 2-acetylpyrazine (**386**) (61, 0.75 mmol) and nitroalkene **510d** (187 mg, 0.60 mmol) for a reaction time of 48 h and purified by column chromatography (5→30% EtOAc/hexane) to afford a colourless oil (158 mg, 85%). R_f = 0.15 20% EtOAc/hexane); $[\alpha]_D^{20}$ –1.0 (*c* 0.92, $CHCl_3$); **IR** (film) 2928, 1730 (C=O), 1701 (C=O), 1549 (NO_2), 1375 (NO_2), 1219, 1198, 1016, 1003, 750 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.23 (1H, d, *J* = 1.5 Hz, Ar**H**), 8.79 (1H, d, *J* = 2.5 Hz, Ar**H**), 8.65 (1H, dd, *J* = 2.4, 1.5 Hz, Ar**H**), 7.31-7.26 (2H, m, Ar**H**), 7.22-7.14 (3H, m, Ar**H**), 5.10 (2H, s, C**H**$_2$$NO_2$), 4.33-4.22 (2H, m, OC**H**$_2$), 3.87 (1H, d, *J* = 19.4 Hz, C**H**$_2$C=O), 3.75 (1H, d, *J* = 19.4 Hz, C**H**$_2$C=O), 2.86-2.78 (1H, m, C**H**$_2$), 2.60-2.52 (1H, m, C**H**$_2$), 2.16-2.03 (2H, m, C**H**$_2$), 1.31 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.2 (C), 172.0 (C), 148.3 (CH), 146.9 (C), 143.6 (CH), 143.5 (CH), 140.2 (C), 128.6 (2 x CH), 128.3 (2 x CH), 126.3 (CH), 76.7 (CH_2), 61.9 (CH_2), 47.1 (C), 41.3 (CH_2), 37.4 (CH_2), 30.2 (CH_2), 14.1 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{19}H_{22}N_3O_5$ $[M+H]^+$: 372.1554, found 372.1568; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (30:70, *i*-PrOH:hexane, 0.1 mL/min, 280 nm, 25 ºC); t_r (minor) = 98.0 min, t_r (major) = 103.2 min; 82% ee.

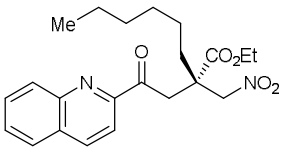


Ethy 2-[2-(1,3-dioxan-2-yl)ethyl]-2-(nitromethyl)-4-oxo-4-(pyrazin-2-yl)butanoate (511g). The title compound was prepared according to General Procedure L from 2-acetylpyrazine (**386**) (61, 0.50 mmol) and *Z*-nitroalkene **510g** (195 mg, 0.75 mmol) for a reaction time of 48 h and purified by column chromatography (10→40% EtOAc/hexane) to afford a pale yellow gum (148 mg, 78%). R_f = 0.22 (40% EtOAc/hexane); $[\alpha]_D^{20}$ –11.9 (*c* 1.51, $CHCl_3$); **IR** (film) 2853, 1730 (C=O), 1701 (C=O), 1549 (NO_2), 1377 (NO_2), 1206, 1142, 1097, 1005, 853 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.24 (1H, br s, Ar**H**), 8.77 (1H, br s, Ar**H**), 8.65 (1H, br s, Ar**H**), 5.04 (1H, d, *J* = 12.2 Hz, C**H**$_2$$NO_2$), 4.96 (1H, d, *J* = 12.2 Hz, C**H**$_2$$NO_2$), 4.49 (1H, t, *J* = 4.9,

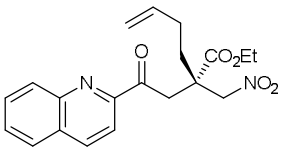
OC**H**O), 4.27-4.17 (2H, m, OC**H**$_2$), 4.06 (2H, ddd, *J* = 11.7, 4.8, 1.1 Hz, C**H**$_2$), 3.84-3.68 (4H, m, 2 x C**H**$_2$), 2.09-1.98 (1H, m, C**H**$_2$), 1.97-1.84 (2H, m, C**H**$_2$), 1.77-1.69 (1H, m, C**H**$_2$), 1.60-1.52 (1H, m, C**H**$_2$), 1.35-1.29 (1H, m, C**H**$_2$), 1.26 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.3 (C), 171.9 (C), 148.1 (CH), 147.2 (C), 143.7 (CH), 143.3 (CH), 101.2 (CH), 76.9 (CH_2), 66.8 (2 x CH_2), 61.9 (CH_2), 46.7 (C), 40.9 (CH_2), 29.5 (2 x CH_2), 25.6 (CH_2), 14.0 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{17}H_{24}N_3O_7$ $[M+H]^+$: 382.1609, found 382.1636; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 23.7 min, t_r (major) = 68.5 min; 81% ee.



1,5-Diethyl 2-(nitromethyl)-2-[2-oxo-2-(1,3-thiazol-2-yl)ethyl] pentanedioate (511h). The title compound was prepared according to General Procedure L from 2-acetylthiazole (**390**) (64 mg, 0.50 mmol) and *Z*-nitroalkene **5510e** (184 mg, 0.75 mmol) for a reaction time of 72 h and purified by column chromatography (5→30% EtOAc/hexane) to afford a colourless gum (117 mg, 63%). R_f = 0.08 (20% EtOAc/hexane); $[\alpha]_D^{20}$ –12.6 (*c* 0.87, $CHCl_3$); **IR** (film) 2982, 1730 (C=O), 1686 (C=O), 1551 (NO_2), 1447, 1379 (NO_2), 1300, 1190, 1018, 756 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.73 (1H, d, *J* = 3.0 Hz, Ar**H**), 5.05 (1H, d, *J* = 12.6 Hz, C**H**$_2$NO$_2$), 4.97 (1H, d, *J* = 12.6 Hz, C**H**$_2$NO$_2$), 4.23 (2H, q, *J* =7.1 Hz, OC**H**$_2$), 4.12 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 3.77 (2H, d, *J* = 2.4 Hz, C**H**$_2$CO), 2.50 (1H, ddd, *J* = 16.4, 10.5, 6.0 Hz, C**H**$_2$), 2.36 (1H, ddd, *J* = 16.2, 10.6, 5.5 Hz, C**H**$_2$), 2.22-2.07 (2H, m, C**H**$_2$), 1.29-1.23 (6H, m, 2 x C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 190.6 (C), 171.8 (C), 171.4 (C), 165.9 (C), 145.0 (CH), 126.8 (CH), 76.8 (CH_2), 62.3 (CH_2), 60.8 (CH_2), 46.5 (C), 41.2 (CH_2), 30.0 (CH_2), 28.8 (CH_2), 14.1 (CH_3), 13.9 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{15}H_{21}N_2O_7S$ $[M+H]^+$: 373.1064, found 373.1074; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (3:97, *i*-PrOH:hexane, 0.4 mL/min, 280 nm, 25 ºC); t_r (major) = 111.2 min, t_r (minor) = 123.7 min; 78% ee.

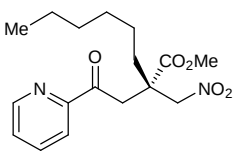


Ethyl 2-(nitromethyl)-2-[2-oxo-2-(quinolin-2-yl)ethyl] octanoate (511i). The title compound was prepared according to General Procedure L from 2-acetylquinoline (**493**) (86, 0.50 mmol) and nitroalkene **510a** (172 mg, 0.75 mmol) for a reaction time of 96 h and purified by column chromatography (1→3% EtOAc/hexane) to afford a colourless oil (26 mg, 13%). R_f = 0.16 (5% EtOAc/hexane); $[\alpha]_D^{20}$ –26.9 (*c* 0.52, $CHCl_3$); **IR** (film) 2929, 1728 (C=O), 1697 (C=O), 1549, 1460, 1377, 1215, 1016, 833, 748 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (1H, d, *J* = 8.5 Hz, Ar**H**), 8.21 (1H, d, *J* = 8.6 Hz, Ar**H**), 8.11 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.88 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.80 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, Ar**H**), 7.67 (1H, ddd, *J* = 8.1, 6.9, 1.1 Hz, Ar**H**), 5.06 (2H, q, *J* = 12.1 Hz, C**H**$_2$NO$_2$), 4.30-4.20 (2H, m, OC**H**$_2$), 4.07 (1H, d, *J* = 19.1 Hz, C**H**$_2$C=O), 3.92 (1H, d, 19.1 Hz, C**H**$_2$C=O), 1.87-1.79 (2H, m, C**H**$_2$), 1.54-1.45 (1H, m, C**H**$_2$), 1.35-1.24 (10H, m, 4 x C**H**$_2$, C**H**$_3$), 0.88 (3H, t, *J* = 6.8 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 199.4 (C), 172.7 (C), 152.4 (C), 147.2 (C), 137.0 (CH), 130.7 (CH), 130.1 (CH), 129.8 (C), 128.8 (CH), 127.6 (CH), 117.8 (CH), 77.0 (CH_2), 61.6 (CH_2), 47.4 (C), 41.2 (CH_2), 35.5 (CH_2), 31.4 (CH_2), 29.3 (CH_2), 23.6 (CH_2), 22.5 (CH_2), 14.0 (2 x CH_3); **HRMS** (ESI) Exact mass calcd for $C_{22}H_{29}N_2O_5$ $[M+H]^+$: 401.2071, found 401.2091; 70% ee. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (10:90, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 7.8 min, t_r (major) = 9.9 min; 70% ee.



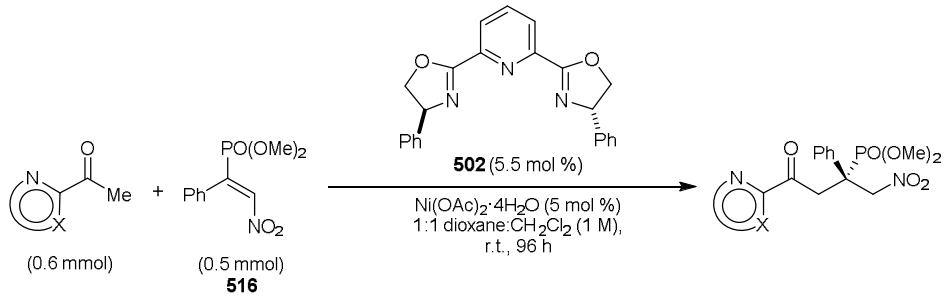
Ethyl 2-(nitromethyl)-2-[2-oxo-2-(quinolin-2-yl)ethyl] hex-5-enoate (511j). The title compound was prepared according to General Procedure L from 2-acetylquinoline (**493**) (86 mg, 0.50 mmol) and *Z*-nitroalkene **5510c** (140 mg, 0.75 mmol) for a reaction time of 96 h and purified by column chromatography (2→6% EtOAc/hexane) to afford a colourless oil (17 mg, 9%). R_f = 0.39 (10% EtOAc/hexane); $[\alpha]_D^{20}$ –13.5 (*c* 0.16, $CHCl_3$); **IR** (film) 2924, 1732 (C=O), 1697 (C=O), 1549 (NO_2), 1377 (NO_2), 1217, 1204, 1003, 833, 752 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.30 (1H, d, *J* = 8.4 Hz, Ar**H**), 8.23 (1H, dd, *J* = 8.3, 0.6 Hz, Ar**H**), 8.11 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.89 (1H, dd, *J* = 8.2, 1.1 Hz,

Ar**H**), 7.81 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, Ar**H**), 7.68 (1H, ddd, *J* = 8.4, 6.9, 1.2 Hz, Ar**H**), 5.85-5.73 (1H, m, =C**H**), 5.13-4.99 (4H, m, =C**H**$_2$, C**H**$_2$NO$_2$), 4.31-4.22 (2H, m, OC**H**$_2$), 4.09 (1H, d, *J* = 19.1 Hz, C**H**$_2$C=O), 3.95 (1H, d, *J* = 19.0 Hz, C**H**$_2$C=O), 2.32-2.22 (1H, m, C**H**$_2$), 2.15-2.06 (1H, m, C**H**$_2$), 2.00-1.89 (2H, m, C**H**$_2$), 1.28 (3H, t, *J* = 7.1 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 199.2 (C), 172.4 (C), 152.3 (C), 147.1 (C), 137.1 (CH), 136.7 (CH), 130.6 (CH), 130.2 (CH), 129.8 (C), 128.9 (CH), 127.7 (CH), 117.8 (CH), 115.7 (CH_2), 77.0 (CH_2), 61.7 (CH_2), 47.2 (C), 41.1 (CH_2), 34.6 (CH_2), 28.1 (CH_2), 14.0 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{20}H_{23}N_2O_5$ $[M+H]^+$: 371.1602, found 371.1610; Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (10:90, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 9.2 min, t_r (major) = 10.9 min; 51% ee.

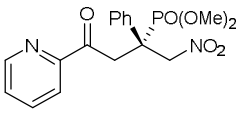


Methyl 2-(nitromethyl)-2-[2-oxo-2-(pyridin-2-yl)ethyl] octanoate (514). The title compound was prepared according to General Procedure L from 2-acetylpyridine (**458**) (61, 0.50 mmol) and *Z*-nitroalkene **513** (151 mg, 0.75 mmol) for a reaction time of 40 h and purified by column chromatography (4→12% EtOAc/hexane) to afford a colourless oil (158 mg, 94%). R_f = 0.24 (20% EtOAc/hexane); $[\alpha]_D^{20}$ –18.1 (*c* 0.99, $CHCl_3$); **IR** (film) 2928, 1736 (C=O), 1697 (C=O), 1549 (NO_2), 1437, 1377 (NO_2), 1358, 1211, 995, 764 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.68 (1H, ddd, *J* = 4.8, 1.7, 0.9 Hz, Ar**H**), 8.02 (1H, dt, *J* = 7.9, 1.0 Hz, Ar**H**), 7.85 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.50 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar**H**), 5.01 (2H, q, *J* = 12.0 Hz, C**H**$_2$NO$_2$), 3.88 (1H, d, *J* = 19.3 Hz, C**H**$_2$C=O), 3.74 (1H, d, *J* = 19.3 Hz, C**H**$_2$C=O), 3.75 (3H, s, OC**H**$_3$), 1.80-1.73 (2H, m, C**H**$_2$), 1.48-1.38 (1H, m, C**H**$_2$), 1.34-1.16 (7H, 4 x C**H**$_2$), 0.87 (3H, t, *J* = 6.8 Hz, C**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.8 (C), 173.1 (C), 152.7 (C), 149.0 (CH), 137.0 (CH), 127.6 (CH), 121.7 (CH), 76.9 (CH_2), 52.5 (CH_3), 47.3 (C), 41.5 (CH_2), 35.5 (CH_2), 31.4 (CH_2), 29.2 (CH_2), 23.7 (CH_2), 22.5 (CH_2), 14.0 (CH_3); **HRMS** (ESI) Exact mass calcd for $C_{17}H_{25}N_2O_5$ $[M+H]^+$: 337.1758, found 337.1760; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 8.8 min, t_r (major) = 10.0 min; 81% ee.

General Procedure M: Michael Addition of 2-Acetylazaarenes to Nitroalkene 516

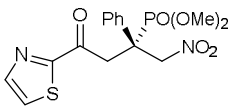


A suspension of $Ni(OAc)_2 \cdot 4H_2O$ (6.2 mg, 0.025 mmol) and ligand **502** (10.2 mg, 0.0275 mmol) in 1:1 dioxane:CH_2Cl_2 (0.3 mL) was stirred at room temperature for 3 h. To the resulting solution was added a solution of the appropriate 2-acetylazaarene (0.60 mmol) and the appropriate nitroalkene (126.8 mg, 0.5 mmol) in 1:1 dioxane:CH_2Cl_2 (0.2 mL), and the reaction mixture was stirred for 96 h. The reaction mixture was then filtered through a short pad of silica gel (washed several times with EtOAc) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the nitroalkane products.



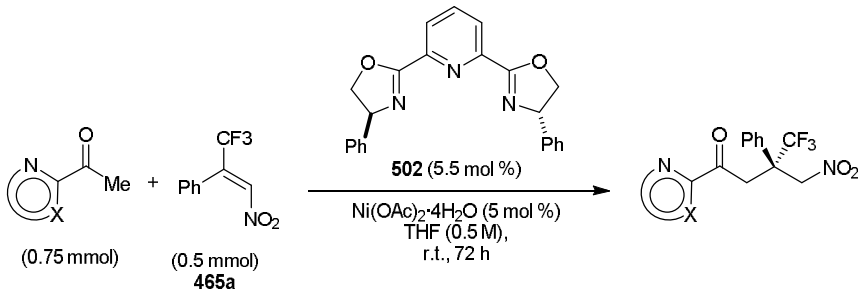
Dimethyl [1-nitro-4-oxo-2-phenyl-4-(pyridin-2-yl)butan-2-yl] phosphonate (518a). The title compound was prepared according to General Procedure M from 2-acetylpyridine (**458)** (73 mg, 0.60 mmol) and purified by column chromatography (80% EtOAc/hexane) to afford a white solid (44 mg, 23%). **m.p.** 153-154 °C (EtOAc); R_f = 0.26 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +62.1 (*c* 0.66, $CHCl_3$); **IR** (film) 2957, 1703 (C=O), 1554 (NO_2), 1437, 1375 (NO_2), 1246 (P=O), 1047, 1026 (P-O), 829, 770 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.74 (1H, ddd, *J* = 4.7, 1.6, 0.9 Hz, Ar**H**), 8.02-7.99 (1H, m, Ar**H**), 7.85 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.54-7.49 (3H, m, Ar**H**), 7.39 (2H, t, *J* = 7.8 Hz, Ar**H**), 7.34-7.29 (1H, m, Ar**H**), 5.79 (1H, dd, *J* = 12.8, 8.3 Hz, C**H**$_2$$NO_2$), 5.63 (1H, dd, *J* = 21.5, 12.8 Hz, C**H**$_2$$NO_2$), 4.48 (2H, ddd, *J* = 33.8, 18.9, 11.8 Hz, C**H**$_2$C=O), 3.53 (3H, d, *J* = 10.7 Hz, OC**H**$_3$), 3.40 (3H, d, *J* = 10.6 Hz, OC**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 198.1 (d,

J = 11.4 Hz, C), 153.2 (d, *J* = 1.8 Hz, C), 149.0 (CH), 137.0 (CH), 134.9 (d, *J* = 8.3 Hz, C), 128.8 (d, *J* = 2.9 Hz, 2 x CH), 128.0 (d, *J* = 3.1 Hz, CH), 127.4 (CH), 127.2 (d, *J* = 5.1 Hz, 2 x CH), 121.8 (CH), 75.7 (CH_2), 54.0 (dd, *J* = 63.2, 7.5 Hz, 2 x CH_3), 45.9 (d, *J* = 136.5 Hz, C), 36.0 (d, *J* = 2.4 Hz, CH_2); **^{31}P NMR** (400 MHz, $CDCl_3$) δ 25.19 (s); **HRMS** (ESI) Exact mass calcd for $C_{17}H_{20}N_2O_6P$ $[M+H]^+$: 379.1053, found 379.1049; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (minor) = 19.6 min, t_r (major) = 29.1 min; 92% ee.

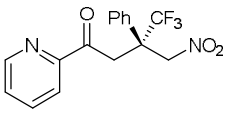


Dimethyl [1-nitro-4-oxo-2-phenyl-4-(1, 3-thiazol-2-yl)butan-2-yl]phosphonate (518b). The title compound was prepared according to General Procedure M from 2-acetylthiazole (**390**) (76 mg, 0.60 mmol) and purified by column chromatography (20→80% EtOAc/hexane) to afford a white solid (42 mg, 22%). **m.p.** 123-124 ºC (EtOAc); R_f = 0.23 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +71.9 (*c* 0.15, $CHCl_3$); **IR** (film) 2954, 1688 (C=O), 1557 (NO_2), 1446, 1384 (NO_2), 1375, 1248 (P=O), 1047, 1026 (P-O), 829, 696 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.73 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.54-7.50 (2H, m, Ar**H**), 7.43-7.38 (2H, m, Ar**H**), 7.35-7.31 (1H, m, Ar**H**), 5.80 (1H, dd, *J* = 13.3, 7.3 Hz, C**H**$_2$$NO_2$), 5.57 (1H, dd, *J* = 18.8, 13.3 Hz, C**H**$_2$$NO_2$), 4.58-4.24 (2H, m, C**H**$_2$C=O), 3.51 (3H, d, *J* = 10.7 Hz, OC**H**$_3$), 3.38 (3H, d, *J* = 10.6 Hz, OC**H**$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 190.1 (d, *J* = 10.1 Hz, C), 166.9 (d, *J* = 2.3 Hz, C), 144.8 (CH), 134.5 (d, *J* = 8.3 Hz, C), 128.9 (d, *J* = 2.8 Hz, 2 x CH), 128.2 (d, *J* = 3.2 Hz, CH), 127.1 (d, *J* = 5.1 Hz, 2 x CH), 126.8 (CH), 75.4 (CH_2), 54.1 (dd, *J* = 79.6, 7.6 Hz, 2 x CH_3), 45.9 (d, *J* = 136.0 Hz, C), 37.0 (d, *J* = 3.0 Hz, CH_2); **^{31}P NMR** (400 MHz, $CDCl_3$) δ 25.53 (s); **HRMS** (ESI) Exact mass calcd for $C_{15}H_{18}N_2O_6PS$ $[M+H]^+$: 385.0618, found 385.0605; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (20:80, *i*-PrOH:hexane, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 24.5 min, t_r (minor) = 34.9 min; 96% ee.

General procedure N: Michael addition of 2-acetylazaarenes to nitroalkene 465a

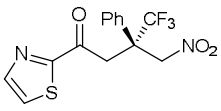


A suspension of $Ni(OAc)_2 \cdot 4H_2O$ (6.2 mg, 0.025 mmol) and ligand **502a** (10.2 mg, 0.0275 mmol) in THF (0.5 mL) was stirred at room temperature for 3 h. To the resulting solution was added a solution of the appropriate 2-acetylazaarene (0.75 mmol) and nitroalkene **465a** (109 mg, 0.5 mmol) in THF (0.5 mL), and the reaction mixture was stirred for 72 h. The reaction mixture was then filtered through a short pad of silica gel (washed several times with EtOAc) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the nitroalkane products.



4,4,4-Trifluoro-3-(nitromethyl)-3-phenyl-1-(pyridin-2-yl) butan-1-one (519a). The title compound was prepared according to General Procedure N from 2-acetylpyridine (**458**) (91 mg, 0.75 mmol) and purified by column chromatography (2→4% Et_2O/hexane) to afford a white solid (137 mg, 81%). **m.p.** 145-146 °C (EtOAc/hexane); R_f = 0.34 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +81.8 (*c* 0.50, $CHCl_3$); **IR** (film) 2918, 1705 (C=O), 1556 (NO_2), 1437, 1371 (NO_2), 1224, 1180, 1151, 995, 767 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.76 (1H, ddd, *J* = 4.8, 1.7, 0.9 Hz, Ar**H**), 7.99 (1H, dt, *J* = 7.9, 1.0 Hz, Ar**H**), 7.86 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.55 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar**H**), 7.42-7.36 (5H, m, Ar**H**), 5.76-5.60 (2H, m, **CH**$_2$$NO_2$), 4.70-4.30 (2H, m, C**H**$_2$C=O); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 197.0 (C), 152.8 (C), 149.1 (CH), 137.1 (CH), 133.5 (C), 129.0 (3 x CH), 127.8 (CH), 126.8 (2 x CH), 125.9 (q, *J* = 284.4 Hz, C), 121.9 (CH), 74.8 (CH_2), 50.0 (q, *J* = 25.5 Hz, C), 35.5 (d, *J* = 1.4 Hz, CH_2); **^{19}F NMR** (400 MHz, $CDCl_3$)

δ –72.87 (s, 3F); **HRMS** (ESI) Exact mass calcd for $C_{16}H_{14}F_3N_2O_3$ $[M+H]^+$: 339.0951, found 339.0955; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10, hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 15.2 min, t_r (minor) = 17.6 min; 80% ee.



4,4,4-Trifluoro-3-(nitromethyl)-3-phenyl-1-(1,3-thiazol-2-yl) butan-1-one (519b). The title compound was prepared according to General Procedure N from 2-acetylthiazole (**390**) (95 mg, 0.75 mmol) and purified by column chromatography (4→12% Et_2O/hexane) to afford a white solid (107 mg, 62%). **m.p.** 165-166 ºC (EtOAc/hextane); R_f = 0.26 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +45.7 (*c* 0.35, $CHCl_3$); **IR** (film) 2918, 1691 (C=O), 1557 (NO_2), 1423, 1379 (NO_2), 1221, 1186, 1157, 962, 742 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (1H, d, *J* = 3.0, Hz, Ar**H**), 7.76 (1H, d, *J* = 3.0 Hz, Ar**H**), 7.45-7.37 (5H, m, Ar**H**), 5.66 (2H, s, **C**$\mathbf{H}_2$$NO_2$), 4.43 (2H, dd, *J* = 49.7, 19.0 Hz, C$\mathbf{H}_2$C=O); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 189.0 (C), 166.1 (C), 145.0 (CH), 133.1 (C), 129.2 (CH), 129.1 (2 x CH), 127.2 (CH), 126.7 (2 x CH), 125.7 (d, *J* = 284.4 Hz, C), 74.6 (d, *J* = 1.3 Hz, CH_2), 50.0 (q, *J* = 25.8 Hz, C), 36.4 (d, *J* = 1.5 Hz, CH_2); **^{19}F NMR** (400 MHz, $CDCl_3$) δ –72.80 (s, 3F); **HRMS** (ESI) Exact mass calcd for $C_{14}H_{12}F_3N_2O_3S$ $[M+H]^+$: 345.0515, found 345.0519; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10, hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 ºC); t_r (major) = 15.2 min, t_r (minor) = 17.3 min; 84% ee.

3.2.5 X-Ray Crystallography Data

The X-Ray crystallography data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) *via* www.ccdc.cam.ac.uk/data_request/cif.

Compound Number	Flack Parameter	CCDC Number
511e	−0.001(9)	YLHWLA
517b	−0.05(4)	SCHWLB
518a	−0.02(13)	YLHWLC
519a	0.04(5)	SCHWLC

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5. Appendix

Publications:[100]

- **Enantioselective Rhodium-Catalyzed Nucleophilic Allylation of Cyclic Imines with Allylboron Reagents,** Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem., Int. Ed*. **2012**, *51*, 8309–8313.
- **Enantioselective Rhodium-Catalyzed Allylation of Cyclic Imines with Potassium Allyltrifluoroborates**, Hepburn, H. B.; Chotsaeng, N.; Luo, Y.; Lam, H. W. *Synthesis* **2013**, 2649–2661.