The Use of
$O$-(Diphenylphosphinyl)hydroxylamines
and Nitrogen-Selenium Ylides in
Transition-Metal-Free Aminations of
$sp^2$ Carbon Centres

A Thesis Submitted by

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Abstract

Due to their abundance in both natural products and synthetic pharmaceuticals, and their diverse and interesting biological properties, nitrogen containing compounds are of great importance to organic chemists. As such, synthetic methodology for the incorporation of nitrogen into organic compounds via the construction of C-N bonds is highly sought after. The research described in this thesis concerns the development of three methodologies for the synthesis of small nitrogen containing compounds via the amination of carbon sp² centres:

1) Synthesis of N-Boc-aziridines
Building upon recent reported methodology utilising O-(diphenylphosphinyl) hydroxylamine (DppONH₂) as a nitrogen source for NH-aziridinations, studies were undertaken into the use of N-Boc-O-(diphenylphosphinyl) hydroxylamine (DppONHBoc) in the synthesis of N-Boc-aziridines. Described herein are studies into the use of DppONHBoc as a nucleophilic nitrogen transfer agent (NNTA) for the aziridination of enones and vinyl sulfones under mildly basic conditions.

2) Amination of aromatic C-H centres
The use of a N-methyl morpholine (NMM)-derived aminimine as an aminating agent in the vicarious nucleophilic amination (VNA) of electron-deficient (hetero)arenes is also reported. Initial studies which used iodide hydrazinium salts as aminimines precursors in the amination of a range of electron-deficient substrates are described. An alternative reaction system utilising the in situ formation of NMM/DppONH₂ hydrazinium salts, in-place of preformed hydrazinium salts, in the vicarious nucleophilic amination reaction was then developed.

3) Synthesis of enantioenriched allylic amines
Finally, the NCS-meditated amination/[2,3]-sigmatropic rearrangement of enantioenriched allylic selenides, utilising a range of amino acid derived and aryl amine nucleophiles, is used to access a wide range of novel vinyl glycine derived unnatural peptides and peptidomimetic products.
I confirm that the material presented within this document is my own work. Where reference is made to the work of others this is clearly acknowledged.

Harry Milner

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Abbreviations

Ac acetyl
ACE angiotensin-converting-enzyme
app. apparent
aq. aqueous
Ar aryl
ATR attenuated total reflectance
Bn benzyl
Boc tert-butoxy carbonyl
br broad
Bt benzotriazolyl
Bu butyl
Cbz benzyloxy carbonyl
cee conservation of enantiomeric excess
Cl chemical ionization
conc. concentration
d.r. diastereomeric ratio
DABCO 1,4-diazabicyclo[2.2.2]octane
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC dicyclohexyl carbodiimide
diastereomeric excess
decom. decomposition
DEAD diethyl azodicarboxylate
DIBAL diisobutylaluminum hydride
DIPEA diisopropylethyl amine
DMAP 4-dimethylaminopyridine
DME dimethoxyethane
DMF N,N-dimethylformamide
DMPU N,N'-dimethyl-N,N'-propylene urea
DMSO dimethylsulfoxide
Dpp diphenylphosphinyl
m.p. melting point
m/z mass/charge ratio
mCPBA meta-chloroperbenzoic acid
Me methyl
Meso mesomeric
min minute(s)
MS molecular sieves
n primary
NCS N-chlorosuccinimide
NFSI N-fluorodibenzenesulfonamide
NMM N-methylmorpholine
NMR nuclear magnetic resonance
NPSP N-(phenylseleno)phthalimide
NRC non-ring-closed
Ns p-nitrobenzenesulfonyl
Nuc generic nucleophile
o ortho
p para
p-TSA para-toluenesulfonic acid
Ph phenyl
PMB p-methoxybenzyl
ppm part(s) per million
Pr propyl
PTC phase transfer catalyst
rac racemic
RDS rate determining step
rt room temperature
Sat. saturated
Ses trimethylsilylethylsulfonyl
SET single electron transfer
SM starting material
SNAr nucleophilic aromatic substitution
\[ \text{tert} \]
\[ t \quad \text{time} \]
\[ T \quad \text{temperature} \]
\[ \text{Tces} \quad \text{trichloroethoxysulfonyl} \]
\[ \text{Tf} \quad \text{triflyl} \]
\[ \text{TFA} \quad \text{trifluoroacetic acid} \]
\[ \text{THF} \quad \text{tetrahydrofuran} \]
\[ \text{TLC} \quad \text{thin layer chromatography} \]
\[ \text{TMS} \quad \text{trimethylsilyl} \]
\[ \text{TOF} \quad \text{time of flight} \]
\[ \text{Tol} \quad \text{tolyl} \]
\[ \text{Tp} \quad \text{trispyrazolylborate} \]
\[ \text{Ts} \quad \text{tosyl} \]
\[ \text{TS} \quad \text{transition state} \]
\[ \text{TSAF} \quad \text{tris(dimethylamino)sulfonium difluorotrimethylsilicate} \]
\[ \text{VNA} \quad \text{vicarious nucleophilic amination} \]
\[ \text{VNS} \quad \text{vicarious nucleophilic substitution} \]
\[ X \quad \text{halide substituent} \]
\[ Y \quad \text{generic substituent} \]
1 General Introduction

The formation of C-N bonds is of great importance to organic chemists due to the abundance of nitrogen in both biologically active natural products and synthetic pharmaceuticals. As such, continued development of methodology for the incorporation of nitrogen into molecules is central to modern organic chemistry. The importance of nitrogen in both naturally occurring and synthetic compounds can be attributed a number of its fundamental properties,¹ i.e. the basic character of the nitrogen lone pair, the hydrogen bond donating of the N-H bond, the capacity of nitrogen to carry a positive charge and, from the perspective of a medicinal chemist, the powerful effect that nitrogen modulation can have on the biological activity, for example the N-demethylation of analgesic morphine, affording normorphine with a corresponding four fold decrease in activity.²

With this in mind, we set out to develop methodology for the synthesis of small nitrogen-containing compounds via the incorporation of C-N bonds into organic molecules. To this end this thesis will describe the work investigating three reactions for amination of sp² carbon centres, accessing synthetically useful-nitrogen containing building blocks. Each chapter will provide a summary of the relevant literature associated with the project before going on to discuss in detail the work carried out for this thesis.

N-Boc-aziridines are versatile building blocks offering opportunities for further manipulation via exploitation of the strained ring system. Chapter 2 will discuss work on the development of N-Boc-O-(diphenylphosphinyl)hydroxylamine as a nucleophilic nitrogen transfer agent for the synthesis of N-Boc-aziridines from both enones and vinyl sulfones.

The direct amination of aromatic systems at C-H positions is a widely sought after and highly useful chemical transformation, circumventing the need for pre-functionalised aromatic systems, i.e. the use of aryl halides, or equivalents, in C-N cross coupling reactions. Whilst recently the development of transition metal catalysed direct C-H amination has been described, this field of chemistry is still relatively young and transition metal-free alternatives are still desirable. To this end vicarious nucleophilic amination of electron-deficient (hetero)arenes provides a simple route to amino-substituted aromatic
ring systems, without the need for pre-activation of the C-H centre or transition metal catalysts. Chapter 3 discusses the work into the use of aminimines as VNA aminating agents for the pseudo-C-H amination of electron-deficient (hetero)arenes. Initial work focused on the use of NMM derived hydrazinium iodide salts as aminating agents in VNA. Subsequent work then focused on the application of a DppONH$_2$/NMM protocol for in situ hydrazinium formation to the VNA reactions, removing the need to handle stoichiometric amounts of hydrazinium salts.

Finally, unnatural peptides and peptidomimetics have emerged as powerful tools in the development of novel drug compounds.$^3$ Here, small molecules designed to mimic the natural peptide structure, but with key changes to the chemical structure, are used to improve drug like properties. Often increased metabolic stability is sought via replacement of a hydrolysable peptide bond with a more stable analogue or by the incorporation of unnatural amino acid side chains into peptides thereby increasing metabolic and conformational stability.$^4$ Building upon previous work from the Armstrong group, Chapter 4 focuses on the use of complex nitrogen sources in the synthesis of enantioenriched vinyl glycine derivatives via the amination/[2,3]-sigmatropic rearrangement of enantioenriched allylic selenides. The use of a range of amino acid amides, amino acid esters and N-aryl amines allows the synthesis of a wide range of vinyl glycine-derived unnatural peptides and peptidomimetics. This methodology was then tested in the synthesis of Perindopril, a marketed pharmaceutical containing a N,N-dicarboxymethylamine peptidomimetic motif.
2 Use of $O$-(Diphenylphosphinyl) Hydroxylamines in the Aziridination of Enones and Phenyl Vinyl Sulfones

In this chapter studies into the use of $N$-Boc-$O$-(diphenylphosphinyl) hydroxylamines (Figure 1) as nucleophilic nitrogen transfer agents (NNTA) in the synthesis of $N$-Boc aziridines will be discussed.

![Figure 1 General structure of $O$-(diphenylphosphinyl) hydroxylamines](image)

Numerous approaches for the synthesis of aziridines have been described in the literature and are covered in depth in the numerous reviews available on the subject. Typically methodologies for the synthesis of aziridines can be grouped into three general categories (Scheme 1); the transfer of a nitrogen source to olefins (route a), the transfer of a carbon source to imines (b) and the intramolecular cyclisation of amine derivatives (c).

![Scheme 1 General methodologies for the synthesis of aziridines](image)

Section 2.1 will focus on introducing literature examples of olefin aziridination (route a, Scheme 1) and in particular will focus on the use of metal nitrenoids and organocatalysts. Readers seeking an overview of other reported aziridination methodologies are directed to the reviews referenced above.

Sections 2.2 and 2.3 will then go on to discuss our work into the use of DppONHBoc as a NNTA for the synthesis of $N$-Boc aziridines from both enones and vinyl sulfones.
2.1 Introduction

2.1.1 Aziridination via Nitrene Additions to Alkenes

The direct addition of a nitrene, or a nitrene equivalent, to an unsaturated hydrocarbon component is well documented as a method of aziridine synthesis. However, the use of free nitrene reagents, often generated by the thermal or photochemical decomposition of azides, is hampered by a number of limitations. These limitations include; the often-harsh reaction conditions required, competitive C-H insertion and poor cis/trans-stereocontrol. The poor observed cis/trans-selectivity results from the generation of both singlet and triplet nitrene intermediates. While singlet nitrenes insert in a concerted stereocontrolled manner (Scheme 2, Eq.1), the generally more stable triplet nitrene inserts in a stepwise manner (Eq. 2) via a transient diradical species that can undergo bond rotation. Facile conversion between singlet and triplet nitrenes, alongside the higher stability of the triplet nitrene, leads to mixtures of cis and trans-products.

The poor stereocontrol afforded by free nitrenes, and the harsh conditions needed to generate them, have led to the development of metal-stabilised nitrenes, which allow for use of milder reaction conditions and afford increased levels of stereocontrol. Furthermore, when combined with the use of chiral ligands, the use of metal-stabilised nitrenes allows the direct enantioselective preparation of aziridines from achiral alkenes.
Copper-catalysed processes are the most widely employed metal-nitrenoid systems utilised in the aziridination of alkenes. The seminal work of Evans in 1993 described the use of bisoxazoline ligands in the CuOTf catalysed aziridination of cinnamate esters (where $R^1 = \text{Me, } \text{tBu and Ph}$) with $N$-tosyliminobenzyliodinate (PhI=NTs) in excellent $ee$ (94-97%) and good yields (60-76%) (Scheme 3).\textsuperscript{16} However, the methodology proved less reliable when applied to simple olefinic substrates such as styrene and trans-$\beta$-methylstyrene (63% and 70% $ee$ respectively).

\begin{equation}
\begin{array}{c}
\text{Ar} = \text{Ph} \\
\text{L}^* = \text{R}^1 = \text{Ph, } \text{tBu, CMe}_2\text{Ph} \\
\text{up to 97% } ee
\end{array}
\end{equation}

Scheme 3 Evans’ asymmetric aziridination of cinnamate esters using Cu-bisoxazoline-nitrenoids

Simultaneously, Jacobsen developed a Cu-catalysed system utilising Schiff base ligands for the aziridination of a range of aromatic olefins (Scheme 4).\textsuperscript{17} Use of Schiff base ligand 1 was found to afford the best results with good yields of the aziridine products (50-79%), though in general only moderate levels of enantioselectivity were observed (30-87% $ee$). However, with one example using a chromene derivative, a high yield (75%) and excellent $ee$ (>98%) were observed.

\begin{equation}
\begin{array}{c}
\text{Ar} = \text{Ph} \\
\text{L}^* = \text{1CH}_2\text{Cl}_2, -40 \degree \text{C}, 15 \text{ min} \\
\text{up to >98% } ee
\end{array}
\end{equation}

Scheme 4 Jacobsen’s asymmetric aziridination of aromatic olefins using Cu-Schiff base-nitrenoids

More recently, Scott has utilised C$_2$-symmetric biaryl Schiff bases in the Cu-catalysed aziridination of cinnamate esters with poor-to-good yields (32-89%) and high levels of enantioselectivity (88-99% $ee$).\textsuperscript{18} As with the examples from Evans and Jacobsen, Scott’s work suffered from poorer enantioselectivity for examples with simple olefin substrates, with the aziridination of styrene only proceeding with a 66% $ee$. Furthermore, the olefin
substrates were often required in excess (1-5 eq.) along with low reaction temperatures (-40 °C) in order to obtain the optimal results.

Kim has also reported the use of diimine ligands in the Cu-catalysed aziridination of simple olefins. Here, bisferrocenyldiamines are used as ligands in the CuOTf, PhI=NTs aziridination system affording moderate-to-good yields (65-88%) and generally good enantioselective (up to 98% ee). However, Kim’s methodology is let down by the requirement of a 10-fold excess of the olefin, relatively high catalyst loadings and yields that lag behind those observed using Scott’s reaction system.

Xu has developed two additional bisoxazoline ligands, AnBoc and cHBox, for the Cu catalysed aziridination of chalcones. The cHBox ligand proved to be the more effective of the two ligands, affording moderate-to-good yields (50-80%) and excellent enantioselectivities (80->99%) for the aziridination of both electron-rich and electron-deficient chalcones (Scheme 5). However, the system suffers from two main drawbacks. Firstly, the requirement of a slight excess of the olefin (1.5 eq.) and secondly, the ligands were, again, not applicable to reactions with styrenes, affording very poor ee (6-15%). Both sets of ligands have been tested in the aziridination of 1,3-dienes, affording vinyl aziridines with modest yields and enantioselectivities and often poor diastereoselectivity.

Ding reports the asymmetric aziridination of cinnamate esters using a C2-symmetric Cu-diimine ligand system, synthesised from D-mannitol, with good-to-excellent enantioselectivities (80->99% ee). The presence of the co-ordinating group (C=O) in the cinnamate ester was found to be vital for the high levels of stereocontrol observed and, as such, the aziridination of simple olefins (e.g. styrenes) proceeded with poor stereocontrol.
Hutchings reports the use of a Cu-exchange zeolite, along with Evans’ bisoxazoline ligands, in the aziridination of simple olefins without co-ordinating groups (e.g. styrenes), substrates often found to be troublesome in the Cu-nitrenoid systems described above.\textsuperscript{24} The use of Cu-exchange zeolite allowed the aziridination of a range of styrenes with moderate-to-good enantioselectivities (64-95\% \textit{ee}). More recently, Li has used Cu\textsuperscript{II} complexes incorporating weakly co-ordinating anions for the racemic aziridination of styrene, with good yields and high levels of \textit{cis/trans} selectivity.\textsuperscript{25} Trost and Dong also report a single example of the use of a \textit{N}-heterocyclic carbene complex in the Cu-catalysed aziridination of an electron-deficient cyclopentene during the total synthesis of (+)-agelastatin A.\textsuperscript{26}

One issue with the use of \textit{N}-tosyliminobenzyliodinate, as a nitrogen source for aziridinations, are the often-problematic de-protactions of the \textit{N}-tosyl aziridines products. Dauban has overcome this by developing a 2-(trimethylsilyl)ethanesulfonyl protected iminobenzyliodinate for use in Cu-catalysed aziridination and has shown the subsequent deprotection of the \textit{N}-Ses aziridines can be achieved in good yields using tris(dimethylamino)sulphonium difluorotrimethylsilicate (TASF).\textsuperscript{27,28} Dauban has also developed methodology for the \textit{in situ} synthesis of iminobenzyliodinate via the reaction of iodosylbenzene (PhI=O) with sulfonamides and applied this to the synthesis of a range of simple and electron-deficient olefins, with yields comparable to examples using the preformed iminobenzyliodinates.\textsuperscript{29} However, when combined with the use of Evans’ chiral bisoxazoline ligand, this \textit{in situ} methodology was found to be less enantioselective than the reaction system reported by Evans, with the aziridination of styrene proceeding with only a 59\% \textit{ee}.

While Cu-nitrenoid systems are by far the most commonly applied to the aziridination of olefins other metal-nitrenoid systems (including Mn, Ru, Rh, Co, Fe and Ag) have been developed. These systems are often complimentary to the Cu systems due to their increased tolerance of substrates often incompatible with Cu-catalysed aziridination, such as use of simple styrene derivatives.
An early example by Katsuki utilised Mn-salen complexes for the aziridination of styrene with PhI=NTs, with good yields (76%) and high enantioselectivity (94%). However, lower yields and enantioselectivity were afforded with the use of substituted styrenes. Komatsu has also utilised Mn-salen-nitrodo complexes, in conjunction with a silver salt additive, in the aziridination of *trans*-substituted styrenes with moderate yields (50-70%) and high enantioselectivities (83-93% *ee*). However, this system suffers from the lower selectivity with the use of styrene and *cis*-substituted styrene derivatives, and the requirement of a large excess (10 eq.) of the olefin.

Katsuki has achieved greater success with the use of Ru-salen complex 3 and a range of *N*-protected azides for the aziridination of a wide range of substrates, including styrenes, an enoate, an enamide, an ene-yne, indene as well as an unfunctionalised 1-octene, with generally moderate-to-good yields (28-99%) and excellent levels of enantioselectivity (92 to >99% *ee*) (Scheme 6).

\[ \text{Scheme 6} \text{ Katsuki’s Ru-salen catalysts for the asymmetric aziridination of terminal olefins} \]

Du Bois provided examples of the use of Rh-catalysis in the racemic aziridination of both aromatic and aliphatic alkenes, including terminal alkyl examples, using sulfamate esters or phosphoramides as nitrogen sources with generally good yields (57-95%) (Scheme 7). The use of Rh\(_2\)(tfacam)\(_4\) (tfacam = CF\(_3\)CONH) allowed for high selectivity for π-functionalisation over the competitive σ-CH functionalisation, often observed with the use of similar Rh catalysts. Later, Du Bois applied this methodology for the diastereoselective intramolecular aziridination of chiral sulfamate esters.
Lebel provides further examples of the use of Rh-catalysis in the aziridination of styrene derivatives using chiral N-tosyloxycarbamates with moderate-to-good yields (51-85%) and poor-to-good diastereoselectivities (70:30 to 98:2 d.r.).

Recently, Zhang developed a CoII-porphyrin catalysed aziridination of styrenes with trichloroethoxysulfonyl azide (Tces-N₃) with moderate-to-good yields (43-93%) and excellent enantioselectivities (80-99% ee). Notably this methodology could be applied to the use of α-methyl styrene and terminal alkyl olefins, albeit with a slight reduction in yields.

Bolm has developed an Fe-catalysed racemic aziridination of a range of olefin substrates generally affording generally good yields (24-90%), although lower yields were observed with cis- and 1,1-dimethyl examples. Use of Evans’ bisoxazoline ligand in the reaction system allowed the asymmetric aziridination of styrene, with a 72% yield and a 40% ee.

Finally, Perez has developed a reaction system using silver complexes bearing trispyrazolylborate ligands (Tp*BrAg) for the racemic aziridination of 2,4-diene-1-ols by PhI=NHTs with good regioselectivity for the allylic alkene and proceeded in a stereocontrolled manner, i.e. E-alkenes afforded trans-aziridines and Z-alkenes afforded cis-aziridines. Perez proposes that co-ordination of the hydroxy group to the oxygen of the N-tosyl protecting group is responsible for directing the aziridination and the high selectivities observed. This hypothesis is further support by poorer results obtained with the use of protected 2,4-diene-1-ols.
2.1.2 Organocatalytic Methods for the Aziridination of Alkenes

In this section, three general types of organocatalysis used in the aziridination of electron-deficient alkenes will be covered, all linked by their use of nucleophilic nitrogen-transfer agents (NNTA). The topics covered will be; the use of chiral quaternary ammonium salts, the use of aminocatalysed processes and finally amine-promoted aziridination with aminimines (N-N ylides).

With the use of NNTA typically the nucleophilic reagent possesses a nitrogen centre with an attached leaving group and reacts via initial conjugate addition to the electron-deficient alkene. This is followed by ring closure/displacement of the leaving group affording the aziridine product (Scheme 8). Variation of the substituents on the nitrogen source allows the synthesis of a range of N-protected aziridines, as well as N-H aziridines not readily accessed via the metal-nitrenoid methodologies discussed above.

2.1.2.1 Use of Chiral Quaternary Ammonium Salts

An early example of the use of organocatalysis in the aziridination of electron-deficient alkenes was reported in 1996 by Prabhakar.41,42 Prabhakar’s use of quaternary salts of cinchona alkaloids as phase transfer catalysts (PTC), with N-hydroxy-N-pivaloylanilines, allowed the aziridination of a range of acyclic electron-deficient alkenes to afford N-aryl aziridines with moderate yields and enantioselectivity (up to 61% ee). Murugan further developed this methodology through the use of PTC 4 with a range of N-aryl-hydroxamic acid and low concentrations of NaOH affording the corresponding N-aryl aziridines in moderate-to-good yields (53-92%) and higher ee (up to 98% ee) than achieved using the Prabhakar methodology (Scheme 9). Furthermore, the use of the pseudo-enantiomer of PTC 4 allows access to the opposite enantiomers with similar yields and enantioselectivity.
The aziridination of electron-deficient alkenes with hydroxamic acids is proposed to proceed by an initial deprotonation of the hydroxamic acid 5, followed by rearrangement via oxaziridine 6 to afford the reactive NNTA N-acyloxyaniline anion 7 (Scheme 10).^43

Tardella and co-workers have applied this PTC methodology to the aziridination of 2-phenylsulfanyl-substituted cyclic enones, of varying ring size, with N-nosylhydroxycarbamate and cinchona alkaloid salt 8, affording the corresponding aziridines with up to 75% ee (Scheme 11).^44

Minakata has reported the aziridination of α,β-unsaturated amides with up to 87% ee using N-chloro-N-sodiocarbamates with a range of cinchona alkaloid derived PTC, although for optimum enantioselectivity a reaction temperature of -20 °C, along with the use of 2 eq. of alkene, was required (Scheme 12).^45 Further reaction with catalytic DMAP in methanol allowed removal of the auxiliary amide group. Minakata subsequently combined this methodology with the use of chiral auxiliaries for the diastereoselective aziridination of α,β-unsaturated amides with excellent stereocontrol (up to >99:1 d.r.).^46
2.1.2.2 Use of Aminocatalysis

Despite the successes with the use of chiral PTC catalysts in the enantioselective aziridination of electron-deficient alkenes, in many cases the reactions were found to be variable in both the yields obtained and the degree of stereocontrol observed. The use of chiral primary and secondary amine catalysts has been found to afford more robust reaction systems with, in general, higher levels of enantioselectivity. Typically, in these processes, the aminocatalyst facilitates the reaction by activation of the enal, or enone, substrate via initial formation of an electrophilic iminium species, followed by conjugate addition of the NNTA reagent, typically a hydroxamic ester, and then ring closure to afford the aziridine product.

Córdova in 2007 reported the use of secondary amine diphenylprolinol catalyst 9 in asymmetric aziridination of a range of enals, using acylated hydroxycarbamates, with moderate-to-good yields (54-78%) and excellent enantiocontrol (84-99% ee), although only moderate diastereoselectivity was observed (4:1 to 19:1 d.r.) (Scheme 13). Córdova has since expanded the scope of this reaction to include α-substituted terminal enals and a range of α,β-disubstituted-α,β-unsaturated aldehydes. Greck also reported the asymmetric aziridination of α-branched enals in good yields and high enantioselectivities under similar conditions using the bis-(3,5-(CF)₃-C₆H₃ prolinol catalyst 10.
Hamada further developed this methodology with the use of sulfonylhydroxycarbamates along with TES-protected prolinol catalyst 11 improving upon diastereoselectivity observed under the Córdova conditions. In particular Hamada applied these conditions to the aziridination of aromatic enals with good yields and excellent levels of enantio- and diastereoselectivity (94-99% ee and >99:1 d.r.). However, the reaction only tolerated the use of electron-deficient aromatics and required a lower reaction temperature of -20 °C.

Jørgensen has applied similar methodology to the aziridination of cyclic 2,4-dienals with TMS-protected prolinol catalyst ent-10, with aziridination occurring regioselectively at the endocyclic double bond, affording aziridines in up to 95% ee (Scheme 14).

Melchiorre has applied a similar approach to the asymmetric aziridination of enones with sulfonylhydroxycarbamates, employing primary amine catalyst 12, to afford trans-aziridine products with good yields and, generally, excellent enantioselectivity (73-99% ee), though long reaction times were required (up to 72 h) (Scheme 15). Substitution at the β-olefin position was well tolerated with a range of alkyl, ester and aromatic examples, while only simple alkyl substitution was reported at the ketone (R^2 = Me and Et).
Melchiorre has subsequently expanded the scope to the asymmetric aziridination of cyclic enones. The use of 5, 6 and 7-membered rings were all well tolerated and underwent aziridination with generally good yields (33-93%) and good levels of stereocontrol (85-99% ee). While β-substitution was well tolerated, α-substitution was not and the cyclic enones were required in slight excess (1.2 eq.). The use of the pseudo-enantiomer of 12 allowed the aziridine of the opposite enantiomer to be accessed in similar yields and enantioselectivity.

Hamada has reported the use of chiral diamine catalyst 13 for the asymmetric aziridination of cyclic enones with sulfonylhydroxycarbamates, with good yields (75-91%) and high enantioselectivity (88-97%), though the scope was limited to unsubstituted examples (Scheme 16).

2.1.2.3 Use of Aminimines

Finally, recent studies have highlighted the efficacy of N-N ylides (also referred to in the literature as aminimines and aminimides) as NNTA for the aziridination of electron-deficient alkenes. The first reported example of the in situ formation of an aminimine and its use in the aziridination of chalcones comes from Ikeda in 1980. Under the Ikeda protocol the aminimine 14 is formed via the ring opening of propene oxide with 1,1-
dimethylhydrazine, which, upon addition of the chalcone substrate, provided the aziridine product in moderate-to-good yields (67-89%) (Scheme 17).

Scheme 17 Ikeda’s aziridination of chalcones with aminimine 14

Xu has utilised hydrazinium salts as aminimine precursors in the aziridination of α,β-unsaturated ketones. Xu employed DABCO derived bishydrazinium salt 15 for the aziridination of a range of chalcones and a single β-alkyl-substituted enone example in generally good yields (15-99%) (Scheme 18). Lower yields were observed with the use of nitro-substituted chalcones and the use of aliphatic enones, enolates and enamides were not tolerated.

Scheme 18 Xu’s aziridination of α,β-unsaturated ketones using bishydrazinium salt 15

More recently, Armstrong and co-workers utilised NMM derived hydrazinium salts 16 for the aziridination of chalcones, in generally moderate-to-good yields (17-95%) (Scheme 19). Two sets of reaction conditions were developed with differing reactivity; use of the iodide salt 16a with KOtBu in DMSO displayed greater reactivity with electron-rich enones, while the use of nitrate salt 16b with NaOH in MeCN afforded better yields with the use of electron-deficient substrates. However, as with the work of Xu, neither set of conditions tolerated the use of alkyl-substituted enones.

Scheme 19 Armstrong’s aziridination of chalcone using hydrazinium salt 16
Subsequent work by both Shi and Armstrong further developed this methodology through the use of tertiary amines and an appropriate electrophilic nitrogen source, allowing for the \textit{in situ} formation of the hydrazinium salts via amination of the tertiary amine mediator. In 2006 Shi reported the use of NMM with aminating agent \( O-(\text{mesitylenesulfonyl}) \) hydroxylamine 17 (MSH) and KOH for the \textit{in situ} formation of aminimine 18. Application of this system to the aziridination of a wide range of chalcones, with a broad range of aromatic substitution, proceeded with moderate-to-good yields (49-85\%) (Scheme 20). Shi also reported that the use of catalytic loadings of the tertiary amine (down to 10 mol\%) were tolerated. Finally, Shi utilised a chiral tertiary amine, Trögers base 19, for the asymmetric aziridination of chalcone with moderate enantioselectivity (67\% ee).

![Scheme 20 Shi's aziridination of chalcone with \textit{in situ} aminimine formation](image)

Armstrong showed that aminimine 18 could be generated in quantitative yields through the reaction of NMM, under basic conditions, with electrophilic aminating agent \( O-(\text{diphenylphosphinyl}) \) hydroxyamine 20 (DppONH\(_2\)) (Scheme 21).

![Scheme 21 Armstrong's enone aziridination with \textit{in situ} formation of NMM-derived aminimine 18](image)

This methodology was then applied to the aziridination of a range of aromatic enone substrates, \( \beta \)-aromatic and \( \beta \)-alkyl, as well as a few \( \alpha,\beta \)-unsaturated esters with generally good yields (32-97\%) and complete \textit{trans}-selectivity (Scheme 22). Further studies have
expanded the substrate scope of this reaction to both the aziridination of α,β,γ,δ-unsubstituted ketones, with high selectivity for the α,β-olefin, providing access to a range of vinyl aziridines,\textsuperscript{60} and the aziridination of tert-butyl cinnamates.\textsuperscript{61} An asymmetric variant using chiral tertiary amines derivatives, of which quinine afforded the highest enantioselectivity, allowed the aziridination of chalcones and heteroaromatic-substituted enones with up to 77% ee.\textsuperscript{62}

\begin{equation}
\text{R}_1\text{O}\text{R}_2\xrightarrow{i) NMM (1.05 eq.), DppONH}_2\text{ (1.05 eq.), 30 min}
\text{ii) substrate, NaOH (2 eq.), 6-40 h}
\text{R}_1\text{N}\text{R}_2\text{NH}
\end{equation}

\text{32-97%}
\begin{itemize}
\item R\textsuperscript{1} = aryl/alkyl
\item R\textsuperscript{2} = aryl, O\textsubscript{Bu}
\end{itemize}

\textbf{Scheme 22} Armstrong’s aziridination of α,β-unsaturated ketones and esters

Page has also utilised electrophilic aminating agent DppONH\textsubscript{2} with bisnaphthalene-based chiral amines in the aziridination of chalcone, affording up to 43% ee.\textsuperscript{63} However, poor conversion was observed even after extended reaction times, with only 10% conversion after 48 hours at room temperature.
2.2 Project Aims

The aziridination protocols, using O-(diphenylphosphinyl) hydroxylamine (DppONH₂), previously developed in the Armstrong group reaction conditions required strong hydroxide or alkoxide bases (pKₐH ca. 15.5-17), the use of which can lead to unwanted side reactions with base sensitive substrates. It was proposed that use of a N-substituted aminating reagent, such as N-Boc-O-(diphenylphosphinyl) hydroxylamine (DppONHBoc) with the increased acidity of its hydrazinium proton, would allow for the use of weaker bases, such as metal carbonates (pKₐH ca. 10.3), in place of the hydroxide/alkoxide bases required for the NMM/DppONH₂ reaction system. The use of the weaker carbamate base should afford an increased functional group tolerance and yields in the aziridination of base sensitive substrates, such as enones possessing enolizable and/or allylic protons.

Initial test reactions, performed within the Armstrong group, had shown promising results for the use DppONHBoc in place of DppONH₂ in the aziridination of enones. A summary of this work is described below in Table 1 and the text following it.

The aim of the work described in this chapter was to continue on from this work and further develop the use of DppONHBoc as an alternative to DppONH₂ in the aziridination of electron-deficient alkenes, allowing access to a range of N-Boc aziridines products, including substrates inaccessible via the DppONH₂/NMM protocols.
2.3 Results and Discussion

2.3.1 Use of DppONHBoc in Enone Aziridination

Initially DppONHBoc 21 was tested in the aziridination reaction, as an alternative to DppONH$_2$, using an enolizable enone prone to side reactions with the use of stronger hydroxide bases.

DppONHBoc itself is easily accessed in near-quantitative yields from $N$-Boc-hydroxylamine and diphenylphosphinic chloride (DppCl) (Scheme 23).$^{65}$

![Scheme 23 Preparation of DppONHBoc](image)

Previous work in the Armstrong group used dialkyl substituted enone 22 as a test substrate for the DppONHBoc mediated aziridination.$^{64}$ Enone 22 was chosen as it contained enolizable protons at both the ketone $\alpha$-position and the allylic position. Only a limited scope of aliphatic enones containing allylic protons have been successfully utilised in the DppONH$_2$/NMM mediated NH-aziridination$^{59}$ and the successful aziridination of an enone with an enolizable proton at the ketone $\alpha$-position has yet to be reported.

Enone 22 was synthesised in one step via a Wittig reaction of the corresponding commercially available phosphorane and aldehyde. The initial studies then tested the DppONHBoc-mediated aziridination of enone 22 with a range of carbonate and hydrogen carbonate bases (Table 1).
Entry | Base | Reaction Conc. (M) | t (h) | Conversion (%)<sup>a</sup> | Yield (%)<sup>a</sup>
--- | --- | --- | --- | --- | ---
1<sup>i</sup> | NaHCO<sub>3</sub> | 0.044 | 16 | <5 | -
2<sup>i</sup> | K<sub>2</sub>CO<sub>3</sub> | 0.044 | 16 | 40 | trace
3<sup>i</sup> | Cs<sub>2</sub>CO<sub>3</sub> | 0.044 | 16 | 63 | 63
4<sup>i</sup> | Cs<sub>2</sub>CO<sub>3</sub> | 0.044 | 40 | 85 | 85 (74)<sup>b</sup>
5<sup>c</sup> | Cs<sub>2</sub>CO<sub>3</sub> | 0.044 | 40 | 76 | 76

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture using Bn<sub>2</sub>O as an internal standard.

<sup>b</sup>Isolated yields, following column chromatography, in parentheses. <sup>c</sup>Reaction performed without NMM.

Table 1 N-Boc aziridination of alkyl enone 22 with DppONHBoc<sup>i</sup>

Initial attempts using NaHCO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub> (Entries 1&2) gave poor conversion of the starting enone and either no observable yield (NaHCO<sub>3</sub>, Entry 1), or only trace yield (K<sub>2</sub>CO<sub>3</sub>, Entry 2) of the desired N-Boc aziridine 23. The use of Cs<sub>2</sub>CO<sub>3</sub> gave a considerable improvement in both the conversion of the starting enone and the yield of the product, possibly due to the increased solubility of Cs<sub>2</sub>CO<sub>3</sub> in organic solvents relative to the sodium and potassium analogues, affording a 63% yield after 16 hours with no other significant product being formed (Entry 3). An increase in the reaction time to 40 hours (Entry 4) afforded an 85% conversion of the starting enone, although the poor stability of the product, during SiO<sub>2</sub> column chromatography, resulted in a reduced 74% isolated yield following purification. Importantly, no side reactions were observed with good mass recovery and a crude reaction mixture made up solely of the enone, the aziridine product and DppONHBoc and its by products.

Finally, a test reaction performed in the absence of NMM (Entry 5) only resulted in a slight decrease in conversion to the desired aziridine product and again with no other side reactions observed. This result seems to suggest a minimal role for the tertiary amine in the reaction and that the DppONHBoc was itself acting as the nucleophilic nitrogen transfer agent, without prior activation as the aminimine.

<sup>1</sup>Reactions performed by Dr R.D.C. Pullin.
Considering these preliminary results, our work initially focused on further optimising the reaction. Here we proposed that simply increasing the concentration of the reaction would allow for an increased conversion without the need to increase the already lengthy reaction time. Further, we wished to ascertain if any aminimine was being formed when the DppONHBoc was used in place of the DppONH$_2$ and, as such, if the DppONHBoc was itself acting as the NNTA for the aziridination of enone 22. Once this work was complete, the scope of the DppONHBoc-mediated $N$-Boc aziridination was then investigated.

A further reaction carried out at double the concentration (0.088 M), and in the absence of NMM, afforded a 92% conversion of the starting enone 22 with a corresponding 92% NMR yield of aziridine 23. Again, loss of product was observed during purification affording an 84% isolated yield of aziridine 23. The reaction was completely diastereoselective for the trans-aziridines, as determined by the $^3$J$_{2H-3H}$ coupling of the aziridine ring (2.6 Hz, generally cis-aziridine = ca. 7-9 Hz and trans-aziridine = ca. 2-4 Hz).$^{53,59}$

One possible reason for the lack of NMM promotion is that the electrophilic amination of NMM was not possible with DppONHBoc and the corresponding salt was not forming. While after 30 minutes a 1:1 solution of the unprotected DppONH$_2$ and NMM (in CH$_2$Cl$_2$) affords a quantitative yield of ammonium diphenylphosphinate salt 24, attempts at an analogous reaction with DppONHBoc showed, by $^1$H NMR, no conversion of either starting material after 30 minutes (Scheme 24).

![Scheme 24 Ammonium diphenylphosphinate salt formation with O-(diphenylphosphinyl) hydroxylamines](image)

The results above support the hypothesis that no hydrazinium salt is formed during the aziridination reactions utilising DppONHBoc and suggests that NMM has no role in promoting the aziridination reaction through aminimine formation. This lack of salt
formation means that DppONHBoc is likely acting as a nucleophilic nitrogen transfer agent, with diphenyl phosphinic acid acting as the leaving group in the ring closure step (Scheme 25), rather than an electrophilic nitrogen source, as is the case in the NMM mediated aziridination with DppONH₂.

Scheme 25 DppONHBoc acting as a NNTA in the N-Boc Aziridination of enones

With the aziridination of enone 22 affording high yields of the N-Boc aziridine product 23, the scope of DppONHBoc as a NNTA in the aziridination of electron-deficient enones was then studied (Table 2). A range of alkyl and aryl substituted enones were tested in the reaction, including examples with enolizable protons at the ketone α-position and/or allylic position, as well as examples with sterically bulky ketone substituents. The enone substrates, when not commercially available, were accessed via Wittig reactions of the corresponding aldehydes and phosphoranes (see Experimental Section 5.2.1). All examples were completely diastereoselective for the trans-aziridines according to ¹H NMR analysis, as determined by the ³J₂H-³H coupling of the aziridine ring (typically ca. 2.6 Hz).
Initially more hindered enones were considered, testing whether this methodology could be complementary to the prolinol catalysed aziridinations described earlier in this chapter (see Section 2.1.2.2), where the aziridination of enones with bulky ketone substituents has proven difficult due to the sterically bulky ketone substituents slowing/preventing condensation of the prolinol catalyst with the enone. The reaction of ethyl substituted enone 25 (Table 2, Entry 2) showed high conversion (95%); however, unlike the methyl

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**Table 2** Substrate scope of DppONHBoc mediated N-Boc aziridination of enones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>Product</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>23</td>
<td>92</td>
<td>92 (84)</td>
</tr>
<tr>
<td>2</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>33</td>
<td>95</td>
<td>72 (54)</td>
</tr>
<tr>
<td>3</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>34</td>
<td>55</td>
<td>25 (24)</td>
</tr>
<tr>
<td>4</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>35</td>
<td>65</td>
<td>29 (24)</td>
</tr>
<tr>
<td>5</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>36</td>
<td>100</td>
<td>94 (89)</td>
</tr>
<tr>
<td>6</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td><img src="equation.png" alt="Equation" /></td>
<td>37</td>
<td>56</td>
<td>16 (11)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture using Br<sub>2</sub>O as an internal standard. <sup>b</sup> Isolated yields, following column chromatography, in parentheses.
substituted example discussed previously (Entry 1), the aziridine 33 was not the only product of the reaction, with a number of other small side product peaks observed in the crude NMR spectrum. Despite this and, again, the poor stability of the product during purification (SiO₂ column), the aziridine product 33 was still isolated in a moderate 54% yield. The use of tert-butyl enone 26 (Entry 3) gave a much lower conversion (55%) and only a 24% isolated yield of aziridine 34. Despite the poor isolated yield, this result was particularly noteworthy as alternative aziridination methodologies utilising prolinol catalysis have not been reported to be compatible with tert-butyl enones and the use of the DppONHBOc aminating agent has allowed the first reported synthesis of aziridine 34.

The aziridination of dialkyl enones is problematic under a number of conditions discussed in the introduction and these substrates often afford lower yields than aryl substituted examples. A number of reasons have been proposed for the increasing discrepancies between the high enone conversion and poorer yields of aziridine product obtained with the use of enone substrates with increasingly bulky ketone substituents. The first is the stability of the N-Boc aziridine products, which were found to decompose (< 1 week) despite being stored at low temperature (-20 °C). Though the bulky tert-butyl ketone substituted aziridine 34 did show the highest stability on silica, with only a 1% loss of product during column chromatography, perhaps due to the bulky substituent preventing loss of product by slowing the rate of nucleophilic attack at the ketone in the product aziridine. A second possible reason would be a decrease in the rate of the ring-closing step, perhaps due to increased steric hindrance associated with the use of increasing bulky ketone substituents, slowing the rate of product formation.

Again, the use of dialkyl enone 27 (Entry 4) afforded a high conversion, 65%, but only a modest (24%) isolated yield of corresponding aziridine 35. The aziridination of enone substrate 28 (Entry 5), with no enolizable protons at the ketone α-position, preceded smoothly giving a 100% conversion, and a pleasing 89% isolated yield of the aziridine product.

The use of enone substrates with extended conjugation of the enone into an aromatic ring failed to afford any conversion of the starting materials (Entries 6-8). While the exact
reason for this observed reactivity is not currently known, it is thought the lower reactivity observed with enones 29, 30 and 31 arises due to the 1,4-addition of DppONHBoc breaking the direct conjugation that exists between the aromatic ring and the α,β-unsaturated ketone, with the corresponding loss of the aromatic resonance stabilisation. Additionally, in the case of tri-substituted enone 31 addition of DppONHBoc is further hindered by the increased steric bulk around the α,β-unsaturated carbons.

In prolinol catalysed epoxidations\textsuperscript{66–68} comparable enone substrates have been tested and a similar trend in reactivity is observed (as with aziridination of enones using DppONHBoc). Where enones with aryl substituents at the allylic position (such as enone 29) typically afford lower yields than the corresponding alkyl-substituted analogues (when the ketone substituent is an alkyl group). However, none of these examples show a complete cut-off in reactivity as observed with the use of aryl enones in the DppONHBoc-mediated aziridination.

Finally, use of cyclic enone 32 allowed access to aziridine 37 in a poor 11% isolated yield, despite a moderate conversion (56%) of the starting material.

While this methodology does have some promise as an alternative to the more standard prolinol catalysed synthesis of N-Boc aziridines, it is hampered by both the limited substrate scope and the variable yields achieved. In order to try to improve the usefulness of this methodology, work was undertaken to expand the scope of this aziridination to other electron-deficient alkenes.
2.3.2 Use of DppONHBoc in Aziridination of Vinyl Sulfones

Two substrates that had proven incompatible with the DppONH₂/NMM methodology were chosen, namely phenyl vinyl sulfone and acrylonitrile (Table 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>t (h)</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>CN</td>
<td>-</td>
<td>40</td>
<td>50</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>SO₂Ph</td>
<td>38</td>
<td>2</td>
<td>85</td>
<td>54 (52)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture using Bn₂O as an internal standard. <sup>b</sup> Isolated yields, following column chromatography, in parentheses.

Table 3 Attempted N-Boc aziridination of electron-deficient alkenes

Whilst attempts with the vinyl cyanide gave a moderate conversion, only minimal yields of the aziridine product were afforded. However, use of the phenyl vinyl sulfone afforded a promising 52% isolated yield of the sulfone-substituted aziridine 38. The remainder of the mass balance was shown to be the non-ring closed (NRC) product 39 (Figure 2) present in a 33% NMR yield. The NRC product 39 was not stable on SiO₂; however, the use of preparative HPLC allowed isolation of NRC product 39, though still with significant loss of the product during purification (18% isolated yield).

![Figure 2 Non-ring-closed (NRC) product](image)

No further reaction of the NRC product 39 was observed upon re-submission to the reaction conditions, suggesting that the Cs₂CO₃ is not a strong enough base to deprotonate at the α-position of the sulfone (pKₐ ~30). Attempts at ring closure with a stronger base, NaOH, resulted in nucleophilic attack at the phosphorus in preference to deprotonation, giving rise to hydroxylamine product 40 (Scheme 26). No further bases were tested for the ring closing of the NRC product and instead a range of alternative bases were later tested in the aziridination with phenyl vinyl sulfone, see below.
Two reasons were proposed for the presence of the NRC product in the crude reaction mixture. Firstly, the aziridination of phenyl vinyl sulfone using DppONHBoc proceeds via a fast addition step followed by a slower rate determining ring-closing step and the reaction was time was not sufficient to allowed to go to completion. Secondly, the preferred explanation, that the addition product was being quenched/protonated under the reaction conditions, preventing ring closure, and that under the weakly basic conditions de-protonation of the resulting NRC intermediate was not possible.

To test these two hypotheses for the presence of the NRC product, initial studies looked at yields of desired N-Boc aziridine product 38 versus the undesired NRC product 39 at various time points over the course of the reaction. Due to the heterogeneous nature of the reaction mixture, reaction monitoring via sampling of a single reaction was not deemed a suitable method of reaction monitoring. As such, multiple reactions were run with the reactions quenched and worked up after a set time period. The $^1$H NMR yields of the starting material (SM), aziridine 38 and NRC product 39 in the crude reaction mixture were then calculated, relative to Bn$_2$O as an internal standard (Figure 3).
The results from the reaction monitoring show an initial rapid decrease in the concentration of the starting material along with a spike in the concentration of the NRC-product 39, which gradually decreases over the course of the reaction. (It should be noted that these results are after the quenching of the reaction with NH₄Cl (sat. aq.). As such the yield of NRC product 39, at each time point, represents the combined concentration in the reaction mixture of the anionic addition intermediate and any protonated NRC product 39.)

The rate of product formation is constant for the first two hours (up to 50% yield) after which rate of product formation dramatically decreases with only an additional 4% yield in the subsequent 2 hours. When left for a longer time period there is limited further conversion of the NRC intermediate to the aziridine product, up to a yield of 59% after 8 hours. After 8 hours no significant further conversion was seen (<1%, data not shown in Figure 3). The lack of significant conversion of the NRC intermediate to the desired aziridine with increased reaction time (> 4 hours) indicates that the more likely reason for presence of the NRC product in the crude reaction mixture is the quenching of the intermediate anion affording the NRC product 39 (which as shown above cannot be deprotonated under the reaction conditions), rather than the reaction simply not being allowed to run to completion.
The reaction monitoring seems to suggest that the reaction is proceeding via a faster addition step, giving rise to the initial spike in the yields of the NRC product, with a slower subsequent ring-closing step (Scheme 27). There also appears to an irreversible formation of NRC product 39 over the course of the reaction, likely due to the quenching of an anionic intermediate, preventing full conversion of the phenyl vinyl sulfone to the aziridine product.

![Scheme 27 Proposed mechanism for the DppONHBoc-mediated aziridination of phenyl vinyl sulfone](image)

With this in mind, studies were undertaken to determine if a change in the base used could affect the rate of the ring-closing step versus any protonation of the addition intermediate and increase the conversion of both the starting material and the intermediate anion.

Initially, a number of inorganic and organic bases were screened. However, no bases were found that afforded any improvement over the use of Cs$_2$CO$_3$. These results are discussed in more detail below (Table 4).
Firstly, a range of alternative inorganic bases was tested in the aziridination of phenyl vinyl sulfone. K$_2$CO$_3$ (Entry 1), shown to be a poor base of the DppONHBoc mediated enone aziridination, again only gave a poor conversion of the starting material and afforded none of the aziridine or the NRC product. The use of sodium hydroxide (Entry 2) gave hydroxylamine 40 as a major product, suggesting that nucleophilic attack of the hydroxide anion at the phosphorus centre occurs more readily than the deprotonation/ring-closure. With the use of a more hindered alkoxide base, potassium tert-butoxide (Entry 3), hydroxylamine product 40 was still formed, though in a lower yield and with a three fold increase in the yield of aziridine 38, compared to the use of sodium hydroxide. However, the use of potassium tert-butoxide resulted in a less clean reaction, with multiple other, unidentified, side products in the crude NMR. The use of a non-nucleophilic base (sodium hydride, Entry 4) gave none of the hydroxylamine 40, but only a 20% yield of the aziridine 38 with the NRC product 39 as the major product (52%).

Secondly, a range of organic bases was then tested. The use of DBU (Entry 7) gave complete conversion of the starting material but only trace amounts of the aziridine product, while the use of DIPEA, triethylamine and 2,6-lutidene failed to afford any conversion of the starting material (Entries 8&9).
Finally, a range of organolithium bases was also tested in the aziridination reaction (dropwise base additions were carried out at -78 °C and the reaction slowly allowed to warm to room temperature with reaction monitoring by TLC). Of these only LiHMDS afforded any of the aziridine product 38, with a maximum yield of 15% afforded when 2 equivalents of LiHMDS was used. Also tested were nBuLi, sBuLi, tBuLi and LDA; however, all caused decomposition of the DppONHBoc and only trace yields of the desired aziridine product.

With the base screen failing to improve upon the yield obtained with the use of Cs$_2$CO$_3$, a solvent screen was carried out to determine if the reactivity could be tuned through the choice of solvent (Table 5).

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Entry} & \text{Solvent} & \text{Conversion} (\%)^a & \text{Yield 38} (\%)^{a,b} & \text{Yield 39} (\%)^a \\
\hline
1 & CH$_2$Cl$_2$ & 96 & 54 (52) & 33 \\
2 & THF & 99 & 66 (64) & 27 \\
3 & MeCN & 100 & 23 & 77 \\
4 & Et$_2$O & 60 & 24 & 25 \\
5 & toluene & 60 & 9 & 43 \\
6 & n-hexane & 20 & 2 & 1 \\
7 & EtOH & 100 & 0 & 0 \\
8 & 1,4-dioxane & 100 & 50 & 31 \\
9 & DMSO & 100 & 55 & 17 \\
10 & DMF & 100 & 52 & 0 \\
\hline
\end{array}
\]

$^a$ Determined by $^1$H NMR spectroscopy of the crude reaction mixture using Bn$_2$O as an internal standard. $^b$ Isolated yields, following column chromatography, in parentheses.

**Table 5** Solvent screen for the N-Boc aziridination of phenyl vinyl sulfone

The results from the solvent screen showed THF to be the best solvent for the aziridination reaction (Table 5, Entry 2), affording a 66% yield of aziridine 38 and 27% of the NRC product 39, with only 6% of the starting material lost to other side reactions. The use of MeCN (Entry 3) afforded a clean reaction with complete conversion of the starting material.
and no loss of mass balance to side reactions. However, it was a poor solvent for the ring-closing step, only affording a 23% yield of aziridine 38. The use of less polar aprotic solvents (Et₂O, toluene and n-hexane) failed to give complete conversion of the phenyl vinyl sulfone and only afforded low-to-fair yields of the desired aziridine (Entries 4-6). The use of a protic solvent was not compatible with the reaction, with the use of EtOH affording 100% conversion of the starting material but none of the desired aziridine product 38 or the NRC product 39. Instead a complex mixture of products was observed in the ¹H NMR spectra of the crude reaction mixture, with peaks suggesting a number of CH₂ environments similar to those in the NRC product 39, likely due to decomposition of either the intermediate anion or the NRC product 39. Use of co-ordinating solvents proved effective with 1,4-dioxane, DMSO and DMF (Entries 8-10) all affording a high yield of the desired aziridine product with 100% conversion of the starting material. However, despite the decrease in the yields of the NRC product the reactions with these solvents showed more loss of material to side reactions than the reactions in THF and CH₂Cl₂.

Whilst the use of Cs₂CO₃ in THF afforded the highest yield of the sulfonyl aziridine 38 (64%), there was still a significant loss of material as the NRC product 39 (approximately 2:1 ratio of the aziridine to NRC product). Finally, an optimisation of the reaction conditions was attempted to see if an improvement in this ratio could be achieved (Table 6).
In the THF/Cs₂CO₃ reaction (Table 6, Entry 1) where the DppONHBoc was used in a two-fold excess, there was an approximately 45% return of DppONHBoc (i.e. just over 1 equivalent was reacted). To test whether the DppONHBoc could be used in lower excess a reaction was carried out using 1.1 equivalents of the DppONHBoc (Entry 2); however, only 75% conversion of the phenyl vinyl sulfone was observed with a 51% yield of the aziridine 38. The use of the DppONHBoc as the limiting reagent failed to offer any improvement in the yield of the reaction, with use of the phenyl vinyl sulfone in two-fold excess affording a slight decrease in yield (62% Entry 3) when compared to the use of DppONHBoc in excess (Entry 1). Changes in the base concentration offered no improvement in yield, with a decrease to two equivalents affording a reduced yield (Entry 4) and an increase to four equivalents (Entry 5) not affording any improvement in the yield, likely due to the reaction already being saturated in Cs₂CO₃ at three equivalents. A test reaction with no base resulted in no conversion of phenyl vinyl sulfone (Entry 6). Finally, reactions at higher reaction temperatures afforded decreased yields of the desired aziridine product 38 likely due to the increased rate of hydrolysis of NRC intermediates to hydroxylamine 40 and the observed slow decomposition of DppONHBoc at elevated temperatures.

**Table 6** Optimisation of the N-Boc aziridination of phenyl vinyl sulfone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Change from Standard Conditions</th>
<th>Conversion (%)</th>
<th>Yield 38 (%)</th>
<th>Yield 39 (%)</th>
<th>Yield 40 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>99</td>
<td>66</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>DppONHBoc (1.1 eq.)</td>
<td>75</td>
<td>51</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>phenyl vinyl sulfone (2.0 eq.)</td>
<td>91</td>
<td>62</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cs₂CO₃ (2.0 eq.)</td>
<td>98</td>
<td>34</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Cs₂CO₃ (4.0 eq.)</td>
<td>100</td>
<td>64</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>no base</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>40 °C</td>
<td>100</td>
<td>46</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>60 °C</td>
<td>100</td>
<td>55</td>
<td>18</td>
<td>13</td>
</tr>
</tbody>
</table>

*Standard conditions: To a mixture of vinyl sulfone (1.0 eq.) and DppONHBoc (2.0 eq.) in THF (0.1 M) is added Cs₂CO₃ (3.0 eq.) and the reaction stirred for 4 hours at room temperature, then quenched with NH₄Cl (sat. aq.). Determined by ¹H NMR spectroscopy of the crude reaction mixture using Bn₂O as an internal standard. 1 eq. of DppONHBoc used.*
2.3.3 Use of Alternative O-(Diphenylphosphinyl) hydroxylamine Aminating Agents

With the optimisation of the reaction conditions failing to afford complete conversion of the NRC product to the desired aziridine product, it was decided to look at changing the electronics of the aminating agent. It was proposed that having more electron-deficient substituents on the phosphorus would make a better leaving group, and as such aid the ring-closing step. Novel O-(bis(3,5-bis(trifluoromethyl)phenyl)phosphinyl) hydroxylamine 41 was initially chosen as there is a literature route to the diphenylphosphinic chloride 42 precursor from commercially available bis(3,5-bis(trifluoromethyl)phenyl)chlorophosphine 43.\(^6^9\) It was proposed that phosphinyl hydroxylamine 41 could be accessed via the reaction of phosphinyl chloride 42 with N-Boc hydroxylamine (Scheme 28). The phosphinyl chloride 42 was not isolated due to fear of hydrolysis to the phosphinic acid. However, the \(^{31}\)P NMR spectrum of the crude reaction mixture showed complete conversion of chlorophosphine 43 and a new \(^{31}\)P shift, at 34.32 ppm (in the expected chemical shift range for a phosphinic chloride) and suggested the desired phosphinyl chloride was formed with approximately 85% purity. However, subsequent attempts at forming the N-Boc-hydroxylamine gave none of the desired product, instead giving ammonium phosphonate salt 44 (Figure 4). Formation of this salt suggests that hydrolysis of either the phosphinic chloride or the product occurred under either the reaction conditions or during work up.

![Scheme 28 Attempted synthesis of bis(3,5-bis(trifluoromethyl)phenyl)phosphinyl hydroxylamine](image-url)
Given the ease of hydrolysis of the bis(3,5-bis(trifluoromethyl)) analogue 41 attempts to synthesise the less electron-poor bis-(4-chlorophenyl) analogue 45 were made. Bis-(4-chlorophenyl) analogue 45 was chosen as while it is a novel compound, there are literature conditions reported for the synthesis of the corresponding phosphinic acid 46 precursor from diethyl phosphite, in two steps, via phosphinic oxide 47 (Scheme 29).

![Scheme 29 Synthesis of bis-(4-chlorophenyl)phosphinic acid 46](image)

Reaction of the phosphinic acid 46 with thionyl chloride allowed access to the phosphinyl chloride, further reaction with N-Boc-hydroxylamine afforded the desired O-(bis-(4-chlorophenyl)phosphinyl) hydroxylamine 45 as a white crystalline solid in 41% yield, following partial recrystallisation from CH2Cl2 (Scheme 30).

![Scheme 30 Synthesis of O-(bis-(4-chlorophenyl)phosphinyl)hydroxylamine 45](image)

Also synthesised was the more electron-rich 4-methoxy analog 48, to allow comparison to the electron-poorer and electron-neutral analogs. It was expected that the more electron-rich methoxy analog would afford a lower yield of the aziridine product and a corresponding higher yield of the NRC product, as the less nucleofugal phosphinyl motif
would slow the rate of the ring-closing step. The 4-methoxy analog 48 was synthesised in two steps, in a 61% overall yield following literature conditions from the phosphinic acid 49 (Scheme 31).

![Scheme 31 Synthesis of O-(bis-(4-methoxyphenyl)phosphinyl)hydroxylamine 48](image)

The two diphenylphosphinyl hydroxylamines where then tested in the aziridination of phenyl vinyl sulfone (Table 7). The use of the 4-chloro analog 45 (Table 7, Entry 2) gave a decreased yield of the NRC product as expected; however, a decreased 40% yield of the aziridine product was also obtained, compared to 66% obtained with DppONHBoc (Entry 1). Also isolated was 35% of hydroxylamine 40, suggesting that the more labile leaving group of 4-chloro analog 45 resulted in increased hydrolysis of the NRC product, preventing ring-closure to the desired aziridine product. Use of the more electron-rich 4-methoxy analog 48, Entry 3, afforded a decreased yield of the aziridine (13%), compared to the use of DppONHBoc, with a corresponding increased yield of the NRC product, 82%, as expected.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conversion (%)</th>
<th>Yield 38 (%)</th>
<th>Yield 39 (%)</th>
<th>Yield 40 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>99</td>
<td>66</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>91</td>
<td>40</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>100</td>
<td>13</td>
<td>82</td>
<td>0</td>
</tr>
</tbody>
</table>

* Determined by 1H NMR spectroscopy of the crude reaction mixture using 

**Table 7** N-Boc aziridination with O-(diphenylphosphinyl) hydroxylamine analogs

The results of this study on the electronic properties of the phosphinyl functionality found that, as expected, a more electron-rich aryl moiety did decrease the yield of the aziridine,
presumably due to the bis-(4-methoxyphenyl)phosphinic acid being a poorer leaving group. However, with the use of the more electron-poor analog the increased rate of hydrolysis of phosphinyl hydroxylamine competes with the ring-closing step and as such no increase in yield of aziridine was observed.

Although other $O$-(diphenylphosphinyl) hydroxylamines were not tested, if this study was continued a phosphinic acid leaving group with electronic properties which lie in between those of the 4-Cl and 4-H substituted diphenylphosphonic acids should be considered. As such the aim of further studies would be to attempt to find a leaving group that is suitably nucleofugal to increase the rate of ring-closing, while not so nucleofugal as to significantly increase the rate of the hydrolysis of the NRC intermediate and thus maximising the yield of the desired aziridine product.

To evaluate possible $O$-(diarylphosphinyl) hydroxylamines it is proposed that the $pK_a$ of the corresponding phosphinic acids could be used to predict a suitable alternative, i.e. find phosphinic acids with $pK_a$ values between that of the bis-(4-chlorophenyl) and (diphenyl)phosphinic acid ($pK_a$ values of 1.62 and 2.32 respectively). However, a lack of reported $pK_a$ data for alternative phosphinic acids meant that an alternative series of compounds would have to be used and, as such, the $pK_a$ values of corresponding benzoic acids were considered (Figure 5).
Using the pKa of analogous benzoic acids as a reference for the leaving group ability/electron-withdrawing properties of the substituents suggests that a benzoic acid with a pKa value within the range of 3.99 (4-Cl) and 4.20 (4-H) would be required. Possible, simple, benzoic acids that fit this criterion include replacing the 4-chloro substituent with a 4-fluoro (pKa of 4-iodobenzoic acid is 4.14) or alternatively either 3-hydroxy or 3-methoxy substituted benzoic acids, both of which have pKa values (4.08 and 4.09 respectively) which lie approximately half way between that of benzoic and 4-chlorobenzoic acids. The use of the corresponding O-(diphenylphosphinyl) hydroxylamines would offer a good starting point for further studies into the effect of ring electronics on the ratio of the desired aziridine product and the, unwanted, hydrolysed and non-hydrolysed NRC products. The O-(bis(4-fluorophenyl)phosphinyl) hydroxylamine and corresponding 3-methoxy analogue would be in particular promising starting points as the commercial available Grignards would allow synthesis of the hydroxylamines via the same pathway used to accesses the 4-chloro analogue (see Scheme 29 & 30 above).

Finally, the tosyl analog, DppONHTs 50, was synthesised to examine whether this methodology could be used to access N-tosyl aziridines. Attempts at synthesising DppONHTs in one step from DppONH₂ and tosyl chloride (with pyridine as a base) were unsuccessful, only affording diphenyl phosphinic acid and returned starting material. An
alternative approach, via N-tosyl hydroxylamine 51 and diphenylphosphinic chloride, proved successful, Scheme 32.

However, use of DppONHTs in the aziridination reaction failed to afford any of the desired N-tosyl sulfonyl aziridine (100% return of starting material), with increased reaction temperatures, up to reflux in THF, still failing to give any conversion.
2.3.4 Vinyl Sulfone Substrate Scope

With work into the optimisation of the reaction complete, our focus then turned to the substrate scope of the reaction. Vinyl sulfones can be accessed via a number of different methodologies, these include; olefination of phosphonate vinyl sulfones\textsuperscript{74} with the corresponding aldehydes,\textsuperscript{75} protodesilylation of allylic silanes,\textsuperscript{76} elimination reactions\textsuperscript{77,78} and oxidation of vinyl sulfides. All four approaches were used in the synthesis of a range of vinyl sulfones to be tested in the aziridination reaction (Scheme 33).

Scheme 33 Synthesis of vinyl sulfones
The vinyl sulfones were then tested in the aziridination reaction, the results of which are discussed below (Table 8).

![Chemical reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Vinyl Sulfone</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product</th>
<th>Aziridine Yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>NRC Product Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4.2:1 E:Z</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>99</td>
<td>61</td>
<td>17(c)</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>94</td>
<td>62</td>
<td>25 (24)</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>96</td>
<td>63</td>
<td>51 (49)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>64</td>
<td>52 (46)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixture using Bn<sub>2</sub>O as an internal standard.  
<sup>b</sup> Isolated yields, following column chromatography, in parentheses.  
<sup>c</sup> Product unstable on silica and could not be isolated.

**Table 8** Substrate scope of the DppONHBoc mediated N-Boc aziridination of vinyl sulfones

The use of 1,2-disubstituted vinyl sulfones (Table 8, Entry 1-3) under the optimised DppONHBoc mediated aziridination conditions failed to afford any conversion of the starting materials, with no scrambling of double bond geometry observed in any of the vinyl sulfone starting materials (in particular with the use of vinyl sulfone 55 (Entry 2) reacted at a mixture of the E and Z-isomers). Entries 1 and 3 were both repeated at elevated temperatures (40 °C and 60 °C), though still no conversion of the vinyl sulfones.
was observed. Changes in the substituent on the sulfone were tolerated, with both alkyl and phenyl substituents tolerated. Aziridination of methyl vinyl sulfone provided a 17% NMR yield of the desired aziridine (Entry 4) and the NRC product observed as the major product (53%); however, the methylsulfone-substituted aziridine was not stable on silica and could not be isolated. The use of ethyl analog 60 (Entry 5) afforded a 24% isolated yield with the NRC product observed as the major product (37% yield). The increased yields of the NRC products afforded by both the alkyl examples suggests either an increase in the rate of proton-transfer/quenching of the anionic intermediates or a decrease in the rate of ring closing compared to phenyl vinyl sulfone.

Changes in the electronics of the phenyl ring were also tolerated, though both a more electron-rich tolyl substituted vinyl sulfone 58 (Entry 6) and a more electron-poor 4-fluoro substituted example 59 (Entry 7) afforded only moderate yields of the N-Boc aziridine products, 49% and 46% respectively. Finally, attempts with a phenyl vinyl sulfoxide proved unsuccessful with complete return of the starting materials (Entry 8).

As with the enone examples (see Section 2.3.1), the aziridination reaction seems very sensitive to the electronics of the alkene, most notably with the use of 1,2-disubstituted vinyl sulfones completely shutting down the reaction.

2.3.5 Aziridination of Ethenesulfonyl Fluoride (ESF)

Despite first being synthesised at the beginning of the 20th century, the chemistry of ESF (65) remained little studied until an in-depth study was published by Hyatt in 1979. Hyatt highlighted in particular its properties as a highly reactive and selective Michael acceptor, particularly with nitrogen nucleophiles, and the stability of the sulfonyl fluoride functionality to a range of reaction conditions under which use of other sulfonyl halides would not be compatible. More recently Sharpless has further explored the chemistry of the sulfonyl fluorides and highlighted the further reactions of sulfonyl fluorides, and their application in affinity labelling and drug discovery. With this in mind, and in the absence of any methodology allowing access to sulfonyl fluoride-substituted aziridines, it was decided to test ESF as a substrate in the DppONHBoc mediated aziridination reaction.
ESF itself is easily accessed via fluorination of 2-chloroethan-1-sulfonyl chloride affording 2-chloroethan-1-sulfonyl fluoride 66 followed by MgO mediated elimination (Scheme 34).  

![Scheme 34](image)

Initial attempts at the DppONHBoc-mediated aziridination, under the conditions optimised for the aziridination of vinyl sulfones, proved unsuccessful with none of the desired aziridine 67 being formed, despite 100% conversion of the ESF. The only product to be isolated in any significant yield was diphenylphosphinic fluoride (DppF) 68 (Scheme 35).

![Scheme 35](image)

Likely mechanisms for the formation of the DppF 68 is fluoride attack on either the starting material or a NRC intermediate. However, as none of the NRC hydroxylamine product was observed in the crude reaction mixture, the reaction of a NRC product (formed after addition of the DppONHBoc) with fluoride was not occurring. A test reaction stirring DppONHBoc with CsF in CH₂Cl₂, after 1 hour afforded a mixture of starting material and DppF 68, suggesting that fluoride anions present in the reaction mixture were reacting with DppONHBoc. A further test reaction with ESF and Cs₂CO₃ showed slow decomposition of the ESF after 3 hours, with complete decomposition after 22 hours. This could perhaps be the source of the fluoride, though another possibility is displacement of the fluoride upon conjugate addition of the DppONHBoc (Scheme 36).

![Scheme 36](image)
A solvent switch to DMF, the solvent most commonly employed in literature reactions with ESF, afforded a trace yield of products (Table 9, Entry 1). Test reactions stirring NaH with ESF showed no conversion of the ESF after 4 hours and looked like a promising alternative to the incompatible Cs₂CO₃. The use of NaH in the aziridination reaction did afford the desired aziridine product, albeit only in a 3% yield of aziridine 67 (with complete conversion of the starting material, Entry 2). Tertiary amine bases have been shown to be compatible with the use of ESF and as such triethylamine was tested and, although it failed to afford any of the aziridine, provided a 98% yield of the NRC product 69 (Entry 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (Eq.)</th>
<th>Conversion (%)</th>
<th>Yield 67 (%)</th>
<th>Yield 68 (%)</th>
<th>Yield 69 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs₂CO₃ (3.0)</td>
<td>100</td>
<td>trace</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>NaH (1.1)</td>
<td>100</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>NEt₃ (2.0)</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>98</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR spectroscopy of the crude reaction mixture using Bn₂O as an internal standard.

Table 9 Effect of base on the N-Boc aziridination of ESF

The discovery of this efficient route to the NRC product 68 (Table 9, Entry 3) allowed optimisation of the ring-closing step of the reaction to be carried out (Table 10) offering the possibility of a two-step synthesis of the desired N-Boc aziridine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Yield 67 (%)</th>
<th>Yield 68 (%)</th>
<th>Yield 70 (%)</th>
<th>Yield 65 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>93</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>60</td>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>50</td>
<td>19</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR spectroscopy of the crude reaction mixture using Bn₂O as an internal standard.  Reaction carried out at 0 °C.

Table 10 Attempted ring closing of NRC sulfonyl fluoride 69
Sodium hydride was chosen as a non-nucleophilic base for initial studies; reaction in CH$_2$Cl$_2$ only afforded trace quantities of the desired aziridine product, with a complex mixture of by-products (Table 10, Entry 1). Again, a solvent switch to DMF afforded better results with an 11% yield of the aziridine 67, with a 60% conversion of the ESF (Entry 2). A decrease in reaction temperature gave reduced conversion of the starting material, but gave a cleaner reaction that alongside an increase in the yield of the desired aziridine product, allowed the characterisation of several other side products. Isolated from a reaction run at lower temperature (0 °C, Entry 3) was 19% of the desired aziridine 67, a 4% yield of ESF (presumably formed via an E1cb mechanism), a 4% yield of DppF and a 3% yield of cyclic sulfonyl hydroxylamine 70. A proposed mechanism for the formation of this cyclic sulfonyl product is via the initial hydrolysis of NRC product 69, followed by cyclisation with displacement of the fluoride.

It was proposed that changing the counterion associated with the base used in the initial deprotonation might influence selectivity in favour of ring closure and away from the elimination of HF and decomposition of the deprotonated intermediate. To test this a small base screen was carried out (Table 11). With previous studies into reactions showing the NRC intermediates to be susceptible to nucleophilic attack at the phosphorus, only non-nucleophilic bases were tested.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>Yield 67 (%)</th>
<th>Yield 68 (%)</th>
<th>Yield 70 (%)</th>
<th>Yield 65 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>NaH</td>
<td>DMF</td>
<td>96</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>KH</td>
<td>DMF</td>
<td>100</td>
<td>5</td>
<td>31</td>
<td>27</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>LiHMDS</td>
<td>THF</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>Phosphazene base P1-1 Bu</td>
<td>THF</td>
<td>100</td>
<td>-</td>
<td>60</td>
<td>56</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR spectroscopy of the crude reaction mixture using Bn$_2$O as an internal standard.

$^b$ Reaction with 15-crown-5 (1.1 eq.)

Table 11 Base screen for the ring-closing of NRC product 69
While changing the base was found to have a significant effect on the ratio of the products obtained, unfortunately none of the bases tested caused an increase in the yield of desired aziridine product 67 compared to that afforded with by NaH. The use of 15-crown-5 (Table 11, Entry 1), to increase the solubility of the sodium hydride, had a negative effect on the yield of the aziridine 67 (4%). The use of KH (Entry 2) again afforded a decreased yield of the desired aziridine product 67 (5%), with DppF (31%) and cyclic sulfonyl hydroxylamine 70 (27%) isolated as the major products. The use of LiHMDS (Entry 3) afforded the ESF as the major product with only trace amounts of the aziridine product observed, along with several unidentified side products. Finally, the use of phosphazene base P1-tBu gave none of the desired aziridine (Entry 4), but did give a 60% yield of DppF with a corresponding 56% yield of cyclic sulfonyl hydroxylamine 70.

Due to time constraints no further work was carried out into the aziridination of ethenesulfonyl fluoride. Whilst the DppONHBoc aziridination of ESF only afforded poor yields of the desired product, a high-yielding route to the non-ring-closed product was found. Initial screening of ring-closing conditions showed some promise, with a maximum 19% yield of the aziridine being achieved. However, multiple other reaction pathways also exist and a more thorough optimisation is needed to increase the selectivity for the desired ring closing reaction over the competitive elimination/retro-Michael pathways.
2.4 Conclusions and Future Work

To summarise, DppONHBoc was successfully utilised as the nitrogen source for the aziridination of a number of electron-deficient alkenes. Attempts at the formation of the hydrazinium salt upon reaction with tertiary amine NMM was unsuccessful suggesting that, unlike DppONH₂, DppONHBoc is able to react directly as a nucleophilic nitrogen transfer agent. However, the substrate scope was found to be limited due to the sensitivity of aziridinations with DppONHBoc to changes in the substitution pattern/electronics of the electrophilic substrates.

Attempts at the application of DppONHBoc to the aziridination of enones saw limited success. Whilst some high isolated yields (up to 89%) were achieved, on the whole, yields were variable and the substrate scope poor. Both aryl and alkyl functionality were well tolerated at the C-1 positions (R²), as was alkyl substitution at the C-3 position (R¹); while further conjugation of the alkene (R¹ = Ph, PhCH=CH) was not tolerated (Scheme 37).

The reaction was also expanded to the aziridination of vinyl sulfones; however, the scope was limited to terminal vinyl sulfones and only moderate yields were observed due to a slow ring-closing step (Scheme 38). Finally, work into the aziridination of ESF was met with limited success, with studies providing evidence of multiple competing reaction paths.
Building upon the results described above, future work (as discussed in Section 2.3.3 above) should focus on increasing the scope of the N-substituted (O-(diphenyl)phosphinyl) hydroxylamines, as this would enable firstly, the electronics of the NNTA to be fine tuned, and the effect of this on the ring-closing step to be further studied and secondly, through altering the N-substituent allow access to a wider range of N-protected aziridines. However, the multi-step synthesis and the poor stability of the electron-poor N-substituted-diphenylphosphinyl hydroxylamines would detract from some of the simplicity of the DppONHBoc aziridination protocol.

Also to be considered would be the use of *in silico* calculations to try to better rationalise the observed reactivity of DppONHBoc with enone and vinyl sulfone substrates, as well as further work to test DppONHBoc as a NNTA in other aziridination protocols, such as in the PTC or amino-catalysed methodologies discussed above (Section 2.1.2)
Chapter 2 (Section 2.1.2.3) introduced the \(O\)-(diphenylphosphinyl) hydroxylamines/NMM protocol for the \textit{in situ} formation of an NMM-derived aminimine 18 (Figure 6) and its use as an efficient nucleophilic nitrogen transfer agent (NNTA) for the aziridination of electron-deficient alkenes. This chapter will discuss studies utilising the same \textit{in situ} tertiary amine-promoted formation of aminimine 18 in the vicarious nucleophilic amination (VNA) of electron-deficient arenes and heteroarenes. VNA allows direct access to primary (hetero)aryl amines which are important building blocks in a number of chemical industries, including the manufacture of agrochemicals, pharmaceuticals, dyes, pigments and rubber.\textsuperscript{81,82}

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{figure6.png}
\caption{NMM derived aminimine 18}
\end{figure}

Section 3.1 will provide a concise introduction into the nucleophilic substitution of hydrogen in electron-deficient aromatics and heteroaromatics. This introduction will provide an overview of the formation and subsequent reactions of \(\sigma^H\)-adducts (Meisenheimer complexes). It will then continue to discuss in more detail vicarious nucleophilic substitution of hydrogen (VNS), providing an overview of the initial development of the methodology as an alkylation strategy, mechanistic studies and its application to the amination and hydroxylation of electron-deficient arenes. For a more comprehensive overview of the field, readers are directed to the following reviews.\textsuperscript{83–86}

Sections 3.2 and 3.3 go on to discuss our work looking at the application of NMM-derived aminimine 18 to the vicarious nucleophilic amination (VNA) of electron-deficient arenes and heteroarenes. Initial studies focus on the use of pre-formed NMM hydrazinium salts.
and later studies on the application of the *in situ* protocol for hydrazinium salt formation in the VNA of electron-deficient arenes.
3.1 Introduction

Aromatic nucleophilic substitution (S$_{\text{N}}$Ar)$^{86,87}$ is a much utilised methodology for the further derivatisation of electron-deficient arenes. Typically S$_{\text{N}}$Ar reactions occur when a strongly electron-withdrawing substituent, often a nitro group, on an aromatic substrate directs nucleophilic attack to the ortho and para-positions. When the addition of the nucleophile occurs at a position where a nucleofugal leaving group is present a $\sigma^X$-adduct 71 (also referred to as a Meisenheimer complex,$^{88}$ a 1:1 adduct formed between an electron-deficient arene and a nucleophile) is formed. Generally the $\sigma^X$-adduct formed is unstable and its formation is followed by spontaneous departure of the leaving group restoring the aromaticity of the arene and affording the substitution product (Scheme 39). As such, formation of the $\sigma^X$-adduct 71, with most nucleophiles, can generally be considered irreversible and is typically the rate-determining step in S$_{\text{N}}$Ar reactions.

![Scheme 39 Formation of $\sigma^H$- vs. $\sigma^X$-adducts of electron-deficient arenes](image)

While S$_{\text{N}}$Ar undoubtedly proceeds though the formation of the $\sigma^X$-adduct 71, studies have shown that the formation of $\sigma^H$-adducts 72, via reversible nucleophilic attack at unsubstituted positions, is a faster process.$^{88-90}$ However, since hydride displacement from the initially formed $\sigma^H$-adduct 72 is energetically unfavourable, a subsequent displacement-addition equilibration leads to the formation of $\sigma^X$-adduct 71 and the S$_{\text{N}}$Ar products (Scheme 39).
While generally direct hydride displacement from $\sigma^H$-adducts cannot occur, formal nucleophilic substitution of hydrogen in electron-deficient (hetero)arenes can occur via alternative reaction pathways. (N.B. one example of a reaction that is proposed to proceed via the direct hydride displacement is the Chichibabin amination reaction.\textsuperscript{91}) Early examples of reactions that are likely to occur via initial formation of a $\sigma^H$-adduct include, the Von Richter reaction\textsuperscript{92} (Scheme 40) and methodology for the formation of benzisoxazoles via the condensation of aromatic nitro compounds with arylacetonitriles\textsuperscript{93} both of which likely proceed via a cyclisation reaction between a ortho-$\sigma^H$-adduct and the nitro group.

![Scheme 40 Mechanism of the Von Richter reaction](image)

As highlighted by the Von Richter reaction above, providing that reaction reagents/conditions are present for the efficient conversion of $\sigma^H$-adducts, nucleophilic substitution of hydrogen in electron-deficient arenes can occur even in the presence of nucleofugal substituents.

Since then a number of general methodologies have been described for the transformation of $\sigma^H$-adducts, allowing the functionalisation of aromatic ring systems without the need for a leaving group.\textsuperscript{84–86} These include; oxidative nucleophilic substitution of hydrogen (ONSH),\textsuperscript{94} cine- and tele-substitutions,\textsuperscript{95} addition of nucleophile/ring-opening/ring-closure reactions (ANRORC),\textsuperscript{96} the conversion of $\sigma^H$-adducts to nitrosoarenes (the Von Richter reaction would be included within this general field)\textsuperscript{93,97} and, finally the most widely applicable and utilised of the methodologies, vicarious nucleophilic substitution (VNS).

3.1.1 Vicarious Nucleophilic Substitution (VNS)

Mąkosza first coined the term vicarious nucleophilic substitution in 1978 to describe the nucleophilic substitution of hydrogen in electron-deficient arenes where a nucleofugal
substituent present on the nucleophile acts as a vicarious leaving group in place of the hydride.\textsuperscript{98} In this first report, Mąkosza described the use of α-chlorophenyl sulfones in the base-mediated alkylation of substituted nitrobenzenes with moderate-to-good yields (48-90\%) (Scheme 41).

![Scheme 41 VNS of nitrobenzene with α-chlorophenyl sulfones](image)

The following, generally accepted, mechanism has been proposed for the VNS of nitroaromatics; an initial reversible formation of σ\textsuperscript{H}-adduct 73 is followed by β-elimination and then, during acidic work-up, re-aromatisation of the ring system (Scheme 42). A more detailed discussion of the mechanism and the mechanistic studies completed is included in Section 3.1.3 below.

![Scheme 42 VNS reaction pathways](image)

Despite Mąkosza being the first to coin the term vicarious nucleophilic substitution, earlier examples of the methylation of aromatic nitro compounds using dimethyloxosulfonium methyldide\textsuperscript{99–101} and trichloromethylithium\textsuperscript{102} are likely to proceed via a VNS mechanism. Also reported, simultaneously to Mąkosza’s first publication, was the first example of the
alkylation of nitrofuran with *N*-ethoxycarbonylmethylpyridinium ylide, again likely to proceed via a VNS reaction mechanism.\(^{103}\)

Since 1978 Mąkosza and others have expanded the scope of the VNS alkylation reactions both in terms of the electron-deficient electrophiles and nucleophiles tolerated.\(^{104–108}\) While any carbanion with a leaving group able to be eliminated as HX should undergo VNS with a sufficiently electron-deficient nitroarene, typically the carbanions utilised have a structure analogous to that of chloromethyl phenyl sulfone (still typically employed as the model carbanion for studies into electrophile scope) where *Y* is a nucleofugal leaving group and *Z* is an electron-withdrawing group capable of stabilising the carbanion (Figure 7). Studies have shown that a range of alkyl, aryl, halide and thiophenyl substituents are well tolerated in the α-position so long as the acidity of the α-proton is not significantly decreased.

![Figure 7](image)

**Figure 7** Carbanion precursors utilised in the VNS of electron-deficient arenes

While any combination of the above substituents should create an efficient nucleophile for the VNS with any nitroarene, limitations can occur when unfavourable addition equilibria arise due to insufficient electron-deficiency or steric hindrance in the nitroarene. A good example of this is the observed reactivity of the carbanion of diethyl chloromalonate, which does not react with nitrobenzene but can react with the more electron-deficient nitrothiazoles.\(^{109}\) Further limitations can arise if the carbanion is too reactive and self condensation can occur, or if the stabilising EWG can also act as a leaving group in the β-elimination step, such as with the use of phenyl sulfoxide.\(^{110}\)

The carbanions shown in Figure 7 have been utilised in the alkylation of a wide range of electron-deficient aromatics\(^{85,111–114}\) and heteroaromatics,\(^{115–117}\) with a general trend for increased reactivity with the use of more electron-deficient electrophilic substrates observed. The electrophiles utilised in VNS reactions fall into two categories. The first category includes aromatic rings activated with nitro groups; examples include
nitrobenzenes, nitronaphthalenes, nitrophenols, nitrofurans, nitrothiophenes, \(N\)-substituted nitropyrrroles and nitropyridines. The second category includes inherently electron-poor heteroarenes; examples include benzothiazole, acridine, 1,2,4-triazines and quinoline.

Generally a good functional group tolerance has been observed for the VNS reaction with both electron-rich and poor substituents well tolerated, so long as overall the (hetero)arene is sufficiently electrophilic enough for a favourable addition equilibrium to exist. However, electrophilic substituents that allowed competitive nucleophile additions can present problems, for example with the use of 3-nitrobenzophenone where alongside the desired alkylation products 74, a second unwanted condensation side product 75 was also formed (Scheme 43).\(^{118}\)

\[\begin{align*}
\text{ArNO}_2 + \text{Cl} + \text{SO}_2\text{Ph} & \xrightarrow{\text{base}} \text{ArNO}_2\text{SO}_2\text{Ph} + \text{ArNO}_2\text{SPh} \\
\text{O} & \xrightarrow{\text{DMSO, rt, 1 h then HCl (aq., 1M)}} \text{O} + \text{O} + \text{S}
\end{align*}\]

<table>
<thead>
<tr>
<th>Product</th>
<th>74</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>with KOH</td>
<td>21%</td>
<td>10%</td>
</tr>
<tr>
<td>with NaOMe</td>
<td>37%</td>
<td>15%</td>
</tr>
<tr>
<td>with 50% NaOH (aq.) and Bu(_4)NH(+)HSO(_4)-, in MeCN</td>
<td>11%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Scheme 43 Competitive Darzens Reaction in the VNS alkylation of \(m\)-phenylketone nitrobenzene

The formation of the condensation side product 75 is proposed to occur via an initial Darzens reaction to give an epoxide 76 followed by a rearrangement to aldehyde 77 and decarbonylation to give the condensation product 75 (Scheme 44). While no mechanism for the rearrangement of epoxide 76 to aldehyde 77 is discussed, a similar rearrangement has been observed in \(\alpha\)-epoxy sulfoxides and sulfones, and is proposed to occur via ring opening of the epoxide with intramolecular migration of the \(p\)-tolylsulfonyl (or \(p\)-tolylsulfinyl) group, though in these examples Lewis acidic conditions or heating (ca. 50°C) was required.\(^{119,120}\)
Negatively-charged arenes are tolerated provided the negative charge is not conjugated with the aromatic π-system; for example with the use of nitrobenzoic acids, deprotonated under the basic VNS conditions.\textsuperscript{121} Examples with direct conjugation of negative charge into the aromatic ring such as the use of \textit{ortho}/\textit{para}-nitrophenols, which under the basic reaction conditions exist as nitrophenolates, failed to afford any of the desired VNS products.\textsuperscript{122} One possible reason for this decreased reactivity is simply that the nitrophenols are too electron-rich; however, both nitroanisoles\textsuperscript{123} and \textit{N,N}-(dimethyl)-nitroanilines\textsuperscript{124} are known to react well in VNS reaction. As such, the lack of reactivity with nitrophenols seems to lie in the direct conjugation of the negative charge of the nitrophenolates formed under the basic conditions, thus hindering the nucleophilic addition of the carbanion.

The \textit{para}-formylation of nitrobenzene via an initial VNS alkylation followed by hydrolysis has been reported by Katritzky using carbanions of tris-(benzotriazol-1-yl)methane.\textsuperscript{125} Carbanions of benzotriazolyl-substituted diarylmethane 78, formed from the corresponding diarylmethanol, have also been utilised as nucleophiles in the synthesis of \textit{p}-(nitroaryl)diarylmethanes with a range of aryl motifs and generally with good yields (Scheme 45).\textsuperscript{108}
Also reported are ring-opening and ring-closing variants of VNS alkylation reactions. Mąkosza reported the ring-opening VNS cyanomethylation of 1-nitronaphthalene with phenylcyano-oxiranes and Cava has reported an intramolecular tandem-Michael-VNS ring closure in the synthesis of alkavinone precursor 79, a key intermediate in the synthesis of anthracycline antibiotics (Scheme 46).

![Scheme 45 Katritzky’s synthesis of p-(nitroaryl)diarylmethanes](image)

**Scheme 45** Katritzky’s synthesis of p-(nitroaryl)diarylmethanes

![Scheme 46 Tandem-Michael-VNS ring closure step in the synthesis of alkavinone precursor 79](image)

**Scheme 46** Tandem-Michael-VNS ring closure step in the synthesis of alkavinone precursor 79

### 3.1.2 Regio- and Chemo-Selectivity of VNS Alkylation Reactions

The regioselectivity of the VNS reaction is largely determined by three factors; the structure of the electrophile, the structure of the carbanion and the reaction conditions (solvent, base, etc.). With the use of inherently electron-deficient polyazaheterocycles, such as 1,2,4-trazines and benzothiazole, the position of the electronegative heteroatoms define the site(s) of substitution and VNS reactions proceed with complete selectivity at those sites. With substrates activated by electron-withdrawing groups (i.e. nitro groups) the situation is more complicated, though in all cases nucleophilic addition is directed to either the para or ortho-positions. The use of unsymmetrical substrates, with the nitro-group in specific positions, can give rise to high levels of selectivity, for example 1-nitronaphthalene shows high levels of selectivity for substitution in the 2-positions, whilst 3-nitrofurans and 3-nitrothiophenes will only react in the 2-positions. However, generally there is not sufficient difference in the electron densities at the ortho and para-positions for selectivity to be imparted by the structure of the
electrophile alone and other factors such as the structure of the carbanion or the reaction conditions also influence regioselectivity.

The influence on regioselectivity exerted by the carbanion is largely a steric effect, though to a lesser extent the nature of the substituents and leaving group can play a role. An increase in the size or number of substituents at the α-position of the carbanion results in an increased preference for para-substitution, in cases where both the ortho and para-positions are freely available. It is thought that the increased steric bulk hinders not only the initial formation of the ortho $\sigma^H$-adducts but also the second elimination step from the ortho $\sigma^H$-adducts. It is proposed that the increased steric bulk hinders the anti-periplanar orientation needed for the β-elimination step.\textsuperscript{111} The use of tertiary carbanions with multiple possible leaving groups, such as carbanions of trihalomethanes, can overcome this steric hindrance in the formation of the ortho-product by statistically favouring the β-elimination and as such increasing selectivity for the ortho-product.\textsuperscript{130}

Finally, reaction conditions also play a role in the regioselectivity of VNS reactions. Typically in weak-base conditions (KOH/DMSO), high levels of para-selectivity are observed with the reaction of nitrobenzene with chloromethyl phenyl sulfones, often with no observed reaction at the ortho-positions when the para-position is unsubstituted. With the use of strong-base conditions (KO\textsuperscript{1}Bu/DMSO) and/or lower reaction temperatures the ortho-product can be observed, though as a minor product.\textsuperscript{131} A more detailed discussion of the effect of reaction conditions on the observed regioselectivity of the VNS alkylation of nitrobenzene can be found in Section 3.1.3.

The regioselectivity of the VNS reaction is strongly affected by the state (level of solvation) of the carbanion in the reaction mixture. A study by Mąkosza found that use of KO\textsuperscript{1}Bu/THF base-solvent system in place of KO\textsuperscript{1}Bu/DMSO resulted in an exclusively ortho-selective alkylation of nitrobenzene with o-nitrobenzyl phenylsulfone.\textsuperscript{124} Mąkosza proposes that the tightly bound K\textsuperscript{+} carbanion present in THF, as opposed to the loosely bound solvated K\textsuperscript{+} carbanion in DMSO, co-ordinates the nitro groups and directs the carbanion addition to the ortho-position. This hypothesis is further supported by studies with HMPT and 18-crown-6 additives. The addition of either of these additives to the reaction mixture, thereby
increasing the solvation of the potassium cation, resulted in decreased selectivity for the ortho-position.

Nilsson took this approach a step further with the use of catalytic copper in the VNS synthesis of 2-(2,6-dinitrophenyl)-malonates, acetates and acetonitrile with high selectivity for the sterically hindered ortho-position (Scheme 47). Here the use of substoichiometric quantities of copper(I) chloride is thought to aid both formation and β-elimination of the σ^H-adduct 80. The use of pyridine as a ligand for the copper was found to be vital for high yields and selectivity, it being proposed that the pyridine both enhances the reactivity of the copper alkoxide and solvates the copper salt formed in the elimination step.

![Scheme 47 Cu-catalysed VNS alkylation of 1,3-dinitrobenzenes](image)

The chemoselectivity for a VNS reaction pathway in preference to a S_NAr pathway, when an appropriate leaving group is present, has been shown in numerous examples. Here chemoselectivity is dependent on the rate of reversible σ^H-adduct formation and subsequent β-elimination versus the, slower, generally, irreversible formation of the σ^X-adduct. Complete selectivity for the VNS pathway is observed with 4-chloro/4-bromonitrobenzene, while the use of 4-fluoro-substituted nitrobenzene results in S_NAr substitution as a minor side-reaction. Even examples using Sanger’s reagent, (2,4-dinitrofluorobenzene) known to be a highly reactive electrophile in S_NAr reactions, can still afford predominantly the VNS products under the appropriate reaction conditions.
3.1.3 Mechanistic Studies of Vicarious Nucleophilic Substitution

The general VNS mechanism first proposed by Mąkosza, via initial formation of a $\sigma^H$-adduct and then elimination of the vicarious leaving group, has been generally accepted, and is supported by the report of the first direct observation, by UV/Vis and NMR, of a VNS $\sigma^H$-adduct 81 (Scheme 48).\(^{134}\)

Further studies have provided additional evidence for this mechanism and have answered some of the questions that surrounded the mechanism (Scheme 49). These questions were as follows:

- Does the original addition occur via a direct addition or a SET pathway?
- What does the dependency of regioselectivity on the reaction conditions (in particular base concentration and temperature) tell us about the formation of the $\sigma^H$-adduct?
- Does the conversion of $\sigma^H$-adduct 82 to intermediate 83 occur via a hydride shift, as originally proposed by Mąkosza,\(^{105}\) or via a $\beta$-elimination?

One of the first studies into the mechanism of the VNS reaction looked at the relative rates of VNS and S\(_n\)Ar reaction of 4-fluoronitrobenzene with the carbanion of $\alpha$-chloromethyl phenylsulfone\(^{135}\) and it was observed that base concentrations were found to have a significant effect on the yields of VNS vs. S\(_n\)Ar substitution (Table 12).
The base dependency on the ratio of VNS vs. $S_N$Ar shown in these competition experiments provides strong evidence for the VNS reaction proceeding via a $\beta$-elimination pathway. Assuming that the formation of intermediate 83 was the rate-determining step, if a hydride shift was responsible for the formation of intermediate 83 then the rate of reaction would be independent of base concentration, whereas a base-induced $\beta$-elimination would be dependent on base concentration. Given that the rate of $S_N$Ar reactions are known to be independent of base concentration then the rate of $S_N$Ar versus VNS should only vary with base concentration if a base-dependent rate-determining step was occurring in the VNS pathway. The observed trend for the increased selectivity for the VNS product 84 with increased base concentration, supports both the hypothesis that the reaction proceeds via a base-induced $\beta$-elimination and that the elimination step is the RDS.

The rate dependency of the $\beta$-elimination on base concentration can also explain the observed increase in ortho-selectivity with increased base concentration/strength.$^{111}$ It is proposed that initially nucleophilic attack occurs at the ortho-position, followed by subsequent equilibration with time to the thermodynamically preferred para-$\sigma^H$-adduct via a dissociation-addition mechanism. At higher base concentrations the rate of $\beta$-elimination increases and the reaction can be thought to be under kinetic control increasing selectivity for the ortho-position. At lower base concentrations the rate of $\beta$-elimination is slower and
the subsequent increased time for equilibration results in an increased selectivity for the thermodynamically preferred \textit{para}-products. A decrease in reaction temperature has been shown to have a similar effect, trapping the kinetic product by slowing the rate of equilibration between the \textit{ortho} and \textit{para}-\(\sigma^H\)-adducts and increasing selectivity for substitution at the \textit{ortho}-positions.

KIE studies have lent further support to the base dependency of the \(\beta\)-elimination step. Reactions with 4-bromo-6-deuterio-2-fluoronitrobenzene revealed a large primary KIE (4.2) at lower base concentration (typical of those utilised in VNS reactions), while an increase in base concentration resulted in a secondary KIE (0.8) being observed (Scheme 50).\textsuperscript{132} These results highlight the base-dependency on the rate of the \(\beta\)-elimination step and that at lower base concentrations the \(\beta\)-elimination step is the RDS, while at higher base concentrations the formation of the \(\sigma^H\)-adducts becomes the RDS.

![Scheme 50 VNS KIE experiments with varying base concentration](image)

The question of the mechanism of the initial nucleophilic addition is a more contentious one, with the two proposed mechanisms; a direct nucleophilic addition, (path a, Scheme 51), and a step-wise SET transfer (path b) proposed by different researchers, based on differing evidence.
Early ESR evidence for the existence of anion radicals upon the treatment of nitrobenzene with carbanions led to the suggestion of the initial nucleophilic attack occurring via a SET mechanism.\textsuperscript{136,137} However, Mąkosza proposes a direct nucleophilic attack, due to the lack of observed inhibition with the use of radical probes (incorporated into the carbanions) in VNS reactions, and argues that the highly sensitive nature of ESR can lead to erroneous results.\textsuperscript{138} Mąkosza also cites a lack of observable paramagnetic broadening in the NMR analysis of the formation of VNS $\sigma^H$-adduct intermediate 81 (see above, Scheme 48) as further evidence for the direct nucleophilic addition in the first step. With a lack of sufficient evidence supporting either mechanism, at this point further studies are required to answer the question of what is the mechanism of the initial nucleophilic addition in VNS.

### 3.1.4 Vicarious Nucleophilic Aminations of Electron-Deficient Arenes

Early examples from Meisenheimer reported the amination of dinitrobenzene with hydroxylamine under basic conditions; however yields were not reported and amination of mono-substituted nitro-arenes was not discussed (Scheme 52).\textsuperscript{139–143} The original report proposes that the reaction proceeds via an internal oxidation-reduction process following a double addition of hydroxylamine, rather than a VNA mechanism, but no mechanism has been proposed for this process.
The substrate scope of the hydroxyamine amination has since been extended to include nitronaphthalenes,\textsuperscript{144} 5-nitropyridines\textsuperscript{145} and 4-nitroisoquinolines.\textsuperscript{145} Seko has further developed this methodology with the use of O-(methyl) hydroxylamine as an aminating agent in the copper-catalysed VNA of nitroarenes.\textsuperscript{146} The copper is proposed to activate the O-(methyl) hydroxylamine to the copper amidate 86 that acts as the active nitrogen source for the VNA of nitroarenes (Scheme 53). More recently Seko has again utilised O-(methyl) hydroxylamine in a similar zinc-catalysed process for the ortho-selective amination of nitropyridines.\textsuperscript{147}

A number of additional nucleophilic nitrogen transfer agents (NNTA) have since been utilised in the VNA of electron-deficient (hetero)arenes with, generally, similar trends in
regioselectivity and chemoselectivity to those observed in the VNS reactions with carbanions. Katritzky has reported the use of 4-amino-1,2,4-triazole 87 as a nitrogen source for the amination of a range of nitrobenzene derivatives with complete para-selectivity in fair-to-good yields (22-91%) (Scheme 54). Similar trends in reactivity, to that of the VNS alkylation of nitrobenzene discussed above (Section 3.1.2), were observed, with higher yields afforded with the use of more electron-deficient electrophiles.

![Scheme 54 Katritzky’s amino-triazole mediated VNA of nitrobenzene](image)

Katritzky further expanded the scope of the VNA reactions with amino-triazole 87 to the amination of 1-nitronaphthalene (62%), 2-nitrofuran (13%) as well as notably the use of substituted amino-triazoles in the synthesis of N-substituted nitroanilines in fair-to-good yields. More recently Suwinski et al. reported the use of aminotriazole 87 in the amination of 1-aryl-4-nitroimidazoles in fair-to-moderate yields (30-72%), though electron-poor aryl substituents at the 1-position were not tolerated, and in the amination of 3,5,6,7 and 8-nitroquinolines with fair-to-good yields.

Mąkosza has reported the use of a wide range of sulfenamides as VNA aminating agents, of which sulfenamides 88-90 (Figure 8) proved to be the most promising for the amination of nitrobenzenes, with good regioselectivity for amination at the 4-position, and nitronaphthalene. More recently Mąkosza has expanded the electrophile scope to include 6-nitroquinoline, nitropyridines, nitrothiophenes, N-methylnitropyroles and N-methyl-5-nitroindole as well as the use of N-disubstituted sulfenamides in the synthesis of N-alkyl and N-arylnitroanilines.
Pagoria has utilised 1,1,1-trimethylhydrazinium iodide 91 (Figure 8) in the amination of a range of meta-substituted nitrobenzenes (Scheme 55) with selectivity for amination at the ortho-position of nitrobenzene (85%, 61:39 ortho:p nitroaniline) even under strongly basic (KOtBu/DMSO) reaction conditions.\textsuperscript{154}

\[ \text{RNO}_2 + \text{N}^+\text{NH}_2\text{I}^- \xrightarrow{\text{KOtBu (2.4 eq.), DMSO, rt, 4 h then} 10\% \text{HCl (aq), 30 min, rt}} \text{RNO}_2\text{NH}_2 \]

**Scheme 55** Pagoria’s VNA of 3-substituted nitrobenzene with 1,1,1-trimethylhydrazinium iodide

1,1,1-Trimethylhydrazinium iodide 91 has also been reported in the amination of 1,3-dinitrobenzene (with generally good yields and good levels of ortho-selectivity),\textsuperscript{155} in the amination of nitroquinolines with moderate-to-good yields\textsuperscript{156} and in the amination of 3,5-dinitro-1H-pyrazole.\textsuperscript{157} Recently ESR studies and \textit{ab initio} calculation have lent some support to the involvement of a SET mechanism in the VNA with 1,1,1-trimethylhydrazinium iodide,\textsuperscript{158} though further studies are required to provide more evidence for this hypothesis.

### 3.1.5 Other Examples of VNS Reactions: Hydroxylation of Nitroarenes and the Alkylation of Electron-Deficient Alkenes

The use of both alkyl and aryl hydrogen peroxides as nucleophiles in the VNS synthesis of nitrophenols have been reported with moderate-to-good yields (Scheme 56).\textsuperscript{159–161} As with the alkylation and amination examples, the substrate scope of this reaction has been extended to a range of nitro-substituted (hetero)arenes including: nitronaphthalenes,
nitropyridines, nitroquinolines and nitrothiophene,\textsuperscript{162} and has been utilised in the regioselective and cost effective synthesis of 4,6-diaminoresorcinol, a precursor for high-strength liquid crystal polymers.\textsuperscript{163}

![Scheme 56 Hydroxylation of nitroarenes via VNS of hydrogen](image)

The nucleophilic substitution of hydrogen in esters of fumaric and maleic acids has also been reported (Scheme 57).\textsuperscript{164} However, due to the lack of a driving force, such as the re-aromatisation of the $\sigma^H$-adducts in the reactions with nitroarenes, the $\beta$-elimination step is often sluggish and the scope is limited. Furthermore, currently no mechanistic studies have been carried out and a competing cyclisation/ring-opening mechanism, in place of the VNS mechanism, cannot be ruled out.\textsuperscript{165}

![Scheme 57 Nucleophilic substitution of hydrogen in electrophilic alkenes](image)
3.2 Project Aims

As introduced in Section 2.1.2.3, the Armstrong group has developed a transition metal-free reaction system for nucleophilic nitrogen transfer through the use of aminimines produced in situ from DppONH₂ and a tertiary amine, typically NMM. The resultant aminimine 18 has the appropriate characteristics needed to act as a nucleophilic nitrogen transfer agent in VNA reactions.

The aim of this project was to evaluate the use of the aminimine 18 as a nucleophilic nitrogen transfer agent in the VNA of electron-deficient arenes and apply the developed methodology to the synthesis of a wide range of aminated arenes and heteroarenes. Initial studies focused on the use of pre-prepared salts, in an approach analogous to that describe by Pagoria. With the initial reactions using pre-formed salt proving successful, the use of the in situ salt formation protocol was then tested (Scheme 58). Development of an in situ reaction should offer a number of advantages over the use pre-prepared salts; firstly avoiding the need to prepare and handle, potentially hazardous, stoichiometric hydrazinium salts and secondly the possibility of altering reactivity and selectivity through the use of alternative tertiary amines.

Scheme 58 Proposed amination of electron-deficient aromatics using DppONH₂/NMM reaction system
Finally, the potential use of sub-stoichiometric amounts of the NMM promoter was studied with an aim of developing a catalytic variant of the NMM mediated VNA of electron-deficient arenes.
3.3 Results and Discussion

3.3.1 Initial Studies Using 4-Aminomorpholinium Salts

Initial studies utilised NMM-derived hydrazinium iodide salt 16a to test the viability of the proposed VNA system and, in particular, the ability of NMM to act as an efficient leaving group in the VNA reaction. The iodide salt 16a was synthesised as a white crystalline solid from 4-aminomorpholine and methyl iodide (70%, Scheme 59).

\[
\text{N} \text{H}_2 \text{N} \xrightarrow{\text{MeI}} [\text{THF, } 0 \degree C \to rt, 30 \text{ min}] \text{N} \text{H}_2 \text{I}^{-}
\]

\text{Scheme 59 Synthesis of 4-amino-4-methyl-morpholinum iodide}

The use of the iodide salt 16a was then tested in the amination of nitrobenzene and for this the protocol from Pagoria’s work, using trimethylhydrazinium iodide, was followed.\textsuperscript{154} Under these conditions nitrobenzene was aminated using the iodide salt in slight excess in the presence of at least 2 equivalents of a strong alkoxide base, typically potassium tert-butoxide, and a strongly co-ordinating solvent; here DMSO is used. The requirement of a co-ordinating solvent is common throughout the VNA methodology and is proposed to have the duel role of stabilising the \(\sigma^+\)-adduct (Meisenheimer complex) intermediate and solvating of the base.

Use of the iodide salt 16a for the amination of nitrobenzene under these conditions afforded complete conversion of the nitrobenzene with the desired amino product 92 afforded in a pleasing yield of 73% (Table 13, Entry 1), although only a slight regioselectivity for the para-position (1:1.2 ortho:para) was observed.
The use of sodium hydroxide (Entry 2), the preferred base of the DppONH$_2$/NMM aziridination methodology, in place of tert-butoxide afforded the same yield with an increased selectivity for para-92. This increased selectivity is likely explained by a decreased rate of the β-elimination step with the weaker hydroxide base, as discussed in Section 3.1.3 above.

A small solvent screen was then carried out to test both solvents known to be effective for VNA reactions (Entries 3&4) and those solvents known to be compatible with the in situ formation of aminimine 18 (Entries 5&6). The use of DMF (Entry 3), often used as an alternative to DMSO in VNS reactions, resulted in a lower yield of nitroaniline (31%), though with almost twice the selectivity for the para-product, when compared to the DMSO reaction. Again this is proposed to be due to the decreased rate of β-elimination. While the use of THF (Entry 4) has been shown to be compatible with some VNS reaction systems, its use in the hydrazinium iodide system was not tolerated affording a 55% conversion of the nitrobenzene with none of the desired product obtained. The use of solvents known to be compatible with the in situ formation of aminimine 18 did not show any compatibility with the VNA reaction. The use of CH$_2$Cl$_2$ only gave return of the starting

---

**Table 13** Use of morpholinium iodide salt 16a in the VNA of nitrobenzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Conversion of Nitrobenzene (%)$^a$</th>
<th>Yield o-92(%)$^b$</th>
<th>Yield p-92(%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KO' Bu</td>
<td>DMSO</td>
<td>100</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>NaOH</td>
<td>DMSO</td>
<td>100</td>
<td>19</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>NaOH</td>
<td>DMF</td>
<td>100</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>NaOH</td>
<td>THF</td>
<td>55</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>NaOH</td>
<td>CH$_2$Cl$_2$</td>
<td>&lt;1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>NaOH</td>
<td>MeCN</td>
<td>85</td>
<td>-</td>
<td>trace</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. $^b$ Isolated yields following column chromatography.
materials (Entry 5), while the use of MeCN (Entry 6) saw almost complete conversion of the nitrobenzene, but only trace amounts of the desired amination product.

With the efficacy of the NMM as a leaving group in VNA of nitrobenzene demonstrated a small study of substrate scope was then performed, looking at a range of nitro-aromatic and electron-deficient heteroaromatic compounds (Table 14).

\[
\begin{array}{cccccc}
\text{Entry} & \text{Substrate} & \text{Conversion of } \text{ArNO}_2 (\%)^a & \text{Product} & \text{Yield} (\%)^b \\
1 & \text{NO}_2 & 100 & \text{N}-\text{NH}_2 & 54\% \text{ (para)} \\
 & & & & 19\% \text{ (ortho)} \\
2 & \text{NO}_2 & 100 & \text{N}-\text{NH}_2 & 79 \\
3 & \text{NO}_2 & 100 & \text{N}-\text{NH}_2 & 88 \\
4 & \text{N} & 100 & \text{N}-\text{NH}_2 & 41 \\
5 & \text{N} & 0 & - & - \\
6 & \text{N} & 92 & \text{S}-\text{NH}_2 & 20 \\
7 & \text{NO}_2 & 100 & \text{S}-\text{NH}_2 & 31 \\
8 & \text{N} & 22 & - & - \\
\end{array}
\]

\( ^a \) Determined by \(^1\)H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. \( ^b \) Isolated yields following column chromatography.

**Table 14** Substrate scope for the VNA using morpholinium iodide salt 16a
The use of more electron-deficient nitrobenzene-derived substrates saw an increase in yields, with 1,3-dinitrobenzene (Table 14, Entry 2) affording a 79% yield of the amination product 93, with substitution exclusively at the 6-position of the 1,3-dinitrobenzene. The amination of 1-nitronaphthalene proceeded with a high yield of 88% (Entry 3) with effectively complete selectivity for the 2-position (a small amount (~1%) of the 4-aminoproduct was observed in the NMR spectrum of crude reaction mixture) in agreement with the selectivity previously reported (See Section 3.1.2 above). One reason for the observed increased reactivity with the use of 1-nitronaphthalene, compared to nitrobenzene, likely lies in the increased resonance stabilisation of nitronaphthalene (61 kcal/mol) when compared to benzene (36 kcal/mol). This increased resonance stabilisation would lower the energy of the intermediate Meisenheimer complex helping drive the addition equilibrium towards the σH-adduct and thus increasing product formation.

The use of electron-deficient heteroaromatics was also tolerated with amination of benzoxazole (Entry 4) affording the 2-amino product 95 in a 41% yield, providing the first example of the VNA of benzoxazole without activation by electron-withdrawing substituents. Attempts at the amination of oxazole (Entry 5) gave no conversion of the starting material, possibly due to either the oxazole being too electron-rich and/or the lack of resonance stabilisation afforded by the benzene ring present in benzoxazole, resulting in the addition equilibrium being shifted too far towards the starting materials. Use of the sulfur analogue benzothiazole (Entry 6) gave a lower yield of 20% and, as with the nitrobenzene examples, the use of a more electron-poor substrate 6-nitrobenzothiazole (Entry 7) afforded an increase in the yield to 31%. With the use of 1-methylbenzimidazole a 22% conversion of the starting material was observed, but none of the desired amination product was recovered.

While the benzazole examples (Entries 4, 6 & 7) only afforded at best moderate yields, the use of the DppONH₂/NMM VNA protocol to access these N-unsubstituted aminobenzazole products offers a simple, complementary approach to the metal-catalysed direct amination methodologies, which typically only allow access to N-substituted aminobenzazole products.¹⁶⁶
One final test reaction that was carried out, prior to attempts at the tertiary amine/DppONH$_2$ *in situ* reaction, was the use of diphenylphosphinate salt 24 in place of the iodide salt. These test reactions with the diphenylphosphinate salt 24 allow a direct comparison to the NMM/DppONH$_2$ *in situ* reaction, and will show the effect, if any, that the change in counter ion has on the reactivity/selectivity of the VNA reaction. DppONH$_2$ itself can be accessed in one step from diphenylphosphinic chloride and hydroxylamine hydrochloride (Scheme 60).

![Scheme 60 Synthesis of DppONH$_2$](image)

For the test reaction the diphenylphosphinate salt 24 was prepared via the reaction of a 1:1 mixture of NMM and DppONH$_2$ in CH$_2$Cl$_2$. Previous studies have shown that complete conversion of the starting material into diphenylphosphinate salt 24 occurs within 30 minutes at room temperature.$^{59}$ After stirring for 30 minutes the reaction mixture was concentrated under reduced pressure and used immediately in the VNA reactions (Table 15.)

![Conversion of nitrobenzene](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Nitrobenzene</th>
<th>Yield o-92(%)$^b$</th>
<th>Yield p-92(%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KO'Bu</td>
<td>100</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>NaOH</td>
<td>100</td>
<td>4</td>
<td>34</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. $^b$ Isolated yields following column chromatography.

**Table 15** VNA of nitrobenzene with diphenylphosphinate salt 24
Use of the diphenylphosphinic salt 24 reduced the overall yields in comparison with the iodide salt 16a, both with the use of potassium tert-butoxide (41%, Table 15, Entry 1) and sodium hydroxide (38%, Entry 2). However, similar trends in reactivity are observed with sodium hydroxide affording greater selectivity for para-92. Despite the lower yields these results validate the use of the diphenylphosphinate salt in the VNA reaction and provide precedent for the use of the in situ salt formation. The one question that remained to be answered was whether the in situ salt formation would be compatible with the solvents required for the VNA reactions.

3.3.2 Initial Attempts at the Amination of Nitrobenzene with In Situ Formation of 4-Amino-4-methylmorpholinium Salts

Literature examples of the in situ formation of the morpholinium salt 24 and its application to the aziridination of electron-deficient alkenes showed CH$_2$Cl$_2$ and MeCN to be the preferred solvents. However, test reactions with pre-formed salts (Section 3.3.1) have shown these to be poor solvents for the VNA reaction, likely due to the lack of stabilisation of the $\sigma^H$-adduct intermediates and the poor solubility/lack of solvation of the alkoxide/hydroxide bases required. As such the initial study focused on finding the optimal solvent system required for the amination of nitrobenzene with in situ formation of diphenylphosphinate salt 24. A range of solvents were tested, both those shown to be compatible with the VNS reactions and those used in Armstrong’s aziridination methodology (Table 16).
Table 16 Solvent screen for the *in situ* salt formation in the VNA of nitrobenzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Conversion of Nitrobenzene (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield α-92 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield p-92 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>NaOH</td>
<td>100</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>NaOH</td>
<td>57</td>
<td>trace</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>NaOH</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>NaOH</td>
<td>71</td>
<td>trace</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NaOH</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>1,4-dioxane</td>
<td>NaOH</td>
<td>100</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>DME</td>
<td>NaOH</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>DMSO</td>
<td>KO&lt;i&gt;°&lt;/i&gt;Bu</td>
<td>97</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>DMSO</td>
<td>NaH/IPA</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>KOH</td>
<td>10</td>
<td>-</td>
<td>trace</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. <sup>b</sup> Isolated yields following column chromatography.

Initial attempts with DMSO and NaOH (Table 16, Entry 1) gave complete conversion of the starting materials but with a reduced yield (18%) when compared to the analogous examples with the pre-prepared salts (Table 15, Entry 2), though much higher regioselectivity was observed (1:17 α:p). One possible reason for this increased selectivity is in the physical properties of the reaction mixture. The use of pre-formed salt in DMSO gave a homogenous reaction mixture, while the protocol with *in situ* salt formation resulted in a thick heterogeneous reaction mixture. The thick heterogeneous reaction mixture might have resulted in a lower base concentration and corresponding decreased rate of β-elimination. Test reactions at half the concentration and twice the reaction time still gave a thick heterogeneous reaction mixture and afforded no significant increase in yield or regioselectivity. Reactions run at lower concentrations still failed to give a homogeneous reaction mixture and were deemed too slow to be useful.

The same trends in reactivity as with the use of pre-formed salt were observed with alternative solvents. The use of DMF resulted in a lower conversion of nitrobenzene and yield of nitroaniline (4%, Entry 2), whilst use of THF afforded complete conversion of the
starting material but none of the desired nitroaniline product was observed (Entry 3). In the in situ reaction the use of MeCN (Entry 4), which had given 0% yield with the pre-formed salt, afforded a low yield of 4% of the desired amination product. The use of CH$_2$Cl$_2$ again showed only minimal conversion of the starting materials (Entry 5). Reactions with alternative co-ordinating solvents 1,4-dioxane and DME (Entries 6&7) also failed to give any significant yield of the desired products.

A small screen of alternative hydroxide and alkoxide bases showed that the use of KO'Bu (Entry 8) gave an increased yield of 26%, when compared to the use of NaOH, though with the expected decreased regioselectivity. Reactions using either NaH/IPA, an alternative base system used in the Armstrong aziridination methodology, or KOH afforded none of the desired amination products.

One possible reason for the lower yields afforded with the in situ salt formation in DMSO, when compared to the pre-formed salts, is that DMSO is hampering salt formation. This proposed poor compatibility of DMSO was highlighted by NMR studies of the salt formation in d$_6$-DMSO. Unlike the quantitative formation of the diphenylphosphinate salt 24 observed in CH$_2$Cl$_2$/MeCN after 30 minutes, reactions in d$_6$-DMSO afforded a complex mixture of products that included a low yield of the desired diphenylphosphinate salt 24. Furthermore, the poor yields compared to the high conversion achieved with the use of DMSO as a reaction solvent suggest that these side-products go on to react with the nitroarenes.

With DMSO shown to be a poor solvent for the in situ VNA reaction, work was then focused on developing a reaction system using CH$_2$Cl$_2$, known to be compatible with the required salt formation.

Two main reasons have been proposed for the poor conversion of nitrobenzene with the use of CH$_2$Cl$_2$; poor solubility/solvation of the base and the corresponding less basic nature of anions in non-coordinating solvent, and the instability of the intermediate Meisenheimer complex. Attempts were made to use additives to overcome the proposed incompatibilities with the use of CH$_2$Cl$_2$ in the VNA reaction (Table 17). Sodium hydroxide
was chosen as the base for these test reactions due to its well-demonstrated compatibility with the NMM/DppONH$_2$ aminating system.

Initial attempts used phase transfer catalysts in an attempt to improve the solubility of the sodium hydroxide base in CH$_2$Cl$_2$. Attempts with tetrabutylammonium chloride in both 10 mol\% (Table 17, Entry 1) and 100 mol\% (Entry 2) failed to give any of the desired product, however almost complete conversion of the nitrobenzene was observed. This complete conversion is in contrast to the reaction without the additive which showed only 5\% conversion of the starting material. The use of the analogous ammonium hydroxide salt, both in 10 mol\% (Entry 3) and in 2.4 equivalent in place of the sodium hydroxide (Entry 4) also gave high conversion but with none of the desired aminated product. The use of 15-crown-ether (Entry 5) in a 1:1 equivalent with the sodium hydroxide also gave none of the desired aminated product, though with lower conversion compared to the use of tetrabutyl ammonium salts.

Table 17 Use of additives in VNA of nitrobenzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion of Nitrobenzene (%)$^a$</th>
<th>Yield o-92 (%)$^b$</th>
<th>Yield p-92 (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{nBu}_4\text{N}.\text{Cl (10 mol%)}$</td>
<td>97</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>$\text{nBu}_4\text{N}.\text{Cl (100 mol%)}$</td>
<td>95</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>$\text{nBu}_4\text{N}.\text{OH (10 mol%)}$</td>
<td>93</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>$\text{nBu}_4\text{N}.\text{OH (2.4 eq.)}$</td>
<td>59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>15-crown-ether (2.4 eq.)</td>
<td>73</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>DMPU (10 mol%)</td>
<td>22</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>DMPU (10 vol%)</td>
<td>43</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>DMSO (10 mol%)</td>
<td>73</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>DMSO (10 vol%)</td>
<td>68</td>
<td>trace</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>Ph$\rightarrow$S$\backslash$O$\rightarrow$S$\rightarrow$Ph</td>
<td>20</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

$^b$ Isolated yields following column chromatography. $^c$ Reaction run without sodium hydroxide.
With the phase transfer catalysts failing to give any of the desired products, a range of additives, chosen to simulate the co-ordinating/solvating effect afforded with the use of DMSO, were tested. The use of co-ordinating solvent DMPU in 10 mol% (Entry 6) gave only 22% conversion of nitrobenzene, though for the first time traces of the desired product was observed. Increasing the amount of DMPU to 10 vol% gave an increased conversion of the nitrobenzene (43%), but still only traces of the desired products. The use of DMSO in similar quantities (Entries 8&9) gave a slight increase in conversion, but still very poor yields of the desired product were afforded. Finally, 1,2-bis(phenylsulfinyl)ethene 98 (Entry 10), used by White as sulfoxide promoter in Pd-catalysed C-H oxidations was tested, here it was hoped that the sulfoxide promoter would mimic the co-ordinating effect of DMSO both solvating the base and stabilising the Meisenheimer complex; however, only a 2% yield of the desired product was observed.

Test reactions with iodide salt 16a (Table 14) had shown improved reactivity over those using the diphenyl phosphinate salt 24 (Table 15). Could the use of iodide additives have a similar effect in increasing the yield of the in situ reaction in DMSO? For these reactions the solvent swap protocol described above (Table 15), with the salt formation in CH₂Cl₂ and the VNA reaction in DMSO, was used to ensure that a full 1.5 eq. of the diphenylphosphinate salt 24 was present (Table 18).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion of Nitrobenzene (%)</th>
<th>Yield α-92 (%)</th>
<th>Yield p-92 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaI (1.1 eq.)</td>
<td>100</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Bu₄N.I (1.1 eq.)</td>
<td>100</td>
<td>trace</td>
<td>10%</td>
</tr>
</tbody>
</table>

*a* Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. *b* Isolated yields following column chromatography.

Table 18 Use of iodide additives in VNA of nitrobenzene
Unfortunately, the use of NaI as an additive afforded none of the desired product (Table 18, Entry 1), while the use of more soluble tetrabutylammonium iodide afforded a 10% yield of the para-product; however, this was still a decrease when compared to the additive-free reaction.

### 3.3.3 Use of More Electron-Deficient Aromatic Electrophiles

With additives and co-solvents failing to afford any increase in the yields of the VNA of nitrobenzene, either in CH$_2$Cl$_2$ or DMSO, it was decided to test both reaction systems with more electron-deficient substrates. The use of both 1,3-dinitrobenzene and 1-nitronaphthalene in VNA reactions with pre-formed iodide salt 16a had shown significantly increased yields when compared to the use of nitrobenzene and were chosen as test substrates (Tables 19 & 20).

![Chemical reaction diagram]

**Conversion of Dinitrobenzene**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Dinitrobenzene (%)$^a$</th>
<th>Yield 93 (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>93</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>86</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. $^b$ Isolated yields following column chromatography.

**Table 19** VNA of 1,3-dinitrobenzene with *in situ* salt formation

As with the results using pre-formed salts, the use of the more electron-deficient aromatic dinitrobenzene, afforded an increased 21% yield of the aminated product (Table 19, Entry 1), although again no aminated product was afforded with the use of DCM (Entry 2), despite high conversion of the dinitrobenzene.
Entry | Base | Solvent | Nitronaphthalene Yield 2-Amino 94 (%)<sup>b</sup> | Yield 4-Amino 94 (%)<sup>b</sup>
--- | --- | --- | --- | ---
1 | NaOH | DMSO | 70 | 20 | 6
2 | NaOH | CH<sub>2</sub>Cl<sub>2</sub> | 72 | 60 | 1
3 | KO<sub>t</sub>Bu | CH<sub>2</sub>Cl<sub>2</sub> | 55 | 40 | 1
4 | NaH/IPA | CH<sub>2</sub>Cl<sub>2</sub> | 15 | 8 | trace

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

<sup>b</sup> Isolated yields following column chromatography.

**Table 20** VNA of 1-nitronaphthalene with *in situ* salt formation

Initial attempts at the use of 1-nitronaphthalene (Table 20, Entry 1) in DMSO gave an increased yield of 26%, as expected with the observed trend of increased reactivity with increased electron deficiency of the aromatic substrates used, c.f. nitrobenzene (18%, Table 16) and dinitrobenzene (21%, Table 19). Pleasingly, unlike with other substrates tested, the use of CH<sub>2</sub>Cl<sub>2</sub> (Table 20, Entry 2) gave similar conversion to the reaction in DMSO, but a significantly higher yield of the aminated products (61%) and a high selectivity for amination at the 2-position. This increased reactivity of 1-nitronaphthalene in CH<sub>2</sub>Cl<sub>2</sub> is proposed to arise due to the increased stability of the intermediate Meisenheimer complex in CH<sub>2</sub>Cl<sub>2</sub>, when compared to those formed with the nitrobenzene substrates, alongside a complete formation of the required diphenyl phosphinate salt. This increased stability is likely due to the increased delocalisation of the negative charge into the second phenyl ring, i.e. the increased resonance stabilisation of nitronaphthalene (61 kcal/mol) when compared to benzene (36 kcal/mol). Interestingly, the use of the stronger alkoxide base (KO<sub>t</sub>Bu, entry 3) gave a decreased yield of 41%, suggesting some incompatibility between the salt/aminimine and strongly basic reaction conditions.

The high selectivity for amination at the 2-position, over the 4-position, of 1-nitronaphthalene is in agreement with reported literature with other nucleophiles, where selectivity of 1-nitronaphthalenene has been found to be less dependent of the steric bulk of the incoming nucleophile when compared to nitrobenzene substrates.<sup>149,168</sup> This is
supported by molecular orbital calculations\textsuperscript{169–171} which have shown that the π-electron density is significantly lower at the 2-position when compared to the 4-position, while in nitrobenzene the π-electron density is comparable at both the 2- and 4-positions.

Also tested was the alternative base protocol from Armstrong’s aziridination methodology using a weaker alkoxide base (NaH/IPA) but this again provided poor conversion and only an 8% yield of the aminated products (Entry 4).

With these results showing that with 1-nitronaphthalene the use of non-coordinating solvents can be tolerated in VNS reaction, a further solvent screen was carried out (Table 21).

\[
\text{O} \quad \begin{array}{c}
\text{P} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{Ph}
\end{array} \quad \begin{array}{c}
\text{NH}_2 \\
(1.1 \text{ eq})
\end{array}
\]

\[
\text{i) NMM (1.1 eq.), solvent, rt, 30 min} \\
\text{ii) NaOH (2.4 eq.), 1-nitronaphthalene (1.0 eq.), 18 h} \\
\text{iii) [H\text{\textsuperscript{+}}, 30 min}
\]

\[
\begin{array}{cccc}
\text{Entry} & \text{Solvent} & \text{Nitronaphthalene} & \text{Yield 2-Amino 94 (%)\textsuperscript{b}} & \text{Yield 4-Amino 94 (%)\textsuperscript{b}}
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Nitronaphthalene (%)\textsuperscript{a}</th>
<th>Yield 2-Amino 94 (%)\textsuperscript{b}</th>
<th>Yield 4-Amino 94 (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>85</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>69</td>
<td>60</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>63</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>CHCl\textsubscript{3}</td>
<td>9</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determined by \textsuperscript{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.  
\textsuperscript{b} Isolated yields following column chromatography.

Table 21 Solvent screen for the VNA of 1-nitronaphthalene with \textit{in situ} salt formation

The use of DMF gave an increased yield of 48% (Table 11, Entry 1) over the use of DMSO, likely due to increased compatibility with the salt formation, but still afforded a lower yield and selectivity than the use of CH\textsubscript{2}Cl\textsubscript{2}. The use of THF gave similar yields (62%) and selectivity to the use of CH\textsubscript{2}Cl\textsubscript{2} (Entry 2), while MeCN gave decreased yield (44%) and selectivity (Entry 3). Finally, the use of chloroform gave poor conversion and yields (2%, Entry 4). For the further studies discussed below, CH\textsubscript{2}Cl\textsubscript{2} was chosen in preference to THF as, while both showed similar reactivity, quantitative salt formation is
known to occur within 30 minutes with CH$_2$Cl$_2$ and similar studies have not been carried out with THF.

With CH$_2$Cl$_2$ shown to be the solvent of choice, next the optimisation of the reaction conditions/protocol was investigated (Table 22).

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>NaOH (eq.)</th>
<th>Conc. (M)</th>
<th>t$^1$ (h)</th>
<th>Conversion of Nitronaphthalene (%)$^a$</th>
<th>Yield 2-Amino 94 (%)$^b$</th>
<th>Yield 4-Amino 94 (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>2.4</td>
<td>0.18</td>
<td>18</td>
<td>64</td>
<td>56</td>
<td>4</td>
</tr>
<tr>
<td>2$^c$</td>
<td>1.1</td>
<td>2.4</td>
<td>0.18</td>
<td>18</td>
<td>82</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>3.0</td>
<td>0.18</td>
<td>18</td>
<td>69</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>5.0</td>
<td>0.18</td>
<td>18</td>
<td>78</td>
<td>60</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>2.4</td>
<td>0.18</td>
<td>24</td>
<td>73</td>
<td>62</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>2.4</td>
<td>0.18</td>
<td>72</td>
<td>70</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>7$^d$</td>
<td>1.1</td>
<td>2.4</td>
<td>0.18</td>
<td>48</td>
<td>64</td>
<td>64</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>2.4</td>
<td>0.06</td>
<td>18</td>
<td>64</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>2.4</td>
<td>0.24</td>
<td>18</td>
<td>61</td>
<td>59</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>1.1</td>
<td>2.4</td>
<td>0.40</td>
<td>18</td>
<td>79</td>
<td>59</td>
<td>6</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

$^b$ Isolated yields following column chromatography. $^c$ 1.5 eq. of DppONH$_2$ added. $^d$ At 24 hours an extra 0.5 eq. of performed diphenylphosphinate salt 24 was added.

Table 22 Optimisation of the VNA of 1-nitronaphthalene with in situ salt formation

An increase in the equivalents of the nucleophile to 1.5 equivalents (Table 22, Entry 1) had no significant effect on either the yield or the selectivity of the reaction. The use of DppONH$_2$ in excess resulted in an increased conversion but a decreased yield of the aminated products (Entry 2). Test reactions showed that DppONH$_2$ can react with the 1-nitronaphthalene in the absence of the tertiary amine; however, this did not afford the desired aminated product.

Increasing the equivalents of the base to 3 or 5 equivalents (Entries 3&4) had no significant effect on the reactivity/selectivity, and only a slight increase in the conversion of
the starting material was observed, likely due to the reaction mixture already being saturated with 2.4 equivalents of sodium hydroxide. An increase in reaction time to 24 hours saw only a slight increase in the conversion and a corresponding increase in yield to 68% (Entry 5). However, further increase in reaction time to 72 hours saw in no further increase in the conversion or yield (Entry 6).

Several possibilities for the reaction stalling were considered, the first being the instability of the aminimine under extended reaction conditions. This was tested by the addition of an extra 0.5 equivalents of the pre-formed diphenylphosphinate salt 24 after 24 hours (Entry 7). The reaction was then allowed to run for an additional 24 hours, but no increase in yields was observed. This lack of increased yields with the addition of the extra equivalents of diphenylphosphinate salt 24 suggests that aminimine stability was not a problem under the reaction conditions.

It was observed that after addition of the base and 1-nitronaphthalene the reaction mixture was observed to instantly change from a clear pale yellow solution to a bright red/brown heterogeneous slurry, which continued to thicken over the course of the reaction. To test if the heterogeneous reaction mixture was causing the reaction to stall due to lowering the concentration of the reactants, reagents or base, the effect of reaction concentration was studied. A reaction run at lower concentration (0.06 M) (Entry 8) afforded a decreased yield though similar conversion of the nitrobenzene was observed. Increased concentrations (Entries 9&10) gave no significant change in yields, though at 0.4 M (Entry 10) an increased conversion was observed. These results suggest that the poor solubility of reagents/reactants in the reaction mixture was not the cause of the reaction stalling.

With optimised reaction conditions (Table 22, Entry 5) providing a yield of 68% of the aminated product, a screen of tertiary amines was used to test if the reactivity of the aminimine could be tuned through choice of the amine promoter (Table 23). Previous work within the Armstrong Group has shown that both secondary amines and aromatic amines (e.g. pyridine and DMAP) failed to promote the analogous aziridination reaction and as such were not included in the amine screen.
The tertiary amine screen started with $N$-methylpiperidine and $N$-methylpyrrolidine (Table 23, Entries 1&2), both shown to be effective tertiary amine promoters in the analogous aziridination reaction. The use of $N$-methylpiperidine gave a slightly reduced yield of 61% (Entry 1) compared to the use of $N$-methylmorpholine (68% yield, Table 22) though with a slightly decreased regioselectivity. The use of a smaller ring size, $N$-methylpyrrolidine, afforded a lower conversion and a corresponding lower 53% yield with only a slightly reduced selectivity (Table 23, Entry 2). Increasing the bulk of the $N$-substituent ($N$-ethylmorpholine) afforded similar conversion but a decrease in yield (54%, Entry 3) and no significant change in regioselectivity. Changes to the heteroatom at the 1-positon, 1,4-dimethylpiperazine, gave a slight increase in conversion but a significantly lower yield.
(42%, Entry 4), again with no significant change to the regioselectivity. Use of bicyclic tertiary amines gave mixed results with quinuclidine affording a decreased yield (54%, Entry 5) while DABCO (64%, Entry 6) gave a similar yield and conversion to the use of N-methylmorpholine. Use of non-cyclic tertiary amines was not well tolerated with both triethylamine and tributylamine affording significantly lower yields of the aminated product (Entries 7&8). Finally the use of quinine, used in the asymmetric aziridination of electron-deficient alkenes, afforded only moderate conversion and poor yields (20%, Entry 9) of the aminated products.

With the amine screen failing to find a tertiary amine that could give any increased reactivity or significantly altered regioselectivity, the substrate scope of the reaction was then studied.
3.3.4 Substrate Scope for the VNA of Electron-Deficient Aromatics with In Situ Formation of the Hydrazine Salt

A range of electron-deficient heteroaromatics, both those activated by a nitro substituent and those inherently electron-deficient, were tested with the in situ reaction (Table 24).

Table 24 Substrate scope for the VNA of electron-deficient heteroarenes with in situ salt formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conversion of ArNO₂ (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N₂O₂</td>
<td>100</td>
<td>H₂N</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>O-N₂O₂</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>S-N₂O₂</td>
<td>21</td>
<td>S-N₂O₂</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>O₂N</td>
<td>100</td>
<td>O₂N-NH₂</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>N</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>S-N₂O₂</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>N₂S</td>
<td>28</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>O₂N-N₂S</td>
<td>66</td>
<td>O₂N-N₂S-NH₂</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

<sup>b</sup>Isolated yields following column chromatography. <sup>c</sup>Also isolated was 35% of dimerized product <sup>101</sup>. <sup>d</sup>3.0 eq. of NaOH added.
3-Nitropyridine is known to be a highly reactive electrophile in VNS reactions, with a $k_{rel}$ of $7.8 \times 10^4$ observed in competition studies with nitrobenzene in VNS reactions with the anion of chloromethyl phenyl sulfone.\textsuperscript{128} The use of 3-nitropyridine in the VNA amination reaction afforded complete conversion of the nitropyridine starting material (Table 24, Entry 1). However, despite the high conversion only a 14% yield of the desired 2-amino product 99 was isolated, as the substrate proved to be too reactive with the major product being a dimerised product 101 (Figure 9) isolated in 35% yield.

![Figure 9 Major product from the VNA of 3-nitropyridine](image)

A proposed mechanism (Scheme 61) for the formation of the dimer product is via an initial VNS reaction to afford intermediate I followed by an addition into a second nitropyridine affording Meisenheimer complex II. This is followed by either subsequent oxidation to afford the dimer product, in a similar mechanism to ONSH reactions\textsuperscript{85,94} or hydride displacement, as proposed in the mechanism of the Chichibabin reaction.\textsuperscript{91,172}

![Scheme 61 Possible mechanism for the formation of dimer product 101](image)

Both nitrofuran and nitrothiophene have been shown to be efficient electrophiles in VNA reactions. However, the use of these substrates in the VNA reaction with NMM-derived aminimines showed poor reactivity, with nitrofuran failing to afford any of the desired
amination products (Entry 2). The use of 2-nitrothiophene saw slightly increased reactivity but still only minimal conversion (21%) and a corresponding low 17% yield of the 3-aminoproduct 100 was observed (Entry 3). With longer reaction times the reaction was seen to stall in the same way as the reactions with 1-nitronaphthalene and as such failed to afford any significant increase in either conversion or yields. The difference in reactivity between the 2-nitrothiophene and 2-nitrofuran can again be related to the resonance stabilisation energies of the heteroaromatic rings, with the more reactive thiophene having a greater resonance stabilisation energy (29 kcal/mol versus 11 kcal/mol of furan).

Again the use of oxazole (Entry 4) failed to afford any conversion; however, pleasingly the amination of benzoxazole was achieved albeit with only poor yields (31%, Entry 5). The use of both 1-methylimidazole and 1-methylbenzimidazole failed presumably because they were too electron-rich for the VNA reaction to occur (Entries 6&7). The use of the in situ protocol for salt formation was unable to aminate benzothiazole (Entry 8) and only afforded a poor yield with the more electron-deficient 6-nitrosubstrate (5%, Entry 9).

Overall the substrate scope highlights the lower reactivity observed with the use of the in situ salt formation protocol (c.f. reactions with pre-formed iodide salts, Table 14 above). Again, increased reactivity can be achieved with the use of more electron-poor substrates and those substrates better able to stabilise the $\sigma^+\text{-H}$-adducts through increased delocalisation of the negative charge formed (i.e. a higher resonance stabilisation energy), e.g. bicyclic arenes/heteroarenes.

3.3.5 Vicarious Nucleophilic Amination of 1-Nitronaphthalene with Sub-Stoichiometric Loadings of Tertiary Amine

In the mechanism of the VNA reaction with in situ formation of aminimine 18, alongside the aminated electron-deficient arene, NMM is returned as a co-product. With the NMM regenerated during the reaction, a catalytic reaction should be possible utilising sub-stoichiometric quantities of NMM. Similar sub-stoichiometric reactions have been reported in the analogous catalytic aziridination mechanism. The use of sub-stoichiometric loadings of NMM was tested in the VNA of 1-nitronaphthalene (Table 25).
The use of 75 mol% of NMM afforded a similar yield (62%) to the use of stoichiometric amounts (Table 25, Entry 2). However, as the conversion of the starting material was only 69% (less than the mol% loadings of NMM) and suggests that no catalytic turnover of the tertiary amine was occurring. Use of lower loadings of NMM, 50 mol% and 25 mol%, (Entries 3&4) gave much lower conversion and yields of the aminated products. Again, in both cases the conversions were lower than the mol% loading of NMM and as such suggest that no catalytic turnover was occurring.

Test reactions had shown the degradation of the DppONH$_2$ upon prolonged stirring (24 h) with NaOH at room temperature. To test if degradation of the DppONH$_2$ was preventing turnover, a reaction was run using a 50 mol% loading of NMM where the DppONH$_2$ was added in two 0.55 equivalent portions (the second 0.55 eq. was added at 6 hours). However, this portionwise addition of the DppONH$_2$ only gave a 14% yield of the 2-amino 94 with an 84% RSM and as such DppONH$_2$ stability was ruled out as a reason for the lack of turnover.

With DppONH$_2$ stability not a problem, it seems that formation of additional diphenylphosphinic salt 24 is not possible once 1-nitronaphthalene and base have been added to the reaction mixture. As such work into the catalytic reaction was stopped, as
catalytic turnover of the NMM does not seem possible under the current reaction conditions.
3.4 Conclusions and Future Work

Pre-formed hydrazinium iodide salt 16a was shown to be a useful nitrogen source for VNA of electron-deficient arenes (Scheme 62). Good yields were observed for the amination of nitro-substituted aromatic compounds, while the use of unactivated heterocycles (i.e. without additional electron-withdrawing substituents) proceeded with lower yields. One pleasing feature of the developed reaction with NNM iodide 16a was the tolerance for the use of a weaker hydroxide base in place of the stronger alkoxide bases utilised in all other reported VNA reactions.

![Scheme 62](image)

**Scheme 62** Scope of the VNA of electron-deficient aromatics with iodide salt 16a

Despite the use of NMM-derived aminimine proving to be well tolerated as a nitrogen source for VNA reactions, development of a protocol with in situ salt formation proved problematic. Solvent compatibility was a major issue with DMSO, the optimal solvent for the VNA reaction using pre-formed iodide salt 16a, not being compatible with the in situ salt formation. Conversely, CH$_2$Cl$_2$ and MeCN, solvents known to be compatible with the in situ salt formation proved ineffective solvents for the VNA reaction.

Solvent screens found that DMSO was the optimal solvent for use with substrates whose σ$^\text{H}$-adducts were not sufficiently stabilised in CH$_2$Cl$_2$, this lack of stability is proposed to be due to lack of stabilisation of the negative charge of the σ$^\text{H}$-adduct. Whilst CH$_2$Cl$_2$ proved
to be the optimal solvent in reactions were the (hetero)arene electrophile was either highly reactive or better able to stabilise the negative charge of the $\sigma^+\text{-adducts}$. In both reaction systems a trend for increased reaction yields with the use of more electron-poor electrophiles was observed (Scheme 63).

![Scheme 63](image)

**Scheme 63** Substrate scope for the VNA of electron-deficient aromatics with *in situ* salt formation

Finally, attempts at the use of sub-stoichiometric quantities of the tertiary amine, NMM, were unsuccessful with no evidence for catalyst turnover observed and the use of lower catalyst loading (<75 mol%) resulting in significantly reduced yields.

If further work were to be carried out into the NMM/DppONH$_2$ reaction system, a possible area of study would be the development of a system for the synthesis of $N$-substituted nitroanilines. However, as shown in Section 2.3.3 synthesis of $N$-substituted $O$-(diphenylphosphinyl) hydroxylamines can be problematic and as such access to $N$-substituted aminimines through the use of pre-formed hydrazinium iodide salt would be a good starting point. A second area that could be explored would be the use of chiral tertiary amines for the synthesis of C-2 symmetric biaryls through an enantioselective VNA desymmetrization. Thirdly, due to the lack of mechanistic understanding for the change in
reactivity with the switch to the *in-situ* protocol further development of the reaction could benefit from a DOE (design of experiment) based optimisation of reaction conditions.
4 [2,3]-Sigmatropic Rearrangement of Allylic Selenimides: The Synthesis of Enantioenriched Vinyl Glycine Peptides and Peptidomimetics

As previously discussed, the synthesis of C-N bonds is an important aspect of synthetic organic chemistry, particularly in both natural product synthesis and medicinal chemistry, and as such development of new methodologies and expansion of the substrate scope of existing methodologies is highly sought after. Whilst previous chapters have focused on the formation of C-N bonds, utilising O-(diphenylphosphinyl) hydroxylamines as nitrogen transfer agents in both the aziridination of electron-deficient alkenes and the amination of electron-deficient aromatics, this chapter will focus on the synthesis of enantioenriched vinyl glycine derivatives via the formation of C-N bonds through the [2,3]-sigmatropic rearrangement of enantioenriched allylic selenimides.

Section 4.1 will firstly discuss current asymmetric methods available for synthesis of vinyl glycine derivatives and then go on to provide an overview of the use of organoselenium chemistry in the synthesis of allylic amines, with particular focus on the methodology available for the amidation of allylic selenides and their subsequent [2,3]-sigmatropic rearrangements.

Sections 4.2 and 4.3 will then discuss our work into the expansion of the scope of the NCS-mediated amination/[2,3]-sigmatropic rearrangement of allylic selenides. Finally, Section 4.4 will discuss the application of this methodology in the formal synthesis of pharmaceutical ACE inhibitor Perindopril.
4.1 Introduction

Vinyl glycine and its substituted congeners are known to be biologically important structures with roles in a large number of biological pathways. In nature D-vinylglycine is produced by the mushroom Rhodophyllis nidorosus,\textsuperscript{173} while the L-antipode is generated in a number of PLP (pyridoxal phosphate) enzyme active sites,\textsuperscript{174} one example of this is its role as an intermediate in the conversion of homoserine to threonine by threonine synthase.\textsuperscript{175} Studies have also shown α-vinyl amino acids to have promise as potential mechanism-based inhibitors of PLP enzymes.\textsuperscript{176} Examples of PLP enzymes include transamidases, racemases and β- and γ-eliminase which act through an initial α-deprotonation\textsuperscript{177} (Figure 10) or in some cases α-decarboxylation.\textsuperscript{178}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{PLP enzyme mechanisms and α-vinyllic amino acid structure}
\end{figure}

Vinyl glycine and its congeners, particularly those with substitution at the γ-position, are believed to function as PLP inhibitors by migration of the alkene to the conjugated (α,β-unsaturated) position forming a new Michael acceptor that then reacts irreversibly with nucleophilic residues present in the active site. A more detailed overview of the biological activity and biological mechanisms of vinyl glycine and its congeners can be found in the following review and the references therein.\textsuperscript{174}

4.1.1 Asymmetric Methodology for the Synthesis of α-Vinyllic Amino Acids

Four general approaches for the synthesis of optically active α-vinyllic amino acids will be discussed in this introduction, these are; the use of enzymatic and kinetic resolutions, the modification of amino acids, the use of chiral auxiliaries and finally the stereoselective reactions of prochiral starting materials.
4.1.1.1 Enzymatic and Kinetic Resolutions

A number of resolutions, both enzymatic and kinetic, have been applied to vinyl glycine targets. An early example by Helboe utilised bakers yeast for the kinetic resolution of D/L-vinylglycine, obtained through the use of a Strecker reaction, affording D-vinylglycine in 39% yield with 82% ee.\(^{179}\)

Later, Pinhey utilised substilisin in the enzymatic ester hydrolysis of N-acetyl vinylglycine ethyl ester 102 affording both antipodes in high ee, 82% ee for the L-vinylglycine 103 and 93% ee for the returned D-vinylglycine ethyl ester D-103.\(^{180}\) Crout reported a complementary approach via a bi-phasic papain-catalysed enzymatic esterification of N-acetyl vinylglycine derivative 103 giving the corresponding L-ethyl ester 102 in 38% yield with high optical purity (as determined by optical rotation) and the returned D-vinyl glycine 103 in 28% yield.\(^{181}\) Both of these enzymatic resolutions are detailed below in Scheme 64.

![Scheme 64 Enzymatic kinetic resolutions of vinyl glycine derivatives](image)

More recently, Deng\(^{182}\) has reported the synthesis of β,γ-unsaturated α-amino acids using a cinchona alkaloid-catalysed kinetic resolution of α-amino acid N-carboxyhydrides 104, accessing α-vinylc amino acids of both antipodes as either the ethyl ester 105 or the carboxylic acid 106 in up to 99% ee. Relevant α-vinyl examples are shown in Table 26. Studies on similar urethane-protected α-amino acid N-carboxyhydrides (where R\(^1\) is a benzyl group) have shown the rate of reaction to have a first-order dependence on the alcohol (in these studies MeOH was used in place of EtOH), the substrate and the (DHQD)\(_2\)AQN, as well as a 1\(^{st}\) order KIE (\(k_{\text{MeOH}}/k_{\text{MeOD}} = 1.3\)) under pseudo-first-order
These results have led to the suggestion of a general base catalysis mechanism, where ring opening by alcoholyis is the rate-determining step.

Table 26 Cinchona alkaloid-catalysed kinetic resolution of acid anhydride 104

<table>
<thead>
<tr>
<th>R'</th>
<th>105 yield (%)</th>
<th>105 ee (%)</th>
<th>106 yield (%)</th>
<th>106 ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>44</td>
<td>99</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>96</td>
<td>57</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>91</td>
<td>48</td>
<td>95</td>
</tr>
</tbody>
</table>

4.1.1.2 Chemical Manipulation of α-Amino Acids

A second approach to the synthesis of vinyl glycine derivatives is the modification of other α-amino acids, where the use of chiral pool starting materials allows the synthesis of highly enantioenriched α-vinyllic amino acids. The synthesis of vinyl glycine from L-methionine reported by Afzali-Ardakani and Rapoport\textsuperscript{184} is a good example of this and has been the basis of a number of more recent syntheses\textsuperscript{185,186}. Initial Cbz-protection of L-methionine ethyl ester is followed by selective oxidation to afford sulfoxide 107. Subsequent pyrolysis and deprotection afforded L-vinyl glycine with no loss of optical purity (Scheme 65).
Other examples of this general approach include the elimination of selenoxides incorporated into homo-L-serine motifs\textsuperscript{187,188}, a Cu/Pb mediated decarboxylation of L-glutamate\textsuperscript{189} and Peterson olefination of L-serine derivatives\textsuperscript{190}.

4.1.1.3 Use of Chiral Auxiliaries

The use of chiral auxiliaries is also widely reported in the synthesis of α-vinylic amino acids; examples include the first reported synthesis of a γ-substituted vinyl glycine derivative by Schöllkopf\textsuperscript{191}. Schöllkopf reported the use of bis-lactam ether 108 with Hudrlik’s vinyl cation equivalent 109\textsuperscript{192} to access, via silyl intermediate 110, γ-substituted vinyl glycine derivative 111 (Scheme 66). However, Schöllkopf’s methodology is let down by a lack of $E$:$Z$ selectivity, presumably due to the mixture of hydroxysilane diastereomers prior to the elimination step. Kirihata has also utilised bis-lactam ether chiral auxiliary 108 in the synthesis of $E$-APPA (d-(E)-2-amino-5-phosphono-3-pentenoic) acid, a constitutional phosphono-amino acid of plumbemycine, a threonine anti-metabolite\textsuperscript{193}.

![Scheme 66 Schöllkopf’s synthesis of γ-substituted vinyl glycine derivative 111](image)

A wider range of γ-substituted vinyl glycine derivatives were synthesised via the initial bromination of derivative 112 followed by alkynylation to give intermediate 113. However, yields in the subsequent reduction of the cyclic intermediate 113 to the vinyl glycine products 114 were generally low and racemisation proved to be a problem with some substrates (Table 27).\textsuperscript{194}
Beaulieu reported the use of L-serine-derived aldehyde 115 in a Wittig reaction to access a range of Z-vinyl glycine derivatives 116 with good Z-selectivity and high stereoselectivity; however, the synthesis of E-vinyl glycines was not possible with this methodology (Table 28).\(^{195}\)

Petasis reactions have been used to synthesise a wide range of racemic E-\(\alpha\)-vinyl amino acids with generally good yields (54-96%) including both di- and tri-substituted examples and a single example of a quaternary \(\alpha\)-disubstituted amino acid, with a wide range of aryl, benzyl and alkyl N-substituents.\(^{196,197}\) A single enantioenriched example was accessed through the use of optically active benzyl amine 119 which allowed the asymmetric synthesis of vinyl glycine derivative 120 in good yield and stereoselectivity (>99% de) (Scheme 67). However, cleavage of the phenylalaminol chiral auxiliary without loss of the alkene functionality has not been achieved.
More recently, the use of an optically active amino sulfoximine 121, in place of the benzyl derived chiral auxiliary 119, allowed cleavage of the chiral auxiliary using thionyl chloride in methanol, in place of hydrogenation conditions used with the benzyl analogue, and thus access to high enantioenriched vinyl glycine methyl ester 122 (Scheme 68). Also reported was an extended range of boronic acids, with the reaction tolerating the use of both electron-rich and poor E-styrenyl boronic acids and linear E-alkenyl boronic acids, all with moderate-to-good yields and excellent stereoselectivity (93-99% ee), though cleavage of the auxiliary was only reported in the case of (γ-phenyl)vinyl glycine 122.

An approach to the synthesis of optically enriched quaternary vinyl glycine derivatives has been described via the de-conjugative α-alkylation of dehydroamino acids. This approach builds upon reported syntheses of racemic (E)-vinyl glycine derivatives via the double deprotonation of dehydroamino acids followed by α-protonation with complete selectivity for the E-products. The use of a range of alkyl, benzylic and allylic halides, along with an 8-phenyl-menthol chiral auxiliary, allowed access to a wide range of α-substituted (E)-vinyl glycines in generally good yields (35-97%), the lower yields were observed with the use of benzyloxyxymethyl chloride, and high diastereoselectivity (>95:5 d.r.) (Scheme 69). The free amino acid could then be accessed in a single step via cleavage of both the ester and carbamate functionality under basic conditions.
The use of a trans-2-(β-naphthyl)menthol auxiliary has also been described, however, with the use of this chiral auxiliary the regioselectivity of the deconjugative addition (α vs. γ) was found to be highly dependent on the nature of the halide electrophiles used, with only harder electrophiles affording high selectivity for the desired α-deconjugative addition product.

**4.1.1.4 Use of Asymmetric Catalysis**

The synthesis of α-vinylic amino acids via the stereoselective addition of nucleophiles into prochiral starting materials, often imines, is a commonly employed approach allowing access to α-vinylic amino acids in often-excellent enantiomeric excess. The asymmetric Strecker reaction is widely utilised in the synthesis of vinyl glycine derivatives, though this methodology is often hampered by poor selectivity and the harsh conditions required. One approach utilising tripeptide ligand 123 in the Ti-mediated 1,2-conjugate addition of cyanide to imine 124 allowed access to amino nitrile derivatives 125 in good yields and stereoselectivity (Scheme 70). The subsequent hydrolysis of the conjugated aminonitrile 125 (R1 = H, R2 = Me) over three steps allowed access to the corresponding vinyl glycine derivative in good yields and with no loss of ee.
The use of Strecker reactions in the synthesis of $\beta$, $\gamma$-substituted vinyl glycine derivatives

A similar approach using $N$-diphenylphosphinoyl ketoimines in a Gd-catalysed Strecker reaction accessed $\alpha$-disubstituted amino nitriles using difluorocatechol ligand 126, including two $\gamma$-substituted-$\gamma,\beta$-unsubstituted amino nitriles 127 and 128 (Scheme 71). A three-step conversion of vinyl glycine derivative 128 to the corresponding quaternary amino acid 129 was reported, with no loss of enantioenrichment.

Finally, Leckta reports a highly enantioselective synthesis of a range $\alpha$-amino acid derivatives (>99% ee) via a [4+2] cycloaddition/ring opening reaction between $O$-benzoquinone imides and chiral ketene enolates. However, only a single vinyl glycine example (131) is reported, accessed from $O$-benzoquinone imide 132 and a chiral ketene enolate, produced in situ from the reaction of acid chloride 133 and a cinchona alkaloid catalyst 134, providing access to $N$-aryl vinyl glycine derivative 135 with excellent...
stereocontrol (Scheme 72). Subsequent oxidative cleavage of the aryl group using cerium ammonium nitrate afforded vinyl glycine 131 in good yield and with no loss of optical purity.

![Scheme 72](image)

Scheme 72 [4+2] cycloaddition/ring opening as a route to vinyl glycine 131

4.1.2 The Role of Selenium in the Synthesis of Allylic Amines.

The [2,3]-sigmatropic rearrangement of allylic selenoxides and selenimides has long been used to gain access to allylic alcohols and allylic amines respectively. The first example of such was reported by Sharpless in 1972 where the *in situ* oxidation of allylic selenide 136 affords selenoxide 137, which then undergoes a [2,3]-sigmatropic rearrangement to afford selenenate 138 which after hydrolysis affords the allylic alcohol 139 in quantitative yields (Scheme 73).

![Scheme 73](image)

Scheme 73 Oxidation/[2,3]-sigmatropic rearrangement of allylic selenides

Subsequently Reich has reported the use of low temperature NMR experiments to study the thermodynamics and kinetics of the selenoxide-selenoate versus the sulfoxide-sulfenate equilibrium. The results of these studies, using the system shown in Scheme 115.
demonstrated that the [2,3]-sigmatropic rearrangement of allylic selenoxides proceeds faster than the corresponding allylic sulfoxide, due to the lower activation energy for the transformation, and that the equilibrium favours the selenate in the selenium series, whereas in the sulfur series the sulfoxide is favoured. The two, proposed, principal contributors to these observations are the weaker C-Se bond strength (versus C-S) and the smaller degree of multiple bonding in the dipolar Se-O bond (versus S-O).

\[
\begin{align*}
\text{1-S sulfoxide} & \quad \text{1-Se selenoxide} \\
\text{2-S sulfenate} & \quad \text{2-Se selenenate}
\end{align*}
\]

Scheme 74 Substrates used in Reich's studies into the selenoxide-selenoate exchange

### 4.1.3 [2,3]-Sigmatropic Rearrangement of Allylic Selenimides

Sharpless subsequently reported the first examples of the allylic amination of olefins and acetylenes using imido-selenium compound 140, synthesised in situ through the reaction of elemental selenium with Chloramine T. The reaction was proposed to proceed via an ene/[2,3]-sigmatropic rearrangement mechanism, as reported for the analogous oxo-process, whereby amination occurs with the olefinic linkage retaining its original position (Scheme 75).

\[
\begin{align*}
\text{R}^1\text{R}^2\text{R}^3 + \text{TsN} \rightarrow \text{Se} \rightarrow \text{NTs} & \quad \xrightarrow{k_{12}} \quad \text{NHTs} \\
\text{NHTs} & \quad \xrightarrow{k_{21}} \quad \text{R}^1\text{R}^2\text{R}^3
\end{align*}
\]

Scheme 75 First reported Se-mediated direct allylic amination of olefins and acetylenes

Sharpless then further developed this chemistry for allylic amination via amination/[2,3]-sigmatropic rearrangement of allylic selenides. In this first example Chloramine T (TsNCINa) was reacted with 10-(phenylseleno)-β-pinene 141 to access 3-(p-toluenesulfonamido)-β-pinene 142 in 44% yield, via the corresponding selenimide 143 (Scheme 76). The analogous rearrangement of
sulfimides was first reported in 1951. A comprehensive overview of the chemistry of sulfimides can be found in the following reviews.

![Scheme 76](image)

Scheme 76 First example of the amination/[2,3]-sigmatropic rearrangement of allylic selenides

Hopkins subsequently reported that the use of methanol, in place of dichloromethane, as the reaction solvent afforded a cleaner reaction with higher yields, though no direct comparison to the reaction reported by Sharpless was made. Hopkins suggests that the methanol plays an important role in the reaction, acting as an efficient nucleophile aiding the cleavage (methanolysis) of the Se-N bond of the selenamide (Scheme 77).

Hopkins also reported the need for anhydrous conditions in order to obtain optimum yields, with the use of Chloramine T hydrate, in place of the anhydrous Chloramine T, resulting in the yield of N-tosyl allylic amine decreasing to 40%.

![Scheme 77](image)

Scheme 77 Amination/[2,3]-rearrangement of allylic selenides

Despite its efficiency in the conversion of allylic selenides into N-tosyl allylic amines, the use of Chloramine T suffers from a number of drawbacks, the foremost being the hazards associated with handling of anhydrous Chloramine T and a second being the often problematic deprotection of N-tosyl amines. With this in mind Hopkins looked at alternatives to the use of Chloramine T. Initial studies with O-alkyl-N-chloro-N-sodiocarbamates afforded the desired N-carbalkoxy allylic amines in good yield.

However, a second approach that negates the need for the use of potentially unstable sodiocarbamates proved more successful. This approach utilises NCS to access the
chloride intermediate 146, which can then react with the nucleophilic nitrogen source (Scheme 78).\textsuperscript{216} Previously Sharpless had employed similar methodology, in the absence of the nitrogen source, to access the corresponding allylic chloride products.\textsuperscript{210} In the presence of competing nitrogen nucleophiles (Hopkins used \(N\)-Boc or \(N\)-Cbz-protected amines), displacement of the chloride affords the selenimide intermediate 147 which can then undergo a \([2,3]\)-sigmatropic rearrangement giving phenylselenohydroxylamine 148. Subsequent cleavage of the weak Se-N bond, via hydrolysis/methanolysis or displacement by attack of an appropriate nucleophile, affords the allylic amine products in good-to-excellent yields. The ease of Se-N bond cleavage highlights one of the key advantages over the sulfur analogues, where additional steps/reagents are required for cleavage of the equivalent S-N bond.\textsuperscript{217}

![Scheme 78](attachment:scheme_78.png)

**Scheme 78** NCS-mediated synthesis of allylic amines from allylic selenides

Hopkins and co-workers noted that the use of several equivalents of NCS was required in order to obtain the optimum yields; this observation was attributed to NCS reacting with the selenium by-products of the reaction and thus preventing competing side-reactions. Hopkins has since expanded this methodology towards the synthesis of a wide range of allylic amines\textsuperscript{218,219} and applied the methodology to the racemic synthesis of protected amino acids.\textsuperscript{220}

Hopkins also reported a study using optically active nitrogen source 149 in an attempt to obtain diastereoselectivity in the amination/[2,3]-sigmatropic rearrangement using achiral allylic selenides. However, the difference in the relative stabilities of the diastereomeric transition states was not sufficient and only relatively low diastereomeric excesses of 17-
37% (Scheme 79) were observed in the rearrangement products and no further work, by Hopkins or others, has been reported using this approach.

![Scheme 79 Diastereoselective amination/[2,3]-rearrangement of allylic selenides](image)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Ph</td>
<td>62</td>
<td>37</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>H</td>
<td>iPr</td>
<td>62</td>
<td>31</td>
</tr>
<tr>
<td>H</td>
<td>nPr</td>
<td>70</td>
<td>17</td>
</tr>
</tbody>
</table>

Recently, Breder has reported the first examples of the use of catalytic selenium in the oxidative allylic amination of electron-neutral linear E-alkenes (Scheme 80), cyclic alkenes and styrene derivatives using NFSI (N-fluorodibenzenesulfonamide) as both the nitrogen source and terminal oxidant, accessing a range of allylic amines in moderate to good yields.²⁲⁴,²⁲⁵ Though the mechanism has yet to be studied, the authors propose it proceeds via initial reaction between the diphenyl diselenide and NFSI affording cationic adduct I, which can then react via addition across the alkene to afford adduct II with a subsequent elimination step affording the allylic amine products. One key question to be answered when considering the proposed mechanism below is the regiochemistry of the alkene addition step. Assuming an initial electrophilic addition of the nitrogen, followed by the nucleophilic addition of the resultant diphenyl diselenide, the opposite regiochemistry would be expected. However, the authors also suggest that an alternative pathway involving the formation of an aziridinium species instead of adduct II cannot be ruled out and may help account for the observed regioselectivity.
The presence of the electron-withdrawing substituent was found to be vital for the high levels of regioselectivity observed in the elimination step, with the use of linear alkenes without the allylic electron-withdrawing substituent affording complex product mixtures. Substitution at the allylic position of the alkene starting material was expansive with a wide range of electron-withdrawing substituents tolerated, including esters, sulfones, nitriles, phosphonates and ketones. The scope at the alkene terminus was less explored with examples of only simple alkyl and benzyl substitution reported.

Scheme 80 Se-catalysed oxidative synthesis of allylic amines
4.1.4 Asymmetric Synthesis of Allylic Amines via [2,3]-Sigmatropic Rearrangement of Allylic Selenimides.

Assuming that the synthesis of allylic amines via allylic selenimides proceeds via the proposed concerted [2,3]-sigmatropic rearrangement then chirality present at either the C1-carbon or the Se centre of the allylic selenide/selenimides should be transferred to the newly formed C-N bonds.\textsuperscript{208,226,227} As such, allylic selenides with substituents at the alkene terminus (C-3 position), which form stereocentres upon rearrangement, are precursors to optically active allylic amines. This transfer of chirality can be controlled at the selenium centre (Eq. 1), at the C-1 position (Eq. 2) or possibly at both stereocentres (Eq. 3) of the allylic selenimide intermediates formed (Scheme 81). Similar C-1 to C-3 chirality transfer in the [2,3]-sigmatropic rearrangement of optically active selenoxides has been used in synthesis of enantioenriched allylic alcohols,\textsuperscript{228–231} and has been utilised in a range of natural product syntheses.\textsuperscript{232,233}

![Scheme 81 Asymmetric amination/[2,3]-sigmatropic rearrangement of allylic selenides](image)

4.1.4.1 Asymmetric Amination of Allylic Selenides

Direct asymmetric amination (Eq. 1, Scheme 81) via an enantioselective imidation of achiral allylic selenides with the use of chiral catalysts would be an ideal method for the synthesis of allylic amines, as the use of simple achiral allylic selenides would be possible. However, to date most direct asymmetric imidations of selenides reported make use of chiral auxiliaries at the selenium centre, which often require lengthy syntheses. Key
examples of the synthesis of optically active selenimides and their use in the synthesis of allylic amines are discussed below.

Early attempts at the synthesis of optically active selenimides suffered from poor yields and low optical purity\textsuperscript{234} and it was not until 1994 that Kamigata reported the first isolation of optically pure selenimides, via the optical resolution of diastereomeric selenimides.\textsuperscript{235} Kamigata also reported studies into the susceptibility of selenimides to racemisation via pyramidal inversion and found them to be more stable, in this regard, than the corresponding sulfur analogs due to an increased activation energy for the inversion.\textsuperscript{236} The increased stability of the selenimides was proposed to arise from the lower valance shell electron-pair repulsion in the selenium imides and/or the lower electronegativity of selenium causing the electrons in the C-Se to sit a greater distance from the selenium than the electrons in the corresponding sulfur imide. More recent examples of the synthesis of optically active selenides include conversion from chiral selenoxides,\textsuperscript{237,238} with retention of configuration and optical purity, and the use of chiral chromatography to separate optically pure selenimides from racemic mixtures.\textsuperscript{239}

The in-situ stereoselective amination followed by [2,3]-sigmatropic rearrangement of allylic selenides, affording the corresponding optically enriched allylic amines, was reported by Uemura in 1995.\textsuperscript{240} Diastereoselective imidation of allylic selenide 151, containing a cinnamyl 2-(1-dimethylaminoethyl)ferrocenyl chiral auxiliary, with \(N\)-(\(p\)-tolylsulfonyl)imino(phenyl)iodinane afforded the desired allylic amine 152 with 87\% ee (the absolute configuration of the products was never determined) (Scheme 82). However, only the single example was reported and further studies found the use of tellurium to be preferential to selenium, with the use of allylic tellurides affording allylic amine 152 with an increased 93\% ee.\textsuperscript{241}

\begin{center}
\begin{tikzpicture}
  \node (150) at (0,0) {150};
  \node (Ph) at (1,0) {Ph};
  \node (PhI=NTs) at (2,0) {PhI=NTs};
  \node (CH2Cl2) at (2,-0.5) {CH2Cl2};
  \node (0) at (2,-1) {0 °C};
  \node (24) at (2,-1.5) {24 h};
  \node (151) at (3,0) {151};
  \node (PhNTs) at (4,0) {PhNTs};
  \node (MeN) at (5,0) {MeN};
  \node (Me) at (5,-0.5) {Me};
  \node (SeFc*) at (6,0) {SeFc*};
  \node (Se) at (6,-0.5) {Se};
  \node (Fc) at (6,-1) {Fc};
  \node (152) at (7,0) {152};
  \node (52) at (7,-0.5) {52\%};
  \node (87) at (7,-1) {87\% ee};

  \draw[->] (150) -- (Ph); \node at (1.5,-0.25) {PhI=NTs};
  \draw[->] (Ph) -- (CH2Cl2); \node at (2.5,-0.75) {CH2Cl2, 0 °C, 24 h};
  \draw[->] (CH2Cl2) -- (151); \node at (3.5,-0.25) {PhNTs};
  \draw[->] (151) -- (MeN); \node at (5,-0.25) {MeN};
  \draw[->] (MeN) -- (Me); \node at (6,-0.25) {Me};
  \draw[->] (Me) -- (SeFc*); \node at (6.5,-0.25) {SeFc*};
\end{tikzpicture}
\end{center}

\textbf{Scheme 82} Uemura’s use of a chiral ferrenyl auxiliary in the diastereoselective imidation of allylic selenides
Uemura also reported the first enantioselective imidation of racemic allylic selenides using copper(I) triflate and a chiral 4,4-disubstituted bis(oxazoline) ligand (Scheme 83). This methodology only achieved a moderate yield and poor ee (32%) in the synthesis of allylic amine 152 and again only a single example was reported. Uemura reports a similar approach using sulfimides accessing α-vinyl sulfenamides in generally poor-to-moderate yields (30-80%) and low-to-moderate ee (up to 58%); however, subsequent cleavage of the S-N bond required to access allylic amine 151 is not reported.

Uemura also reported the use of selenide-containing optically active oxazoline auxiliaries in the copper-catalysed imidation with N-(p-tolylsulfonyl)imino(phenyl)iodinane, affording selenimides with up to 76% de; however, this chemistry has yet to be applied to substrates capable of undergoing sigmatropic rearrangement.

Koizumi reported a different approach to optically enriched allylic selenimides via the nucleophilic substitution of chloride in chiral allylic chloroselenuranes 152, synthesised in five steps from 2-exo-hydroxy-10-bornyl bromide 153. Nucleophilic substitution at the selenium centre with lithiated carbamates and amides afforded the selenimides 154, that could then undergo the [2,3]-sigmatropic rearrangement to access allylic amines in moderate to good yields (57-86%) and high enantioselectivity (up to 93% ee), though the use of only two allylic selenides is reported (Scheme 84).
Koizumi observed that increased steric bulk on the nitrogen source caused an increased enantioenrichment in the allylic amine products. It was proposed that this increased stereoselectivity arises due to the increased steric bulk causing an increased preference for an endo-transition state (where the lone pair sits in the endo position of the 5-membered envelope transition state), minimising the interactions between the R¹ and R² substituents (Scheme 85). Koizumi has subsequently utilised the same bornyl chiral auxiliaries in the synthesis of enantioenriched homoallylic selenides via [2,3]-sigmatropic rearrangement of selenonium ylides.²⁴⁶

Currently the moderate yields, generally low optical purities and limited substrate scope reported for the synthesis of allylic amines via the asymmetric amination of allylic selenides limits the usefulness of this methodology. Furthermore, where higher ee were
observed the use of chiral auxiliaries was required, complicating the synthesis of the allylic selenide substrates. As such the use of optically active allylic selenides, with enantioenrichment at the C1 position, currently offers a more attractive route to optically active allylic amines.

4.1.4.2 Synthesis of Optically Active Allylic Selenides and Their Use in the NCS Mediated Amination/[2,3]-Sigmatropic Rearrangement

The synthesis of enantioenriched allylic selenides for the use in the amination/rearrangement reaction (Eq. 2, Scheme 81) has to date proved more successful than the direct asymmetric amination methodology in the synthesis of optically active allylic amines, both in terms of the reported enantioenrichment of the products and the reported substrate scope.

Hopkins reported the first use of enantioenriched allylic selenides in the amination/[2,3]-sigmatropic rearrangement, accessing N-protected optically active amino acid 155 in up to 84% ee (Scheme 86).\textsuperscript{247} The limiting factor in this synthesis was the lack of methodology for accessing highly enantioenriched allylic selenides. Hopkins accessed allylic selenide 156 from the corresponding enantioenriched α-selenoaldehyde 157 which in turn were synthesised from ethyl-(S)-lactate in three steps. Furthermore, the synthesis afforded variable results and inconsistent enantiopurity due to the configurational instability of selenoaldehyde 157.

\[ \text{Scheme 86 Synthesis of N-Cbz amino acids via amination/[2,3]-sigmatropic rearrangement} \]
More recently, Tunge has reported the use of a Pd-catalysed decarboxylative kinetic resolution of selenocarbonate 158 (Scheme 87), to access allylic selenide 159 in up to 96% ee. Use of allylic selenide 159 in the amination/rearrangement reaction with 4-tert-butyl aniline afforded allylic amine 160 with only minor loss of optical purity (92% ee).

Scheme 87 Pd-catalysed decarboxylative kinetic resolution of selenocarbonate 158

Two similar one-pot α-selenylation/olefination methodologies for the synthesis of allylic selenides were developed simultaneously by Armstrong and Posner (Scheme 88). Both methodologies make use of an initial prolinol ether-catalyzed α-selenylation of aldehydes, using N-(phenylseleno)phthalimide (NPSP), as described by Melchiorre, followed by a subsequent olefination step. For the olefination step Armstrong utilised a Horner-Wadsworth-Emmons (HWE) olefination allowing access to a range of di- and tri-substituted E-allylic selenides with up to 97% ee. Use of Ando-modified phosphonates, with phenyl ethers in place of the ethyl ethers ((PhO)2P(O)CH2CO2R), in the HWE reaction also allowed access to Z-allylic selenides with similar levels of stereocontrol. Posner’s methodology employed a Wittig olefination to access a range of di-substituted E-allylic selenides, which were then applied to the synthesis of enantioenriched allylic alcohols and chlorides in up to 97% ee.
Armstrong then employed the enantioenriched tri-substituted allylic selenides in the synthesis of simple enantioenriched α-disubstituted vinyl glycine derivatives, via the NCS-mediated amination/rearrangement with simple carbamates, in moderate-to-good yields (31-81%) and with high retention of optical purity (up to 97% ee) (Scheme 89). It was observed that both the E- and Z-allylic selenides under the amination/rearrangement conditions afforded E-allylic carbamates as the sole products, though with opposite stereochemistry at the newly formed C-N bond. This allows access to both enantiomers of the vinyl glycine products without the need for unnatural proline organocatalysts in the α-selenenation step. Similar selectivity has also been observed in analogous amination/rearrangements of allylic sulfides.²¹⁷

The following transition state models can be used to explain this observed selectivity for the E-isomer. If, as commonly accepted, the reaction proceeds via a concerted [2,3]-sigmatropic rearrangement then the observed selectivity for the E-isomer can be explained, at least partly, by a preference for the bulkier R¹ group to adopt the pseudo-equatorial position in the 5-membered transition state (Scheme 90). This transoid transition state TS1 avoids the destabilising 1,3-allylic interaction between the R¹ and R²
substituents found in the cisoid transition state TS2. The same argument applies to the rearrangement with the Z-allylic selenide, though with the 1,3-allylic strain occurring between the R1 substituent and the ester group at the C-3 position, again giving rise to a preference for the transoid transition state TS3 and as a result the E-isomer as the major product.

![Scheme 90 Explanation of stereocontrol in [2,3]-sigmatropic rearrangement of allylic selenides](image)

When considering the mechanism of the reaction it is apparent that upon the electrophilic chlorination of the selenium, via reaction with the NCS, a second stereocentre is formed. Whilst the stereochemistry at the selenium of the allylic selenimide can play a role in the chirality transfer of the sigmatropic rearrangement (see Section 4.1.4.1), studies into the
stereochemistry of [2,3]-sigmatropic rearrangements have shown that the interactions between the substituents on the Y atom (at the C-1 position, in this case Se) and the C-2/C-3 substituents are generally much weaker than those between the C-1 and C-2/C-3 substituents. As such, where C-1 is a stereocentre the configuration at selenium can be assumed to have a relatively minor influence on the relative energies of the transition states of the [2,3]-sigmatropic rearrangement and as such the C-1 to C-3 chirality transfer. This lack of influence that the chirality at the Se-centre has on the configuration of the rearrangement products also means that any inversion of chirality at the Se-centre will have no significant role on the chirality transfer/stereo-outcome of the reaction.
4.2 Project Aims:

While there are numerous examples of the use of amination/[2,3]-sigmatropic rearrangement of allylic selenides as a route to allylic amines, there are limited examples featuring the use of more complex nitrogen sources, i.e. moving away from the use of simple amine or carbamate substrates. Previous work from the Armstrong group focused on the scope with respect to the allylic selenide, in particular substitution at the C1- and C3-positions. The aim of this project was to expand the scope to include more complex nitrogen sources. More specifically we wished to apply the NCS-mediated amination/rearrangement methodology to the synthesis of a wide range of novel unnatural amino acids, peptides, and peptidomimetic vinyl glycine derivatives. The three product classes chosen as targets were:

- Vinyl glycine peptides, through the use of N-protected amino acid amides at nitrogen source;

- N,N-dicarboxymethylamines, a peptidomimetic motif found in a number of pharmaceuticals, through the use of amino acid esters. This methodology was further tested in the formal synthesis of Perindopril, an on-market ACE inhibitor;

- N-Aryl amino acids, through extension of the substrate scope to a range of N-aromatic/heteroaromatic amines.
4.3 Results and Discussion:

4.3.1 Synthesis of Enantioenriched Allylic Selenides:

For the synthesis of the enantioenriched vinyl glycine products we first required a route to the enantioenriched allylic selenides required for the [2,3]-sigmatropic rearrangement. As described above (Scheme 88), recently both Armstrong and Posner have described one-pot α-selenenation/olefination protocols for synthesising highly enantioenriched allylic selenides. For the purpose of the work described in this thesis the Posner protocol was the method of choice, though only for practical reasons. The methodology developed by Armstrong requires a filtration prior to the HWE step in order to prevent a low yielding olefination step, whereas the use of Wittig conditions developed by Posner circumvents this, allowing for a genuine one-pot protocol.

The Posner conditions were applied to the synthesis of four novel allylic selenides 160-163 with the high levels of enantioselectivity desired (94-96% ee) (Table 29). With the scope of the allylic selenides already explored in the work previously described by the Armstrong group,249 the simple alkyl and benzyl substrates were chosen based on the known stability of similar allylic selenides during the amination/rearrangement reactions and known high levels of enantioselectivity afforded in the α-selenation step. Corresponding racemic samples were synthesised though the use of pyrroloidine in place of the prolinol ether in the initial α-selenation step and were used for HPLC comparison to the enantioenriched products.
We also wished to test the tolerance of Posner’s methodology to the use of α,α-disubstituted phosphoranes, providing a route to tri-substituted allylic selenides. However, attempts at the synthesis of tri-substituted allylic selenide 164 via Posner’s protocol were unsuccessful with significant loss of enantiopurity observed in the allylic selenide product, 164. However, the use of Armstrong’s HWE protocol allowed access to the desired tri-substituted allylic selenide 164 in 95% ee (Scheme 91).

Scheme 91 Asymmetric synthesis of tri-substituted allylic selenide 164

4.3.2 Amination/[2,3]-Sigmatropic Rearrangement Using Amino Acid Amides

With a route to the allylic selenides in place, attention was then turned to the expansion of the substrate scope for the [2,3]-sigmatropic rearrangement reaction. The use of amino acid amides, previously untested as nucleophiles in the NCS-mediated amination/[2,3]-
sigmatropic rearrangement reaction, would allow the synthesis of vinyl glycine peptides (Scheme 92) in an approach complementary to more traditional amide coupling reactions.

Scheme 92 Dipeptide synthesis via NCS-mediated amination/[2,3]-sigmatropic rearrangement of enantioenriched allylic selenides

As discussed above (Section 4.1.4.2), the work of Armstrong made use of benzyl carbamate as the nitrogen source for the amination/rearrangement reaction with a range of tri-substituted allylic selenides to synthesise a number of vinyl glycine derivatives. In this protocol, the nitrogen source (3.0 eq.) and the allylic selenide (1.0 eq.) are first stirred for 30 minutes with trimethyl orthoformate (5.9 eq.) and p-TSA (~1 mg) in dry methanol, removing any residual water from the reaction mixture.

As observed in the work of Hopkins, it is important the reaction mixture is as dry as possible with yields decreasing with an increased water concentration in the reaction mixture. One explanation for this can be found in the ready formation of selenoxide from either the reversible reaction of water molecules with the selenimides, via a relatively stable hydrate intermediate (Scheme 93), or reaction of water with the intermediate-chloro species. The resultant selenoxide can then undergo a [2,3]-sigmatropic rearrangement affording the unwanted allylic alcohol product resulting in a decreased yield of the desired allylic amines. Furthermore, the rapid racemisation of selenoxide, through pyramidal inversion via a proposed hydrate intermediate, is widely reported, leading to a loss of enantiopurity in the selenimide intermediate (Scheme 94). However, this racemisation was not expected to be problematic in our work as the transfer of chirality during the sigmatropic rearrangement is predominantly controlled by the stereochemistry at the C1 position and not the configuration of the Se centre.

Scheme 93 Selenium imide-selenoxide equilibrium
After the reaction mixture has been dried, the reaction mixture is then cooled to 0 °C and DIPEA added before addition of NCS (2 eq.). The reaction is allowed to stir for a further 5 minutes before quenching with 1M HCl (aq.). These conditions required little optimisation for the use of amino acid amides, the only notable changes being the use of the nitrogen source, the amino acid amides, as the limiting reagent, and a required increased reaction time of 20 minutes (following the NCS addition). These optimised conditions were then applied to the synthesis of a range of di-peptide vinyl glycine derivatives (Table 30).

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*Optimisation studies carried out by Dr D.P.G. Emmerson and will not be discussed in any further detail in this thesis.*
Initial results using both Cbz- and Boc-protected proline amino acid amides (Table 30, Entries 1 and 2) both gave a 60% yield of the desired vinyl glycine products. However, the presence of rotameric products prevented accurate determination of the E:Z and diastereomeric ratios by $^1$H NMR analysis.

The use of non-cyclic valine derived amino acid amide 167 gave a yield of 55% and an E:Z ratio of 6:1. Examples of amination/rearrangement reactions with tri-substituted allylic selenides performed previously by the Armstrong group have all have shown either complete or a very strong preference for the formation of the E-product. The reasons for

$^iv$ Reaction performed by Dr D.P.G. Emmerson, for experimental details and data see the following reference.
this observed selectivity lies in the strong preference for a transoid transition state, as shown in Scheme 90 above. The lower E:Z selectivity observed with the use of di-substituted allylic selenide 162, compared to the previously reported use tri-substituted allylic selenides, can be attributed, at least partially, to the reduced steric bulk at the C-3 position of the allylic selenide. This reduced steric bulk reduces the influence of 1,3-allylic strain on the energy difference between the preferred transoid and the cisoid transition states (see Scheme 90 above) and decreases the selectivity for the E-product.

Also visible in the ¹H NMR spectra of the vinyl glycine products were minor peaks due to the presence of small amounts of the minor diastereomer of the E-product. An amination/rearrangement reaction carried out using racemic allylic selenide 162 confirmed that the extra peaks present in the product mixture were a result of the presence of the minor diastereomer of the E-product. (N.B. This approach was repeated for all examples reported in order to confirm that the presence of the additional minor product peaks was a result of the presence of the minor diastereomer of the E-product and not other reaction by/side products.)

Assuming that the [2,3]-sigmatropic rearrangement of allylic selenides proceeds with complete transfer of chirality, as previously observed, ¹⁹⁹,²⁴⁹,²⁵¹,²⁵³ the formation of the minor diastereomeric E-product would be expected to arise from the minor R-enantiomer of the allylic selenide starting material (Scheme 95).

![Scheme 95](image_url)
A second explanation for the formation of the minor diastereomer would be epimerisation at the α-position (R³ substituent in Scheme 95) of the amino acid amide moiety either in the starting material or the product. A possible mechanism for this racemisation of N-Boc/Cbz-protected amino acid is the deprotonation at the α-position and subsequent delocalisation of the negative charge formed (Scheme 96). However, racemisation by this pathway under the reaction conditions is thought to be unlikely with the majority of substrates tested, due to the low acidity of the α-protons of the amino acid amides and the low strength of base employed (DIPEA). A second reported mechanism for the racemisation of N-Boc/Cbz-protected amino acids is, where a suitable leaving group is present, via β-elimination following the initial α-deprotonation. However, due to the substrates testing lacking a suitable leaving group racemisation by this route was unlikely to cause any racemisation under the reaction conditions.

Unfortunately, accurate determination of the diastereomeric ratio was not possible in most vinyl glycine products formed, due to a lack of baseline-resolved peaks in the ¹H NMR spectrum and failure to separate all of the product peaks under a range of chiral HPLC conditions. This problem quantifying the exact d.r. of the vinyl glycine products was encountered with the majority of the examples reported (Tables 30, 32 & 33). However, an approximate estimate of the d.r. could be made, in examples where complete baseline resolution of the ¹H NMR peaks was not possible, via partial integration of partially overlapping multiplet peaks of the two diastereomeric products. While this approach does not allow for accurate quantification of the d.r., it does indicate that no significant epimerisation of the vinyl glycine products was observed in any of the examples reported.
The use of phenylalanine amide 168 (Entry 4) gave a 59% yield with a 7:1 $E:Z$ ratio and, pleasingly in this case, baseline resolution of the $^1$H NMR peaks allowed the d.r. to be accurately determined as 97.5:2.5. Assuming that no epimerisation of the optically pure amino acid amides occurred over the course of the reaction, the lack of significant decrease in enantiomeric purity from the starting material 162 (96% $ee$) during formation of the product 168 (97.5:2.5 d.r.) lends support to the hypothesis that the yield of the minor diastereomer is afforded due to the reaction of the minor enantiomer of the allylic selenide starting material (see Scheme 95 above).

The use of phenyl glycine amide 169 (Entry 5, 69% yield, 7.5:1 $E:Z$) gave a d.r. of 88.5:11.5. In this case the significant epimerisation observed is proposed to arise from epimerisation of the C-Ph bond (in the amino acid amide motif) under the reaction conditions. Literature studies have shown that arylglycine amino acids are readily racemised in the presence of tertiary amine bases through the reversible abstraction of the acidic proton on the $\alpha$-carbon by tertiary amine bases with an observed 50% loss of optical purity of benzyloxy carbonyl-L-phenylglycine p-nitrobenzyl ester after 9 minutes in DMF in the presence of DIPEA (2 eq.).$^{254–256}$

Finally the use of a more sterically hindered gem-dimethyl amino acid amide 170 (Entry 5) afforded a poor yield of 39%. Interestingly the more hindered amino acid amide gave a much increased $E:Z$ (>20:1), suggesting that the substitution on the amino acid amide also plays a significant role in the preference for the transoid versus the cisoid transitions state and the $E:Z$ selectivity observed. This is supported by the observed increased $E:Z$ selectivity observed with increased steric bulk in the $\alpha$-substituent (R group) of the amino acid amides in Entries 3, 5&6.

Next the synthesis of longer peptide chains was studied, utilising di- and tri-peptide amides. The use of dipeptide 177 and tripeptide 178 were well-tolerated allowing access to the corresponding tripeptide 179 and tetrapeptide 120 in moderate yields and with no significant loss of enantioenrichment (Scheme 97).
Studies were then carried out to further expand the scope of amino acid amides to examples where the α-substituent of amino acid amides was not a simple alkyl or aryl substituent, allowing the functional group tolerance of the amination rearrangement to be tested. To test this, serine, tyrosine, tryptophan and azido-lysine amino acid amides, along with commercial available N-Boc-L-Asn-OH, were chosen.

4.3.3 Synthesis of Amino Acid Amides

Serine amino acid amide 181 was synthesised starting from N-Boc-L-Ser-OH, via cyclisation to serine lactone 182\(^{257}\) followed by ring opening with ammonia affording the desired amino acid 181 in an overall 40% yield (Scheme 98).\(^{258}\)

The other amino acid amides selected were accessed via coupling reactions of the corresponding amino acid with aqueous ammonia using EDCI and HOBt in DMF (Table 31).\(^{259}\)

\(^{v}\) Reaction performed by Dr D.P.G. Emmerson, for experimental details and data see the following reference.\(^{323}\)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Acid</th>
<th>Amino Acid Amide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-Boc-L Tyr-OH</td>
<td><img src="183" alt="BocNH-CONH2" /></td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>N-Cbz-L Trp-OH</td>
<td><img src="184" alt="CbzHN-CONH2" /></td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>N-Fmoc-Lys(N$_3$)-OH</td>
<td><img src="185" alt="Fmoc-NH-CONH2" /></td>
<td>63</td>
</tr>
</tbody>
</table>

**Table 31** Synthesis of amino acid amide
4.3.4 Functional Group Tolerance of Amination/[2,3]-Sigmatropic Rearrangement Reaction with Amino Acid Amides

The amino acid amides were then tested in the amination/rearrangement reaction with allylic selenide 162, the results of which are shown below in Table 32.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino Acid Amide</th>
<th>Product</th>
<th>Yield (%)</th>
<th>E:Z</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BocHN CONH₂</td>
<td>186</td>
<td>42</td>
<td>8.5:1</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>2</td>
<td>BocHN CONH₂</td>
<td>187</td>
<td>32</td>
<td>7:1</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td>CbzHN CONH₂</td>
<td>188</td>
<td>48</td>
<td>7.5:1</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>4</td>
<td>Fmoc CONH₂</td>
<td>189</td>
<td>77</td>
<td>4:1</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>5</td>
<td>BocHN CONH₂</td>
<td>-</td>
<td>&lt;1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Of E,Z mixture after column chromatography. *a Determined by ¹H NMR analysis of purified product mixture. *b d.r. of E-isomer. *c Estimated through integration of peaks in partially overlapping multiplets.

Table 32 Functional group tolerance of the amination/rearrangement reaction

Hydroxyl functionality was tolerated, though only moderate yields were obtained with the use of serine-derived amino acid amide 181 affording vinyl glycine 186 in a 42% yield (Table 32, Entry 1) and a still lower yield was afforded with the use of tyrosine-derived
amino acid amide 183 (32% yield, Entry 2). The reason for the decrease in yield with the use of hydroxy functionality is unclear, though perhaps one explanation is the competitive displacement of the chloride from the chloride intermediate 146 (see Scheme 78) preventing full conversion to the selenimide and instead affording a selenium species unable to undergo the [2,3]-sigmatropic rearrangement. The use of tryptophan amino acid amide 184 was also tolerated giving the desired product in a 48% yield (Entry 3). Pleasingly, azido functionality was well tolerated with azido-lysine amide 185 affording the desired product in a good yield (77%, Entry 4).

As with the examples discussed above, low levels of the minor diastereomer of the E-product were observed in all examples. Again, lack of baseline separation of diastereomeric peaks in \(^1\)H NMR analysis and problems with separation of the product peaks via chiral HPLC prevented the accurate quantification of the d.r. However, in all cases partial integration of multiplets in the \(^1\)H NMR spectrum indicated that no significant epimerisation was observed.

The use of Boc-\(\text{N-L-Asn-OH}\) (Entry 5) afforded only trace amounts of the desired products, highlighting the lack of tolerance for carboxylic acid functionality under the amination/rearrangement conditions.

### 4.3.5 Amination/[2,3]-Sigmatropic Rearrangement using Amino Acid Esters

The use of amino acids as the nitrogen source for the [2,3]-sigmatropic rearrangement of allylic selenides would allow access to a range of vinyl glycine derivatives containing the \(N,N\)-dicarboxymethylamine structural motif. This \(N,N\)-dicarboxymethylamine peptidomimetic motif, an analogue of the more readily hydrolysed peptide bond, is found in a number of pharmaceutical products including a family of angiotensin-converting enzyme (ACE) inhibitors (Figure 11). A range of amino acid esters were tested under the amination/rearrangement conditions to validate this methodology as a route to the desired \(N,N\)-dicarboxymethylamine products.
Examples of ACE inhibitors containing $N,N$-dicarboxymethylamine motif

Initial attempts at the amination/rearrangement of allylic selenide 162 with $\text{NH}_2\text{-L-Ala-OBn}$ under the reaction conditions developed for the amino acid amide reactions afforded the desired product (190) in only 33% yield, with 35% of an undesired allylic alcohol side product (191) and a 17% return of allylic selenide 162 (Scheme 99).

Scheme 99 Initial attempt at amination/rearrangement using amino acids

It was thought that perhaps the amine was reacting with the NCS, thus preventing full conversion of the chloride intermediate to the selenimide and resulting in a decreased yield of the desired product with increased formation of the selenoxide, which underwent a [2,3]-sigmatropic rearrangement affording the allylic alcohol product 191. This problem was overcome with a change in the addition order whereby the amino acid was added last, after the NCS addition. Reaction monitoring by TLC indicated complete conversion of the allylic starting material within 2 minutes of the NCS addition and no returned allylic selenide was recovered in the crude product mixture. The change in addition order, with the amino acid amide added 2 minutes after the NCS afforded an improved 72% yield of 190 (Table 33, Entry 1) with less than 5% of allylic alcohol 191.

These improved conditions were then applied to the synthesis of a small range of $N,N$-dicarboxymethylamines (Table 33).
The $E:Z$ ratio for the reaction with the amino acid esters is improved when compared to those of the amino acid amide examples discussed above with essentially complete selectivity for the $E$-product in almost all cases. This selectivity again highlights the influence of the nitrogen source in the $E:Z$ selectivity. For the same reasons as with the use of amino acid amides (discussed above) the diastereomeric ratio could not be accurately determined for the majority of the examples. However, the use of NH$_2$-L-Phg-CO$_2$Me (Entry 2, 60% yield) did allow the diastereomeric ratio to be determined as 96:4, although in this case a slight loss of enantioenrichment was observed, allylic selenide 162 being of 96% ee. As discussed above, the proposed explanation for this is epimerization of the phenylglycine C-Ph bond, though to a lesser extent than in the examples with phenylglycine amino acid amide 169 due to the less acidic nature of the amino acid ester $\alpha$-proton compared to that of the amino acid amide.

Again hydroxyl functionality was tolerated with a serine example (Entry 3) giving a 54% yield, although for this example a lower reaction temperature, -45 °C, was required to
prevent loss of enantiopurity, with reactions run at 0 °C and -20 °C giving similar yields (57% and 55% respectively) but with significant loss of enantioenrichment.

A tri-substituted allylic selenide, $R^1 = \text{Me}$, (Entry 4) was also employed in the reaction, albeit with a poorer yield of 46% (when compared to similar disubstituted examples). Attempts using $\text{NH}_2\text{-L-Asn-CO}_2\text{Bn}$ (Entry 5) afforded none of the desired product with the major product isolated being allylic alcohol 191 in a 22% yield.

4.3.6 Amination/[2,3]-Sigmatropic Rearrangement Using N-Aromatic and N-Heteroaromatic Amines

The last nitrogen source to be tested in the NCS mediated amination/[2,3]-sigmatropic rearrangement was N-aryl amines, in particular N-heteroaromatic amines the use of which is previously unreported with this methodology. This expansion in substrate scope provides a new route for the synthesis of N-aryl amino acids, a motif found in a number of medicinally and biologically important compounds; examples are found in hepatitis C virus replicator inhibitors,\(^{261}\) ACE inhibitors,\(^{262}\) anticoagulant factor Xa inhibitors,\(^{263}\) the GPIIb/IIIa fibrinogen receptor antagonist Lotrafiban\(^{264}\) and compounds with antiulcer activity.\(^{265}\)

Typically N-aryl amino acids are accessed via Ullman-type chemistry,\(^{266-268}\) and while this method is convenient for the synthesis of enantioenriched products it relies upon the availability of the corresponding enantioenriched starting material. While this may be trivial in the case of chiral pool amino acids, the synthesis of unnatural amino acids can often be non-trivial. Furthermore, often harsh conditions are required and while couplings with benzene functionality are commonplace, couplings of amino acids with heteroaromatic substrate are not. A number of alternative methods for the synthesis of enantioenriched N-aryl amino acids starting from pro-chiral starting materials have also been developed, examples include asymmetric Mannich reactions using chiral amino sulfonamide organocatalysis,\(^{269}\) enantioselective aza-Friedel-Crafts reactions\(^ {270}\) and an asymmetric Petasis reaction,\(^{271}\) although none of these examples report the synthesis of N-heteroaromatic products.
As such, the use of \(N\)-aromatic and \(N\)-heteroaromatic amines in the amination/rearrangement methodology would allow access to a range of novel \(N\)-aryl vinyl glycine derivatives including a range of \(N\)-heteroaromatic amino acids for which, currently, there is a lack of examples.

Initial investigations were undertaken using 2-aminothiazole and the results of this optimisation are shown below in Table 34. One key difference that was made to the examples above, using amino acid amides and esters, is that in the examples with \(N\)-(hetero)aryl amines the conditions were optimised for the use of the commercially available amines in excess, in order to limit the amount of the synthetically more valuable enantioenriched allylic selenide required.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. 2-Aminothiazole</th>
<th>Addition Order (^a)</th>
<th>(T_1) (^{\circ}\text{C})</th>
<th>(t_1) (min)</th>
<th>(t_2) (min)</th>
<th>Yield 195 (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>Reverse</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>Normal</td>
<td>0</td>
<td>-</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>Reverse</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>Reverse</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>59</td>
</tr>
<tr>
<td>5(^c)</td>
<td>1.0</td>
<td>Reverse</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>Reverse</td>
<td>0</td>
<td>0.5</td>
<td>10</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>Reverse</td>
<td>0</td>
<td>5</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>Reverse</td>
<td>-20</td>
<td>2</td>
<td>10</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>Reverse</td>
<td>-40</td>
<td>2</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

\(^a\) Addition orders: Reverse = 2-aminothiazole added after NCS, Normal = 2-aminothiazole added at the start of the reaction with \(162\). \(^b\) After flash column chromatography. \(^c\) 1.5 equivalent of \(162\) used.

**Table 34** Optimization of amination/rearrangement reaction using 2-aminothiazole

Initial attempts using the conditions from the amino acid ester examples (Table 33) but with the 2-aminothiazole in excess gave a 60% isolated yield of the desired \(E\)-vinyl glycine product (Table 34, Entry 1) with complete conversion of the allylic selenide starting material. Use of the reaction conditions from the amino acid amide examples, where the
nitrogen source is present in the reaction mixture prior to the addition of the NCS (Entry 2), resulted in a reduced yield of 47%, presumably again caused by the reaction of the amine with the NCS. Changing the equivalents of the thiazole was not beneficial, with a decrease in equivalents reducing the yield (Entry 3) and an increase having no positive effect on the yield (Entry 4). A test reaction with the allylic selenide used in excess gave a reduced yield of 50% (Entry 5), suggesting that despite the amine being added last some reaction with the NCS was still occurring. Changes to the time between the NCS addition, both an increase and decrease in time (Entries 6&7), resulted in a decrease in yield. Finally a decrease in the reaction temperature gave an increase in yield affording the desired allylic amine product 195 in a 73% yield (Entry 8). Further reduction in temperature gave no further improvement in the yield despite an increase in reaction time (Entry 9).

The optimised conditions were then applied to the synthesis of a wide range of enantioenriched vinyl glycine derivatives (Table 35). All examples showed complete selectivity for the E-isomer and highlight the high levels of retention of optical purity afforded by [2,3]-sigmatropic rearrangements (94.5-100% cee).

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>cee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="structure1.png" alt="Amine Structure" /></td>
<td>195</td>
<td>73</td>
<td>89</td>
<td>94.5</td>
</tr>
<tr>
<td>2</td>
<td><img src="structure2.png" alt="Amine Structure" /></td>
<td>196</td>
<td>74</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td><img src="structure3.png" alt="Amine Structure" /></td>
<td>197</td>
<td>82</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td><img src="structure4.png" alt="Amine Structure" /></td>
<td>198</td>
<td>75</td>
<td>94^d</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td><img src="structure5.png" alt="Amine Structure" /></td>
<td>199</td>
<td>61</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td><img src="structure6.png" alt="Amine Structure" /></td>
<td>200</td>
<td>49</td>
<td>93^d</td>
<td>99</td>
</tr>
</tbody>
</table>
As discussed above the optimised conditions for the amination/rearrangement reaction using 2-aminothiazole gave a good yield of 73%; however, there was a slight loss of enantiopurity (Table 35, Entry 1, 89% ee, 94.5% cee). (N.B. Upon scale up (12 mmol) the synthesis of allylic selenide 162 afforded a slightly decreased ee, hence the allylic selenide starting material used for these reactions had a 94% ee.) The use of 2-aminobenzothiazole was similarly high-yielding, affording the desired product in a 74% yield (Entry 2) with complete conservation of the enantiopurity of the starting allylic selenide (100% cee). A more electron-rich ring system, 2-amino-5-methoxybenzothiazole, was found to give an increased yield of 82% (Entry 3).
A number of aniline derivatives were also tested, with aniline itself (Entry 4) giving a yield of 75%. The use of the more electron-rich \( p \)-toluidine in this case gave a slightly decreased yield of 61% (Entry 5) and the use of sterically more hindered \( o \)-toluidine saw further decrease in the yield (49%, Entry 6). The use of electron-rich substrate \( p \)-methoxyaniline afforded a significantly lower 31% yield of the vinyl glycine product (Entry 7). Test reactions showed there to be a significant side reaction occurring between the 4-methoxyaniline and the NCS, accounting for the observed decrease in yield. Decreasing the number of equivalents of the NCS was observed to have a beneficial effect on the observed yields, with the best results (54%) obtained when using 1.1 eq. of NCS, though this was with a 22% return of allylic selenide 162. Reactions run with subsequent addition of extra equivalents of NCS once the reaction had started afforded no improvement upon the 54% yield. The use of a more electron-deficient substrate, \( p \)-nitroaniline, gave an increased yield of 85% (Entry 8). Hydroxy functionality was again tolerated as highlighted by the use of 3-aminobenzyl alcohol (Entry 9, 62% yield).

The scope was then expanded to a range of pyridine examples, with 2-aminopyridine (Entry 10) affording the desired vinyl glycine derivative in a 71% yield. Iodo-, bromo- and nitrile-substitution were also well tolerated, as highlighted in Entries 11-13. The use of pyrazole and benzimidazole amine heterocycles was found to give poor yields with 3-aminopyrazole only affording 26% (Entry 14) and 2-aminobenzimidazole affording 43% yield (Entry 15). Finally, oxazole functionality was well tolerated with ethyl 2-(4-aminophenyl)oxazole-4-carboxylate affording the desired product in 70% yield.

4.3.7 Other studies: Proof of Retention of Configuration in Amination/Rearrangement Reactions

Whilst it is proposed that, by analogy to the corresponding sulfimide rearrangement,\textsuperscript{272} the amination/[2,3]-sigmatropic rearrangement of allylic selenides with amines and carbamates proceeds with complete retention of configuration,\textsuperscript{218,226} no studies have been undertaken to confirm this. We sought to test this hypothesis and provide more evidence for the proposed reaction mechanism. This was achieved through the synthesis of vinyl glycine derivative 211, followed by ozonolysis with a NaBH\(_4\) work up which afforded serine
derivative 212 in 82% ee ([α]D24 -11.7 (c = 1.02, EtOH)) (Scheme 100). Comparison of the observed optical rotation to reported literature values273 (>99% ee, [α]D22 -13.7 (c = 1.03, EtOH)), synthesised from chiral pool L-serine derivatives, show good agreement. This provides evidence for the retention of the configuration, and more support for the proposed amination/[2,3]-sigmatropic rearrangement mechanism.

![Chemical Reaction Diagram](attachment:image.png)

**Scheme 100** Proof of retention of configuration in the [2,3]-sigmatropic rearrangement
4.4 The Use of the Amination/[2,3]-Sigmatropic Rearrangement in the Synthesis of ACE Inhibitor Perindopril

Perindopril is an angiotensin converting enzyme (ACE) inhibitor, containing the \(N,N\)-dicarboxymethylamine motif, currently marketed for the treatment of hypertension, congestive heart failure and coronary artery disease, as well as being taken to help prevent complications following heart attacks and procedures to increase the flow of blood through the heart.\(^{274}\) Perindopril 213 itself is an acid-ester prodrug whose active metabolite perindoprilate is accessed \textit{in vivo} via hydrolysis of the ethyl ester. Perindopril was first synthesised in 1982 via the tert-butyl ester 214 as a single all \(S\)-diastereomer, though the yields were not reported (Scheme 101).\(^{275}\) The 3D structure was later confirmed in 2011, with the report of the first crystal structure.\(^{276}\)

![Scheme 101 First reported synthesis of Perindopril](image)

Various syntheses of Perindopril have been reported, mainly in the patent literature, and a number of key examples can be found in Scheme 102 below. One approach taken is via a key amide bond forming step using perhydroindole esters with a pre-activated L-alanine amino acid as either the oxazolidinedione\(^{277}\) or its sulfur analogue\(^{278}\) (Scheme 102, route \(a\)). Similar routes using amide couplings via either the acid chloride\(^{279}\) or directly from the carboxylic acid\(^{280}\) are also reported (route \(b\)). An alternative approach is via a C(sp\(^3\))-N bond formation step installing the secondary amine motif; examples of this approach include \(S_N2\) displacement using enantiomerically pure \(\alpha\)-halo\(^{281}\) or \(\alpha\)-sulfonyloxy esters\(^{281,282}\) (route \(c\)). Syntheses are also reported making use of a \(S_N2\) displacement
using enantiomerically pure α-propyl amino esters\textsuperscript{263} (route d) and the stereoselective reductive amination using ethyl 2-oxopentanoate (route e).\textsuperscript{275}

\begin{center}
\includegraphics[width=\textwidth]{scheme102}
\end{center}

Scheme 102 Selected examples of literature syntheses of Perindopril

4.4.1 Proposed Route for Perindopril Synthesis

We envisaged that a new step-efficient and highly enantioselective synthesis of Perindopril could be achieved via utilisation of the amination/[2,3]-sigmatropic rearrangement methodology. The initial proposed synthetic route (Scheme 103) starts with protection of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid as the benzyl ester 215. Here a protecting group that can be removed under the same reduction conditions needed to remove the alkene functionality is key to a step-efficient synthesis. Subsequent amide bond formation and deprotection will give amino acid 216. Amination/[2,3]-sigmatropic rearrangement with allylic selenide 163 will give Perindopril precursor 217 with a final hydrogenation/hydrogenolysis reaction allowing both reduction of the double bond and deprotection of the carboxylic acid affording Perindopril in five steps from the commerically available octahydroindole-2-carboxylic acid.

152
NH₂-L-Ala-OBn was used as a test substrate for the key amination/[2,3]-sigmatropic rearrangement step with allylic selenide 163, as there are no examples to date of the amination/[2,3]-rearrangement of an allylic selenide with a methyl substituent in the C1. Pleasingly, under the reaction conditions described above (Table 33) the desired product 218 was isolated in a 62% yield with a 10:1 E:Z ratio. Subsequent Pd-catalysed reduction of the double bond/hydrogenolysis of the benzyl ester afforded N-[(S)-1-carbethoxybutyl]-(S)-alanine (97%, 219), a key intermediate in a number of Perindopril syntheses (Scheme 104).²⁸⁰,²⁸²

**Scheme 103 Proposed synthetic route to Perindopril**

**Scheme 104 Synthesis of N-[(S)-1-carbethoxybutyl]-(S)-alanine 219**

### 4.4.2 Initial Attempts and Undesired Diketopiperazine Formation during Perindopril Synthesis

Initial benzyl protection of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid proceeded smoothly using p-TSA and benzyl alcohol in toluene under Dean-Stark conditions to afford the benzyl ester 215 as the p-TSA salt in a quantitative yield (Scheme 105).
A range of conditions were then tested for the amide coupling with \( N\)-Boc-Ala-OH, described below in Table 36, with the use of a DIPEA/EDCI/HOBt system giving the best results (Entry 4).

Interestingly if the \( p\)-TSA salt 215 was first reacted with NaHCO\(_3\) and then with the zirconium(IV) catalyst, instead of the desired amide coupling product a 69% yield of a diketopiperazine 221 product was observed (Scheme 106), presumably formed via an initial amide bond formation followed by cyclisation aided by the zirconium Lewis acid.

\[
\text{Scheme 105 Protection of \( (2S,3aS,7aS)\)-octahydroindole-2-carboxylic acid as benzyl ester 215}
\]
Deprotection of N-Boc amino acid 220 was achieved via stirring in an 1:4 mixture of TFA:CH₂Cl₂ affording the desired amination/rearrangement precursor 222 as the TFA salt (Scheme 107).

However, when submitted to the amination/rearrangement conditions, TFA salt 222 with allylic selenide 163 failed to give the desired vinyl glycine product and instead afforded a 63% yield of the diketopiperazine product 221 (Scheme 108).

While formation of this diketopiperazine 221 has not been reported in any of the chemical literature, Perindopril itself is known to be relatively chemically unstable with clinical Perindopril administered as either the tert-butyl amine or L-arginine salt and the N-substituted diketopiperazine 223 (Figure 12) is reported to be its major biological degradation product.²⁸⁵

Test reactions stirring the rearrangement precursor 222 with base (DIPEA) in MeOH afforded rapid, complete conversion (< 5 min) of the rearrangement precursor 222 to diketopiperazine 221. Attempts at changing the order of addition, with TFA salt 222 added
at the start of the reaction, DIPEA added after the NCS and changes to the reaction
temperature both increase and decrease all failed to afford any of the desired products. At
this point it seemed unlikely that changes to reaction conditions alone would prevent the
rapid cyclisation and work instead focused on varying the ester-protecting group with the
aim of decreasing the rate of the unwanted cyclisation relative to the rate of amination of
the chloride intermediate, i.e. via the use of a more sterically hindered ester.

It is worth noting that, while not explicitly mentioned in the literature references, it is
perhaps the undesired formation of diketopiperazine 221 that leads to the use of the
unsaturated analogues of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid in many of the
literature examples discussed above (see Scheme 102 and references found in the text).
Use of the unsaturated analogue was discounted as a viable approach for this synthesis
due to the extra steps required for the syntheses of the unsaturated analogue of the
octahydroindole-2-carboxylic acid280 and the increased cost of the starting materials
required, preventing development of an efficient and economical synthesis.

4.4.3 Use of Alternative Ester Protecting Groups

In order to maintain the step-efficiency of the synthesis, a more sterically bulky ester-
protecting group that could still be removed under hydrogenolysis conditions was sought.
With this in mind the bulkier diphenylmethyl ester 224 was prepared from the reaction of
(2S,3aS,7aS)-octahydroindole-2-carboxylic acid with diphenyldiazomethane 225 in 62%
yield. The diphenylmethyl ester was chosen over the more sterically hindered trityl ester,
as it was thought that the acid-labile trityl ester might present a problem during the Boc-
deprotection following the amide coupling step.

Reaction under the optimised amide coupling conditions used above afforded N-Boc
amino acid 226 in a 92% yield. However, attempts to deprotect Boc-protected 226 in 1:4
TFA:CH$_2$Cl$_2$ afforded the diketopiperazine product in 60% yield, with only 38% yield of the
desired deprotected product (Scheme 109). Attempts using anhydrous 2M HCl in ether
gave 27% yield of the desired deprotected product 227 and 51% of the diketopiperazine
221. The use of lower concentrations of acid gave poor conversion of the protected
starting material 226 and still failed to selectively deprotect the amine without subsequent cyclisation.

![Chemical Structure](image)

**Scheme 109** Use of diphenyl methyl protecting group in the Perindopril Synthesis

Whilst not as acid labile as a trityl ester, diphenylmethyl esters are still relatively acid labile and either the acid conditions were aiding the hydrolysis of the diphenylmethyl protecting group, and aiding the formation of the diketopiperazine product, or the diphenylmethyl ester is still not sterically hindered enough to prevent the cyclisation. In an attempt to by-pass the need for acidic de-protection conditions, use of a N-(p-methoxybenzyl) protected aniline for the amide coupling was attempted whereby cleavage of the PMB protecting group, with CAN or DDQ, would by-pass the need for acidic conditions and as such limit the levels of diketopiperazine formation. However, attempts at the amide coupling with diphenylmethylester 224 and N-PMB-Ala-OH under the optimised conditions gave no conversion of the starting materials over 24 hours (Scheme 110). Poor solubility of the N-PMB-Ala-OH was noted and in hindsight it is likely that double protection of the amine functionality would be necessary to facilitate this amide coupling.

![Chemical Structure](image)

**Scheme 110** Attempted synthesis of PMB-protected analogue

At this point it was decided to test the stability of the tert-butyl analogue to the cyclisation. Though this approach adds extra steps to the start of the synthesis it allows the use of N-
Cbz-Ala-OH in the amide coupling step with tert-butyl ester 228 and therefore removed the need for an acidic deprotection step. Synthesis of tert-butyl ester 228 was achieved in 3 steps with a 77% overall yield and subsequent amide coupling under the optimised conditions gave the N-Cbz product 229 in 89% yield. Facile deprotection of Cbz group under hydrogenation conditions afforded the amination/rearrangement precursor 230 in 5 steps with a 72% overall yield without any formation of the unwanted diketopiperazine product (Scheme 111).

The tert-butyl ester was then subjected to the optimised amination/rearrangement conditions using allylic selenide 163 (Scheme 112). Initial attempts at 0 °C afforded the desired amination/rearrangement product 164 in 26% yield with 52% of the undesired diketopiperazine product 221. A lower reaction temperature (-20 °C) afforded an increase in the yield of the desired product 231 (40%, E:Z 4:1), though still in a 1:1 ratio with the undesired diketopiperazine product 221. Further decrease in the reaction temperatures (-40 °C) resulted in a significantly slower reaction with no significant improvement in the yield of the desired product.
Initial attempts at the reduction of the double bond using H₂ 10% Pd/C were unsuccessful with no conversion of the starting material. The use of Pd(OH)₂ and PtO₂ also failed to give any of the desired product and while Raney nickel did allow access to the desired product, yields were variable. Finally the use of a higher pressure of hydrogen, 4 bar, with 10% Pd/C allowed access to the reduced tert-butyl ester analogue of Perindopril 232, thus completing a 7 step formal synthesis of Perindopril with an overall 28% yield and a 96:4 d.r. (determined by ¹H NMR and comparison to the diastereomeric mixture prepared using racemic allylic selenide 163).²⁷⁵
4.5 Conclusions and Future Work

To summarise, an increased scope of nitrogen sources for the NCS-mediated amination/[2,3]-sigmatropic rearrangement of enantioenriched allylic selenides is reported, accessing a wide range of novel, enantioenriched vinyl glycine derivatives (Scheme 113). The three classes of nitrogen sources utilised were; amino acid amides in the first reported synthesis of vinyl glycine dipeptides via this methodology; amino acid esters in the highly diastereoselective synthesis of \( N,N \)-dicarboxymethylamine peptidomimetic products; \( N \)-heteroaromatic amines in the first reported synthesis of highly enantioenriched \( N \)-heteroaryl amino acids via the amination/[2,3]-sigmatropic rearrangement methodology. Generally moderate-to-good yields were obtained with good retention of the optical purity observed throughout; however, some decrease in yield was observed with the use of more hindered substrates.

This methodology was then tested in the synthesis of pharmaceutical ACE inhibitor Perindopril. However, the undesired cyclisation of the rearrangement precursors (230 and its analogues) to diketopiperazine 221 limited both the choice of acid protecting groups and the yield from the key [2,3]-rearrangement step (Scheme 114). Despite this difficulty,

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\( \text{Scheme 113 New substrate scope for the NCS-mediated amination/[2,3]-sigmatropic rearrangement of allylic selenides}^\text{vi} \)

\( ^{\text{vi}} \) Another 8 examples with amino acid amides were performed by Dr D.P.G. Emmerson and can be found in discussion above and the following reference.323
the synthesis of Perindopril was accomplished in 7 steps with an overall 28% yield and 96:4 d.r.

Scheme 114 Summary of Perindopril synthesis via NCS-mediated amination/[2,3]-sigmatropic rearrangement

Despite the difficulties with the diketopiperazine formation in the Perindopril synthesis the work covered in this chapter highlights the versatility of this methodology as a method for accessing highly enantioenriched allylic amines. As such, future work developing the NCS mediated amination/[2,3]-methodology would focus on new target syntheses to test this methodology.

One other area that could be explored is the [2,3]-sigmatropic rearrangement of optically active selenonium ylides allowing access to optically enriched homoallylic selenides (Scheme 115). While Koizumi has reported their synthesis via the bornyl chiral axially methodology, there is, to the best of our knowledge, no reported synthesis of selenonium ylides directly from enantioenriched allylic selenides.
Scheme 115 Possible route to access optically enriched homoallylic selenides from allylic selenides

\[ R_2^1 \text{Se} \rightarrow \text{NCS} \rightarrow \left[ R_2^1 \text{Se} \rightarrow \text{R}_2^2 \text{CO}_2 \text{R}_3^3 \right] \rightarrow \left[ Y \rightarrow \text{SeR}_1 \rightarrow \text{X} \rightarrow \text{R}_2^2 \text{CO}_2 \text{R}_3^3 \right] \]

X and Y = EWG
5 Experimental

5.1 General Procedures

Unless stated otherwise, all non-aqueous reactions were carried out under argon using anhydrous solvents in oven (160°C) or flame dried glassware. Solvents: Anhydrous solvents acetone, MeCN, CHCl₃, 1,4-dioxane, DME, DMF, DMSO and IPA were used as commercially supplied. Anhydrous CH₂Cl₂, THF and toluene were purified using an Innovative Technology INC. PureSolv™ Solvent Purification System. MeOH was dried by refluxing over magnesium and iodine, then distillation and stored for at least 3 days over 3Å molecular sieves prior to use. H₂O was distilled for use in reactions. Reagents: mCPBA was purified by dissolving in CH₂Cl₂ and washing with pH 7.5 phosphate buffer, dried over MgSO₄ and concentrated under reduce pressure. Aldehydes and amine bases were distilled immediately prior to use. Anhydrous NMM was purchased for VNA reactions and used as supplied. NCS was purified by re-crystallisation from toluene prior to use. Commercial organometallic solutions were titrated against salicylhydrazine immediately prior to use. All other reagents were used as commerically supplied unless stated otherwise.

Chromatography: Flash column chromatography, unless stated otherwise, was carried out using silica gel 40-63 µm (VWR Prolabo). Analytical thin layer chromatography (TLC) was carried out using glass back plates pre-coated with silica gel F₂₅₄ and visualised by ultraviolet light and potassium permanganate, anisaldehyde, ceric ammonium nitrate or ninhydrin stains as appropriate.

IR Spectroscopy: Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer by means of a Universal ATR Sampling Accessory. Selected peaks (νmax) are reported in wavenumbers (cm⁻¹).

NMR Spectroscopy: ¹H NMR spectra were recorded at 400 MHz on Bruker AV400 instruments and chemical shifts (δH) are reported in ppm with respect to the residual solvent peak (CDCl₃ (δH = 7.26 ppm), d₆-acetone (δH = 2.05 ppm), d₆-DMSO (δH = 2.50 ppm) and CD₃OD (δH = 3.31 ppm)) and assigned the qualifiers: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants (J) are reported in Hz to the nearest 0.1 Hz. ¹³C NMR spectra were recorded at 100 MHz on Bruker AV400
instruments. Chemical shifts (δC) are reported in ppm referenced with respect to the residual solvent peak (CDCl₃ (δC = 77.0 ppm), d₆-acetone (δC = 29.84 ppm), d₆-DMSO (δC = 39.5 ppm), CD₃OD (49.00)). ³¹P spectra were recorded at 162 MHz on a Bruker AV400 spectrometer. NMR yields are calculated by comparison to an internal standard, either 1,3,5-trimethoxybenzene or dibenzylether. Calibrations were carried out with known quantities of standard and products to ensure accuracy.

Mass Spectrometry: Was carried out using CI+ (NH₃) or EI+ and were recorded using Micromass Platform II or AutoSpecQ instruments. Only molecular ions and fragments from molecular ions are reported.

Melting Points: Melting points were obtained using a Reichert hot plate microscope and are uncorrected.

Optical rotations were recorded on an Optical Activity Ltd. Polarimeter at 589 nm (Na D-line) with a path length of 0.5 dm, concentrations (c) are quoted in g /100 ml and specific rotations, [α]ᵢ°D, are quoted in units of 10⁻¹degcm²g⁻¹.

HPLC analysis was carried out on a modular, multi-wavelength JASCO instrument with 250 mm columns from Daicel Chemical Industries Ltd.
5.2 Experimental Details

5.2.1 Experimental Details for Chapter 2: Use of O-(Diphenylphosphinyl) Hydroxylamines in the Aziridination of Enones and Phenyl Vinyl Sulfones

**N-Boc-O-(diphenylphosphinyl) hydroxylamine, 21**

According to the procedure of Whiting,\(^6\) to a stirred solution of tert-butyl N-hydroxycarbamate (2.5 g, 18.8 mmol) in CH\(_2\)Cl\(_2\) (67 mL) at 0 °C was added triethylamine (3.2 mL, 28.2 mmol) followed by a dropwise addition of a solution of diphenylphosphinic chloride (3.59 mL, 18.8 mmol) in CH\(_2\)Cl\(_2\) (8.5 mL). The reaction was allowed to warm to room temperature and stirred for an additional 3 hours. H\(_2\)O (80 mL) was added and the reaction mixture was extracted into CH\(_2\)Cl\(_2\), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure to afford the title compound as a white solid (6.19 g, 99%); m.p. 173-176 °C (lit.\(^6\) 172-174 °C); \(v_{\text{max}} / \text{cm}^{-1}\) 3077, 2975, 2895, 1750, 1482, 1443, 1366, 1275, 1217, 1158, 1132, 1080; \(\delta_H\) (400 MHz, CDCl\(_3\)) 8.48 (1H, br s, NH), 8.00-7.90 (4H, m, 4 x ArH), 7.59-7.52 (2H, m, 2 x ArH), 7.49-7.41 (4H, m, 4 x ArH), 1.39 (9H, s, C(CH\(_3\))\(_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 155.8, 132.8 (d, \(^4J_{\text{CP}}\) 2.5), 132.4 (d, \(^3J_{\text{CP}}\) 10.1), 128.7 (d, \(^1J_{\text{CP}}\) 135.7), 128.4 (d, \(^2J_{\text{CP}}\) 13.5), 82.9, 27.9; \(\delta_P\) (162 MHz, CDCl\(_3\)) 40.0; m/z (ES+) 334 (100%, [MH]+); HRMS (ES+/TOF) found 334.1206, C\(_{17}\)H\(_{21}\)NO\(_4\)P requires 334.1208. These data are consistent with literature values.\(^6\)

\((E)-6\)-Phenyl-3-hexen-2-one, 22

According to the procedure of Yamazaki,\(^2\) to a stirred solution of 3-phenylpropionaldehyde (395 \(\mu\)L, 3.0 mmol) in THF (10 mL) was added 1-triphenylphosphoranylidene-2-propanone (1.05 g, 3.3 mmol). The reaction mixture was stirred at 60 °C for 6 hours, concentrated under reduced pressure and purified by flash column chromatography (15:1 \(^9\)hexane:EtOAc) affording the title compound as a colourless oil (426.5 mg, 82%); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.35-7.26 (2H, m, 2 x ArH), 7.26-7.15 (3H, m, 3 x ArH), 6.82 (1H, dt, \(J\) 16.0 and 6.8, CH\(_2\)CH=CH), 6.10 (1H, dt, \(J\) 15.9 and 1.5,
CH₂CH=CH₂), 2.85-2.75 (2H, m, PhCH₂), 2.59-2.52 (2H, m, CH₂CH=CH₂), 2.33 (3H, s, CH₃); δC (101 MHz, CDCl₃) 198.5, 147.0, 140.6, 131.7, 128.5, 128.3, 126.2, 34.4, 34.1, 26.9. These data are consistent with literature values.²⁸⁸

(E)-7-Phenylhept-4-en-3-one, 25

Based on the procedure of Yamazaki,²⁸⁸ to a stirred solution of 1-(triphenylphosphanylidene)butan-2-one (400 mg, 1.2 mmol) in THF (3.6 mL) was added hydrocinnamaldehyde (159 µL, 1.2 mmol). The reaction mixture was stirred overnight at 60 °C, concentrated under reduced pressure and purified via flash column chromatography (20:1 n-hexane:EtOAc) affording the title compound as a clear oil (105 mg, 46%); νmax / cm⁻¹ 3064, 3027, 2978, 2937, 1699, 1671, 1455, 1356, 1201, 1124; δH (400 MHz, CDCl₃) 7.33-7.27 (2H, m, 2 x ArH), 7.23-7.15 (3H, m, 3 x ArH), 6.85 (1H, dt, J 15.9 and 6.8, CH₂CH=CH₂), 6.12 (1H, dt, J 15.9 and 1.5, CH₂CH=CH₂), 2.79 (2H, dd, J 8.7 and 6.7, CH₂CH=CH₂), 2.63-2.48 (4H, m, PhCH₂ and CH₂CH₃), 1.09 (3H, t, J 7.8, CH₃); δC (101 MHz, CDCl₃) 201.1, 145.7, 140.7, 130.5, 128.5, 128.3, 126.2, 34.5, 34.1, 33.3, 8.11; m/z (ES⁺) 230 (100%, [MH+MeCN]⁺), 189 (52%, [MH]+); HRMS found 189.1284, C₁₃H₁₇O requires 189.1279.

(4E)-2,2-Dimethyl-7-phenylhept-4-en-3-one, 26

Based on the procedure of Yamazaki,²⁸⁸ to a stirred solution of 3-phenylpropionaldehyde (131 µL, 1. mmol) in THF (3 mL) was added (3,3-dimethyl-1-(triphenylphosphoranylidene)-2-butanone (396 mg, 1.1 mmol). The reaction mixture was stirred overnight at 60 °C, concentrated under reduced pressure and purified via flash column chromatography (9:1 n-hexane:EtOAc) affording two isomeric products (the major E isomer and the minor Z-isomer).

(4E)-2,2-dimethyl-7-phenylhept-4-en-3-one was isolated as a white solid (85.3 mg, 39%); m.p. 31-33 °C; νmax / cm⁻¹ 3062, 3027, 2970, 2930, 2868, 1739, 1688, 1623, 1476, 1454, 1366, 1229, 1217, 1077; δH (400 MHz, CDCl₃) 7.13-7.05 (2H, m, 2 x ArH), 7.03-6.95 (3H,
m, 3 x ArH); 6.78 (1H, dt, J 15.2 and 6.8, CH₂CH=CH), 6.28 (1H, dt, J 15.2 and 1.5, CH₂CH=CH), 2.62-2.56 (2H, m, PhCH₂), 2.39-2.31 (2H, m, CH₂CH=CH), 0.93 (9H, s, C(CH₃)₃); δC (101 MHz, CDCl₃) 204.4, 146.2, 141.0, 128.54, 128.52, 126.2, 125.0, 34.7, 34.4, 26.3, 25.9; m/z (ES+) 217 (100% [MH]+); HRMS (ES+/TOF) found 217.1600; C₁₅H₂₁O requires 217.1592.

(4Z)-2,2-dimethyl-7-phenylhept-4-en-3-one was isolated as a colourless oil (13.0 mg, 6%); νmax / cm⁻¹ 3064, 3027, 2966, 2930, 2868, 1684, 1612, 1479, 1454, 1365, 1074; δH (400 MHz, CDCl₃) 7.32-7.25 (2H, m, 2 x ArH), 7.23-7.15 (3H, m, 3 x ArH), 6.41 (1H, dt, J 11.7 and 1.7, CH₂CH=CH), 6.14 (1H, dt, J 11.6 and 7.3, CH₂CH=CH), 2.94-2.87 (2H, m, CH₂CH=CH), 2.76 (2H, t, J 7.6, PhCH₂), 1.12 (9H, s, C(CH₃)₃); δC (101 MHz, CDCl₃) 206.9, 147.4, 141.5, 128.6, 128.5, 126.0, 123.7, 43.8, 35.3, 34.4, 26.4; m/z (ES+) 217 (100% [MH]+); HRMS (ES+/TOF) found 217.1597; C₁₅H₂₁O requires 217.1592.

(E)-Hept-3-en-2-one, 27

Based on the procedure of Yamazaki, to a stirred solution of 1-(triphenylphosphanylidene)propan-2-one (318 mg, 1.0 mmol) in THF (3 mL) was added butyraldehyde (90 μL, 1.0 mmol). The reaction mixture was stirred overnight at 60 °C, concentrated under reduced pressure and purified via flash column chromatography (20:1 nhexane:EtOAc) affording the title compound as a clear oil (103 mg, 92%); δH (400 MHz, CDCl₃) 6.78 (1H, dt, J 15.9 and 6.9, CH₂CH=CH), 6.05 (1H, dt, J 16.0 and 1.6, CH₂CH=CH), 2.25-2.12 (5H, m, CH₂CH=CH and C(O)CH₃), 1.42 (2H, app. hept., J 7.4, CH₃CH₂), 0.92 (3H, t, J 7.4, CH₃CH₂); δC (101 MHz, CDCl₃) 198.7, 148.3, 131.4, 34.4, 26.8, 21.3 and 13.6. These data are consistent with literature values.

(3E,5E)-6-Phenylhexa-3,5-dien-2-one, 30

Based on the procedure of Yamazaki, to a stirred solution of cinnamaldehyde (126 μL, 1.0 mmol) in THF (3 mL) was added 1-triphenylphosphoranylidene-2-propanone (349 mg, 1.1 mmol). The reaction mixture was stirred overnight at 60 °C, concentrated under
reduced pressure and purified via flash column chromatography (20:1 hexane:EtOAc) affording the title compound as an off-white solid (81.7 mg, 48%); m.p. 67-68 °C (Lit. 67-68 °C); ν\text{max} / cm\(^{-1}\) 3083, 3059, 3032, 3002, 2971, 1740, 1666, 1649, 1614, 1592, 1452, 1360, 1256, 989; δ\(_{\text{H}}\) (400 MHz, CDCl\(_3\)) 7.52-7.44 (2H, m, 2 x ArH), 7.41-7.27 (4H, m, 3 x Ar and 1 x CH), 7.04-6.81 (2H, m, 2 x CH), 6.26 (1H, d, J 15.7, CH), 2.32 (3H, s, CH\(_3\)); δ\(_{\text{C}}\) (101 MHz, CDCl\(_3\)) 198.4, 143.4, 141.2, 135.9, 130.5, 129.2, 128.8, 127.2, 126.6, 27.4. These data are consistent with literature values.

General Procedure A: N-Boc-Aziridination of Enones:

To a stirred solution of N-Boc-O-(diphenylphosphinyl) hydroxylamine (133 mg, 0.4 mmol) in CH\(_2\)Cl\(_2\) (2.3 mL) was added Cs\(_2\)CO\(_3\) (195 mg, 0.6 mmol) and then the enone substrate (0.2 mmol). The reaction mixture was allowed to stir for 40 hours at room temperature and then quenched with NH\(_4\)Cl (sat. aq., 1 mL), extracted into CH\(_2\)Cl\(_2\), dried over Na\(_2\)SO\(_4\) and then concentrated under reduced pressure to afford the crude product mixture which was further purified via flash column chromatography.

(±)tert-Butyl-2-acetyl-3-phenethyl-trans-aziridine-1-carboxylate, 23

Following general procedure A, using (E)-6-Phenyl-3-hexen-2-one (26.11 mg, 0.15 mmol). Purification by flash column chromatography (9:1 hexane:EtOAc) afforded the title compound as a colourless oil (37 mg, 75%); δ\(_{\text{H}}\) (400 MHz, CDCl\(_3\)) 7.32-7.26 (2H, m, 2 x ArH), 7.23-7.16 (3H, m, 3 x ArH), 2.92-2.83 (2H, m, PhCHCH and CH\(_2\)CHCH\(_2\)), 2.74 (1H, dt, J 14.0 and 8.1, PhCHCH\(_2\)), 2.67 (1H, dt, J 6.2 and 2.6, CH\(_2\)CHCH\(_2\)), 2.12 (3H, s, CH\(_3\)), 1.96-2.04 (1H, m, PhCH\(_2\)CHH), 1.67-1.76 (1H, m, PhCH\(_2\)CHH), 1.46 (9H, s, C(CH\(_3\))\(_3\)); δ\(_{\text{C}}\) (101 MHz, CDCl\(_3\)) 202.2, 159.0, 140.6, 128.5, 128.4, 126.1, 81.8, 46.6, 44.9, 33.0, 29.3, 27.9, 27.6. These data are consistent with literature values.
(±)tert-Butyl 2-phenethyl-3-propionyl-trans-aziridine-1-carboxylate, 33

Following the general procedure A, using (E)-7-phenylhept-4-en-3-one (33.0 mg, 0.17 mmol). Purification by flash column chromatography (9:1 n-hexane:EtOAc) afforded the title compound as a colourless oil (27.5 mg, 54%); ν \text{max} / cm^{-1} 3088, 3065, 3026, 2978, 2936, 1724, 1714, 1455, 1368, 1311, 1155; δ_H (400 MHz, CDCl_3) 7.31-7.25 (2H, m, 2 x ArH), 7.22-7.16 (3H, m, 3 x ArH), 2.91-2.81 (2H, m, CH_2CH and PhCH), 2.80-2.65 (2H, m, CH_2CH and PhCH), 2.54-2.31 (2H, m, CH_2CH and PhCH), 1.98 (1H, ddt, J 14.0, 8.2 and 5.7, PhCH_2CH), 1.73 (1H, dtt, J 14.4, 8.2 and 5.7, PhCH_2CH), 1.45 (9H, s, C(CH_3)_3), 1.05 (3H, t, J 7.3, CH_3); δ_C (101 MHz, CDCl_3) 204.7, 159.1, 140.7, 128.5, 128.4, 126.1, 81.6, 46.0, 44.8, 35.9, 33.1, 33.0, 27.9, 7.3; m/z (ES+) 367 (33%, [M+MeCN+Na]^+), 304 (24%, [MH]^+), 289 (28%, [MH-CH_3]^+), 204 (100%, [MH-CO_2^tBu]^+); HRMS (ES+/TOF) found 367.2014, C_{20}H_{28}N_2O_3Na requires 367.1997.

(±)tert-Butyl 2-phenethyl-3-pivaloyl-trans-aziridine-1-carboxylate, 34

Following general procedure A, using (4E)-2,2-dimethyl-7-phenylhept-4-en-3-one (22.2 mg, 0.10 mmol). Purification by flash column chromatography (30:1 n-hexane:EtOAc) afforded the title compound as a colourless oil (8.3 mg, 24%); ν \text{max} / cm^{-1} 2973, 2933, 2870, 1726, 1477, 1455, 1367, 1314, 1257, 1225, 1158; δ_H (400 MHz, CDCl_3) 7.31-7.24 (2H, m, 2 x ArH), 7.22-1.26 (3H, m, 3 x ArH), 3.22 (1H, d, J 2.7, CH_2CH), 2.88-2.73 (2H, m, PhCH_2), 2.70 (1H, dt, J 6.1 and 2.5, CH_2CH), 1.99-1.75 (2H, m, PhCH_2CH), 1.45 (9H, s, C(CH_3)_3), 1.17 (9H, s, C(CH_3)_3); δ_C (101 MHz, CDCl_3) 207.7, 159.3, 140.9, 128.5, 128.4, 126.1, 81.4, 45.3, 43.9, 42.4, 33.4, 32.9, 28.0, 25.4; m/z (ES+) 354 (100% [MNa^+]^+), 232 (63% [MH-CO_2^tBu]^+); HRMS (ES+/TOF) found 354.2047; C_{20}H_{29}NO_3Na requires 254.2045.
(±)**tert-Butyl 2-acetyl-3-propyl-trans-aziridine-1-carboxylate, 35**

Following general procedure A, using (E)-hept-3-en-2-one (27.4 mg, 0.24 mmol). Purification by flash column chromatography (4:1 n-hexane:EtOAc) afforded the title compound as a colourless oil (12.2 mg, 24%); ν\text{max} / cm\textsuperscript{-1} 3006, 2976, 2934, 2875, 1725, 1424, 1368, 1313, 1250, 1153; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 2.97 (1H, d, J 2.7, CHC\textsubscript{CH}), 2.65 (1H, dt, J 5.9 and 2.7, CH\textsubscript{2}CH), 2.26 (3H, s, CO\textsubscript{CH}), 1.61-1.37 (13H, m, includes 1.45 (9H, s, C(CH\textsubscript{3})\textsubscript{3}) and 2x alkyl CH\textsubscript{2}), 0.96 (3H, t, J 7.1, CH\textsubscript{2}CH\textsubscript{3}); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 202.6, 159.1, 81.7, 46.6, 45.3, 33.2, 29.0, 27.9, 20.1, 13.6; m/z (ES+) 291 (17%, [M+MeCN+Na]\textsuperscript{+}), 213 (21%, [MMe\textsubscript{3}]+), 128 (100%, [M-Me\textsubscript{2}CO\textsubscript{t}Bu\textsuperscript{+}]); HRMS (ES+/TOF) found 291.1693, C\textsubscript{14}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3}Na requires 291.1685.

(±)**tert-Butyl 2-benzoyl-3-methyl-trans-aziridine-1-carboxylate, 36**

Following general procedure A, using (E)-1-phenylbut-2-en-1-one (29.2 mg, 0.2 mmol). Purification by flash column chromatography (9:1 n-hexane:EtOAc) afforded the title compound as a pale yellow oil (46.3 mg, 89%); ν\text{max} / cm\textsuperscript{-1} 2978, 2934, 1718, 1678, 1598, 1450, 1367, 1304, 1222, 1150, 1015; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 8.07-7.98 (2H, m, 2x ArH), 7.65-7.55 (1H, m, ArH), 7.53-7.44 (2H, m, 2x ArH), 3.69 (1H, d, J 2.7, C(O)CH), 2.96 (1H, qd, J 5.5 and 2.7, CH\textsubscript{3}CH\textsubscript{2}), 1.43-140 (12H, m, contains 1.42 (9H, s, C(CH\textsubscript{3})\textsubscript{3}) and alkyl CH\textsubscript{3}); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 193.6, 159.5, 136.8, 133.5, 128.7, 128.3, 81.6, 44.3, 41.3, 27.9, 16.8; m/z (ES+) 325 (17%, [M+MeCN+Na]\textsuperscript{+}), 162 (100%, [M-Me\textsubscript{2}CO\textsubscript{t}Bu\textsuperscript{+}]); HRMS (ES+/TOF) found 325.1537 ([M+MeCN+Na]\textsuperscript{+}), C\textsubscript{17}H\textsubscript{22}N\textsubscript{2}O\textsubscript{3}Na requires 325.1535.

(±)**tert-Butyl 2-oxo-7-azabicyclo[4.1.0]heptane-7-carboxylate, 37**

Following general procedure A, using cyclohexenone (14.1 μL, 0.15 mmol). Purification by flash column chromatography (4:1 n-hexane:EtOAc) afforded the title compound as a colourless oil (3.4 mg, 11%); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 3.08 (1H, ddt, J 5.9, 2.4 and 1.2, CHCHCH), 2.89 (1H, d, J 2.4, C(CHCH)), 2.54-2.47 (1H, m, alkyl CH), 2.27-2.21 (1H,
m, alkyl CH), 2.09-1.92 (2H, m, 2 x alkyl CH), 1.83-1.73 (1H, m alkyl CH), 1.69-1.59 (1H, m, alkyl CH), 1.45 (9H, s, C(CH₃)₃); δC (101 MHz, CDCl₃) 204.2, 160.6, 82.2, 43.4, 40.4, 36.8, 27.8, 22.6, 17.3. These data are consistent with literature values.⁵⁴

**Bis(3,5-bis(trifluoromethyl)phenyl)phosphinic chloride, 42**

![Bis(3,5-bis(trifluoromethyl)phenyl)phosphinic chloride](image)

According to the procedure of Spencer,⁶⁹ through a solution of bis(3,5-bis(trifluoromethyl)phenyl)chlorophosphine (1 g, 2.0 mmol) in toluene (10 mL) was bubbled dry oxygen for 5 hours. After this time the reaction mixture was concentrated under reduced pressure to afford the title compound as an off-white solid, which was used without further purification. δH (400 MHz, CDCl₃) 8.37 (2H, br s, 2 x ArH), 8.34 (2H, br s, 2 x ArH), 8.17 (2H, br s, 2 x ArH); δP (162 MHz, CDCl₃) 34.3. These data are consistent with literature values.⁶⁹

**Bis(4-chlorophenyl)phosphine oxide, 47**

![Bis(4-chlorophenyl)phosphine oxide](image)

According to the procedure of Harger,⁷⁰ to a stirred solution to diethyl phosphite (1.28 mL, 10 mmol) in THF (15 mL) under nitrogen at 0 °C was added (4-chlorophenyl)magnesium bromide (1.0 M in THF, 30 mL, 30 mmol). The reaction mixture was stirred for 3 hours at 0 °C then quenched with H₂O (10 mL), diluted with toluene (40 mL) and 6M HCl (aq., 10 mL). The crude mixture was then stirred for a further 30 minutes at room temperature. The organic layer was then separated and washed in sequence with H₂O, NaHCO₃ (sat. aq.) and brine then dried over MgSO₄ and concentrated under reduced pressure. Titration in Et₂O at -18 °C overnight afforded the title compound as a white solid (1.52 g, 56%); m.p. 132-133 °C (Lit.²⁹² 131-133 °C); δH (400 MHz, CDCl₃) 8.07 (1H, d, ¹Jₕₚ 484, PH), 7.66-7.59 (4H, m, 4 x ArH), 7.53-7.47 (4H, m, 4 x ArH); δC (101 MHz, CDCl₃) 139.5 (d, ⁴Jₜₖ 2.9), 132.5 (d, ³Jₜₖ 12.6), 129.5 (d, ²Jₜₖ 13.5), 129.4 (d, ¹Jₜₖ 103.1); δP (162 MHz, CDCl₃) 18.7. These data are consistent with literature values.²⁹³
Bis-(4-chlorophenyl)phosphinic acid, 46

![Chemical Structure](image)

According to the procedure of Harger,\textsuperscript{70} to a solution of bis(4-chlorophenyl)phosphine oxide (1.5 g, 5.53 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (5 mL) was added hydrogen peroxide (30% v/v, 3.5 mL, 5.53 mmol). The reaction mixture was allowed to stir at room temperature for 24 hours. 2M NaOH (aq.) was added until the aqueous layer was pH 14 and the organic layer was separated. The aqueous layer was then acidified using 2M HCl (aq.) and extracted into EtOAc. The combined organic layers were dried over MgSO\textsubscript{4} and concentrated under reduced pressure afforded the title compound as a white crystalline solid (1.2 g, 76%); m.p. 133-135 °C (Lit.\textsuperscript{294} 133-135 °C); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 9.38 (1H, br s, OH), 7.62-7.54 (4H, m, 4 x ArH), 7.35-7.29 (4H, m, 4 x ArH); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 138.8 (d, 4\textsubscript{JCP} 3.6), 132.5 (d, 3\textsubscript{JCP} 11.5), 130.4 (d, 1\textsubscript{JCP} 143.8), 128.8 (d, 2\textsubscript{JCP} 14.1); δ\textsubscript{P} (162 MHz, CDCl\textsubscript{3}) 30.7. These data are consistent with literature values.\textsuperscript{295}

\textit{tert}-Butyl bis(4-chlorophenyl)phosphoryl)oxycarbamate, 45

![Chemical Structure](image)

Based on the procedure of Whiting,\textsuperscript{65} a stirred solution of bis(4-chlorophenyl)phosphinic acid (720 mg, 2.5 mmol) in thionyl chloride (6 mL) under nitrogen was heated to reflux for 2 hours. The reaction mixture was cooled to room temperature and excess thionyl chloride removed under reduced pressure. The crude reaction mixture was then dissolved in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) and cooled to 0 °C, \textit{tert}-butyl hydroxycarbamate (333 mg, 2.5 mmol) and triethylamine (0.52 mL, 3.75 mmol) were added and the reaction mixture allowed to warm to room temperature over 3 hours. H\textsubscript{2}O (90 mL) was then added and the crude reaction mixture extracted into CH\textsubscript{2}Cl\textsubscript{2} (3x), dried over MgSO\textsubscript{4} and concentrated under reduced pressure. Partial re-crystallisation from CH\textsubscript{2}Cl\textsubscript{2} afforded the title compound as a white solid (414 mg, 41%); m.p. decomp. >165 °C; ν\textsubscript{max} / cm\textsuperscript{-1} 3086, 2981, 2906, 1753, 1587, 1474, 1392, 1368, 1252, 1222, 1162, 1086; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 8.24 (1H, br s, NH), 7.92-7.81 (4H, m, 4 x ArH), 7.51-7.40 (4H, m, 4 x ArH), 1.41 (9H, s, C(CH\textsubscript{3})\textsubscript{3}); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3})
155.6, 139.8 (d, \(^4\)\(J_{CP}\) 3.8), 133.7 (d, \(^3\)\(J_{CP}\) 11.1), 129.0 (d, \(^2\)\(J_{CP}\) 14.1), 126.9 (d, \(^1\)\(J_{CP}\) 139.1), 83.4, 27.9; \(\delta_P\) (162 MHz, CDC\(_3\)) 37.8. m/z (ES+) 439 (11%, [(M+MeCN+Na)+4]\(^+\)), 467 (53%, [(M+MeCN+Na)+2]\(^+\)), 465 (100%, [M+MeCN+Na]\(^+\)), 404 (25%, [MH+2]\(^+\)), 402 (30%, [MH]\(^+\)), 349 (7%, [(MH+4)-C\(_4\)H\(_9\)]\(^+\)), 347 ((50%, [(MH+2)-C\(_4\)H\(_9\)]\(^+\)), 345 (80%, [MH-C\(_4\)H\(_9\)]\(^+\));

HRMS (ES+/TOF) found 402.0444, C\(_{17}\)H\(_{19}\)NO\(_4\)\(_35\)Cl\(_2\)P requires 402.0429.

tert-Butyl (bis(4-methoxyphenyl)phosphoryl)oxycarbamate, 48

According to the procedure of Vedejs,\(^{71}\) a solution of bis(4-methoxyphenyl)phosphinic acid (1g, 3.59 mmol) in thionyl chloride (8 mL) under nitrogen was heated to reflux for 2 hours. The reaction mixture was cooled to room temperature and the excess thionyl chloride was removed under reduced pressure. The crude reaction mixture was then re-dissolved in CH\(_2\)Cl\(_2\) (16 mL) and cooled to 0 °C, tert-butyl hydroxycarbamate (0.487g, 3.59 mmol) and triethylamine (0.751 mmol, 5.39 mmol) were added and the reaction mixture was allowed to warm to room temperature and stirred at room temperature for a further 3 hours. The reaction mixture was then diluted with H\(_2\)O (10 mL), the aqueous layer was separated and extracted into CH\(_2\)Cl\(_2\) (3x). The combined organic layers and dried over MgSO\(_4\) and concentrated under reduced pressure. Purification via flash column chromatography (1:1 \(^\text{\textsuperscript{\textregistered}}\)hexane:EtOAc) afforded the title compound as a white crystalline solid (866 mg, 61%); m.p. 60-62 °C; \(\nu_{\max} / \text{cm}^{-1}\) 3101, 2978, 2897, 2839, 1747, 1717, 1597, 1504, 1250, 1128; \(\delta_H\) (400 MHz, CDC\(_3\)) 8.52 (1H, br s, NH), 7.90-7.81 (4H, m 4\(\times\) ArH), 6.98-6.91 (4H, m, 4\(\times\) ArH), 3.83 (6H, s, 2\(\times\) OCH\(_3\)), 1.39 (9H, s, C(CH\(_3\))\(_3\)); \(\delta_C\) (101 MHz, CDC\(_3\)) 163.0, 155.9 (d, \(^4\)\(J_{CP}\) 5.2), 134.0 (d, \(^3\)\(J_{CP}\) 12.0), 120.4 (d, \(^1\)\(J_{CP}\) 143.3), 113.9 (d, \(^2\)\(J_{CP}\) 14.4), 82.6, 55.3, 27.8; \(\delta_P\) (162 MHz, CDC\(_3\)) 40.9; m/z (ES+) 457 (47%, [M+MeCN+Na]\(^+\)), 394 (100%, [MH]\(^+\)), 338 (28%, [MH-C\(_4\)H\(_9\)]\(^+\)); HRMS (ES+/TOF) found 394.1430; C\(_{19}\)H\(_{25}\)NO\(_6\)P requires 394.1420.

N-Hydroxy-4-methylbenzenesulfonamide, 51

According to the procedure of Porcheddu,\(^{296}\) to a stirred solution of hydroxylamine hydrochloride (831 mg, 12.0 mmol) in MeOH:H\(_2\)O (5 mL, 3:2) was added magnesium
oxide (628 mg, 15.6 mmol), then a solution of tosyl chloride (1 g, 5.2 mmol) in THF (34 mL) was added. The reaction mixture was stirred vigorously for 2 hours then filtered through Celite followed by a short pad of silica. The filtrate was then concentrated under reduced pressure to afford the title compound as a white solid (424 mg, 44%); m.p. 152-153 °C (Lit. 153°C); δ_H (400 MHz, d_6-DMSO) 9.55 (1H, d, J 3.2 heteroatom-H), 9.49 (1H, d, J 3.2 heteroatom-H), 7.72 (2H, d, J 8.2, 2x ArH), 7.42 (2H, d, J 8.0, 2x ArH), 2.40 (3H, s CH_3). These data are consistent with literature values.

N-(Diphenylphosphoryl)oxy)-4-methylbenzenesulfonamide, 50

\[ \text{Ph}_2P=O \quad \overset{O}{\text{NHTs}} \]

To a stirred solution of N-hydroxy-4-methylbenzenesulfonamide (395 mg, 2.11 mmol) in CH_2Cl_2 (9 mL) at 0 °C was added triethylamine (324 μL, 2.32 mmol) followed by diphenylphosphinic chloride (690 mg, 2.11 mmol) as a solution in CH_2Cl_2 (1.4 mL). The reaction mixture was allowed to warm to room temperature and stirred for an additional 4 hours. The reaction mixture was then diluted with H_2O (10 mL) and stirred for an additional 30 minutes during which time a thick white slurry was formed. The solid was collected via filtration to afford the title compound as a white solid (590 mg, 72%); m.p. gradual decomp. >200 °C; ν_{max} / cm\(^{-1}\) 2959, 2931, 2817, 2763, 1593, 1442, 1240, 1220, 1173, 1158, 1093; δ_H (400 MHz, d_6-DMSO) 11.2 (1H, d, J 1.9, NH), 7.84-7.72 (6H, m, 6 x ArH), 7.68-7.61 (2H, m, 2 x ArH), 7.58-7.51 (4H, m, 4 x ArH), 7.47-7.42 (2H, m, 2 x ArH), 2.41 (3H, s, CH_3); δ_C (101 MHz, CDCl_3) 144.9, 133.1, 132.9, 131.8 (d, 3J_CP), 129.7, 129.2 (d, 1J_CP), 128.7 (d, 2J_CP 13.0), 128.9, 21.1; δ_P (162 MHz, CDCl_3) 36.9; m/z (ES+) 388 (100%, [MH]^+), 338 (84%); HRMS (ES+/TOF) 388.0764, C_{19}H_{19}NO_4SP requires 388.0772.

Diethyl [(phenylthio)methyl]phosphonate, 52

\[ \text{EtO}_2P=\overset{S}{\text{Ph}} \]

Prepared according to the procedure of Enders, \(^{74}\) a solution of triethyl phosphite (20.5 mL, 120 mmol) and chloromethyl phenyl sulfide (8.0 mL, 60 mmol) was stirred at reflux for 12 hours. The reaction was cooled to room temperature. Excess triethyl phosphite was removed under reduced pressure (1.3 mbar) through short path distillation apparatus and the crude product further purified via fractional distillation at reduced pressure using a 19
cm Vigreux column to afford the title compound as a colourless oil (13.8 mg, 88%); b.p. 178-180 °C at 0.97 mmHg (Lit. 74 130-135 °C at 0.08 mmHg); \(\nu_{max} / \text{cm}^{-1} \) 3459, 2980, 2905, 1582, 1481, 1439, 1392, 1247, 1163, 1049, 1021, 965, 826, 741, 690; \(\delta_{H} \) (400 MHz, CDCl\(_3\)) 7.45 - 7.41 (2H, m, 2 x ArH), 7.31 - 7.27 (2H, m, 2 x ArH), 7.26 - 7.17 (1H, m, ArH), 4.18 - 4.08 (4H, m, 2 x C\(_2\)H\(_2\)CH\(_3\)), 3.19 (2H, d, \(J = 14.0\), CH\(_2\)SPh), 1.29 (6H, t, \(J = 7.1\), 2 x CH\(_2\)CH\(_3\)); \(\delta_{C} \) (101 MHz, CDCl\(_3\)) 135.5 (d, \(2J_{CP} = 5.7\)), 129.6, 129.0, 126.8, 62.7 (d, \(2J_{CP} = 6.5\)), 28.5 (d, \(1J_{CP} = 148.5\)), 16.3 (d, \(2J_{CP} = 6.0\)). These data are consistent with literature values. 74

**Diethyl [(phenylsulfonyl)methyl]phosphonate, 53**

\[
\text{EtO}_2\overset{P}{\text{Ph}}\overset{\text{SO}_2\text{Ph}}{\text{Ph}}
\]

Prepared according to the procedure of Enders, 74 to a stirred solution of diethyl [(phenylthio)methyl]phosphonate (13.8 g, 53 mmol) in a 1:1 mixture of EtOH:EtOAc (70 mL) at 0 °C was added dropwise a solution of oxone (97.7 g, 159 mmol) in H\(_2\)O (400 mL). The reaction mixture was allowed to warm to room temperature and stirred for a further 4 hours, then concentrated under reduced pressure and the crude reaction mixture extracted into CH\(_2\)Cl\(_2\). The organic layers were combined and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc) afforded the title compound as an off-white crystalline solid (14.7 g, 95%); m.p. 48-49 °C (Lit. 74 51 °C); \(\delta_{H} \) (400 MHz, CDCl\(_3\)) 8.02-7.96 (2H, m, 2 x ArH), 7.73-7.63 (1H, m, ArH), 7.62-7.52 (2H, m, 2 x ArH), 4.22-4.09 (4H, m, 2 x CH\(_2\)CH\(_3\)), 3.76 (2H, d, \(J = 16.8\), CH\(_2\)SO\(_2\)Ph), 1.29 (6H, t, \(J = 7.1\), 2 x CH\(_2\)CH\(_3\)); \(\delta_{C} \) (101 MHz, CDCl\(_3\)) 140.0, 134.1, 129.1, 128.4, 63.4 (d, \(J = 6.4\)), 53.8 (d, \(J = 137.5\)), 16.2 (d, \(J = 6.4\)). These data are consistent with literature values. 74

**(E)-Styryl phenyl sulfone, 54**

\[
\text{Ph} = \overset{\text{SO}_2\text{Ph}}{\text{Ph}}
\]

Prepared according on the procedure of Wnuk, 75 to a stirred solution of diethyl [(phenylsulfonyl)methyl]phosphonate (292.0 mg, 1.0 mmol) in dry THF (5 mL) at –78 °C was added dropwise a solution of LiHMDS (1.1 mL, 1.0 M in THF) and the reaction was stirred for a further 20 minutes at -78 °C. Benzaldehyde (112 \(\mu\)L, 1.1 mmol) and then allowed to warm to -40 °C over 2 hours. Glacial acetic acid (0.1 mL) was added and volatiles removed under reduced pressure. The crude reaction mixture was dissolved in

175
EtOAc, washed with NaHCO$_3$ (sat. aq.) then brine and dried over MgSO$_4$. Further purification by flash column chromatography (20:1 $^5$hexane:EtOAc) afforded the title compound as a colourless crystalline solid (212 mg, 86%); m.p. 75-76 °C (Lit$^{299}$ 76 °C); $\delta$$_H$ (400 MHz, CDCl$_3$) 8.00-7.92 (2H, m, 2 x ArH), 7.69 (1H, d, $J$ 15.4, PhCH=CH), 7.66-7.59 (2H, m, 2 x ArH), 7.59-7.53 (2H, m, 2 x ArH), 7.44-7.45 (3H, m, 3 x ArH), 6.86 (1H, d, $J$ 15.5, PhCH=CH); $\delta$$_C$ (101 MHz, CDCl$_3$) 142.3, 140.6, 133.4, 132.4, 131.2, 129.3, 128.6, 128.0 127.7, 127.3. These data are consistent with literature values.$^{299}$

Phenyl ((E)-prop-1-en-1-yl) sulfone, 55

![SO2Ph] Based on the procedure of Wnuk$^75$ to a stirred solution of diethyl [(phenylsulfonyl)methyl]phosphonate (292.0 mg, 1.0 mmol) in dry THF (5 mL) under argon at -78 °C was added dropwise a solution of LiHMDS (1.1 mL, 1.0 M in THF) and the reaction was stirred for a further 20 minutes at -78 °C. Acetaldehyde (61.7 $\mu$L, 1.1 mmol) was added and the reaction mixture allowed to warm to -40 °C over 2 hours. Glacial acetic acid (0.1 mL) was added and volatiles removed under reduced pressure. The crude reaction mixture was dissolved in EtOAc, washed with NaHCO$_3$ (sat. aq.) then brine and dried over MgSO$_4$. Further purification via flash column chromatography (3:1 $^6$hexane:EtOAc) afforded the title compound as a 4.2:1 mix of the E:Z-isomers (136.5 mg, 75%); m.p. 59-60 °C; $\delta$$_H$ (400 MHz, CDCl$_3$) 7.90-7.86 (2H, m, 2 x ArH), 7.61-7.59 (1H, m, ArH), 7.56-7.51 (2H, m, 2 x ArH), 6.98 (1H, dq, $J$ 15.0 and 6.9, CH$_3$CH=CH), 6.35 (1H, dq, $J$ 15.0 and 1.8, CH$_3$CH=CH), 1.92 (3H, dd, $J$ 7.0 and 1.7, CH$_3$); $\delta$$_C$ (101 MHz, CDCl$_3$) 142.5, 140.7, 133.2, 131.8, 129.2, 127.6, 17.3. These data are consistent with literature values.$^{300}$ The following distinct signals were observed for the Z-isomer; $\delta$$_H$ (400 MHz, CDCl$_3$) 7.94-7.91 (2H, m, 2 x ArH), 2.17 (3H, dd, $J$ 6.9 and 1.3, CH$_3$); $\delta$$_C$ (101 MHz, CDCl$_3$) 142.5, 133.3, 113.3, 127.2, 14.1.

(But-2-en-1-ylsulfonyl)benzene, 56

![SO2Ph] According to the procedure of Funk$^76$ to a stirred solution of sodium benzenesulfinate (1.642 g, 10.00 mmol) in DMF (50.0 ml) was added (E)-1-bromobut-2-ene (1.029 ml, 10 mmol). The reaction mixture was stirred at room temperature for 44 hours then quenched
with H₂O (300 mL), extracted into EtOAc (3x), passed through a hydrophobic frit and concentrated under reduced pressure. Further purification via flash column chromatography (4:1 Hexane:EtOAc) afforded the title compound as a colourless oil (1.75 g, E:Z 5:1, 89%); δₜ (400 MHz, CDCl₃) for major E-isomer 7.90-7.83 (2H, m, 2 × ArH), 7.67-7.62 (1H, m, ArH), 7.58-7.52 (2H, m, 2 × ArH), 5.60-5.52 (1H, m, CH₃CH=CH), 5.47-5.38 (1H, m, CH=CHCH₂), 3.73 (2H, m, CH₂); δₓ (101 MHz, CDCl₃) 138.6, 136.5, 133.8, 128.96, 128.46, 117.0, 60.1, 18.1. The following peaks were observed for the minor Z-isomer; δₜ (400 MHz, CDCl₃) 3.86 (2H, m, CH₂), 1.31 (3H, d, J 7.1, CH₃); δₓ (101 MHz, CDCl₃) 129.02, 128.52, 116.2, 154.8, 12.7. These data are consistent with literature values.²⁰¹

(E)-(But-1-en-1-ylsulfonyl)benzene, 57

According to the procedure of Funk,⁷⁶ to a stirred solution of (but-2-en-1-ylsulfonyl)benzene (440 mg, 2.25 mmol) in THF (11 ml) at -78 °C was added dropwise butyllithium (1.6 M in n-hexane, 1.58 ml). The reaction mixture was stirred for at -78 °C for 10 minutes before the dropwise addition of chlorotrimethylsilane (0.855 ml, 6.75 mmol). After an additional 30 minutes at -78 °C the reaction mixture was stirred 0 °C for 15 minutes followed by the addition of H₂O (10 mL). CH₂Cl₂ (15 mL) was added and the aqueous layer separated and extracted into CH₂Cl₂ (3x), the combined organic layers were passed through a hydrophobic frit and concentrated under reduced pressure. The crude reaction mixture was then used in the next step without further purification.

The crude reaction mixture was dissolved in toluene (0.9 mL) and trifluoromethanesulfonic acid (198 μL, 2.243 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature overnight, cooled to 0 °C and quenched with H₂O (10 mL) then NaHCO₃ (10 mL, sat. aq.). The reaction mixture was extracted into EtOAc (3x), the combined organic layers were then passed through a hydrophobic frit and concentrated under reduced pressure. Purification via flash column chromatography (20:1 n-Hexane:EtOAc) afforded the title compound as a single isomer, clear oil (291.1 mg, 60% over two steps); δₜ (400 MHz, CDCl₃) 7.89-7.84 (2H, m, 2 × ArH), 7.63-7.57 (1H, m, ArH), 7.55-7.49 (2H, m, 2 × ArH), 7.03 (1H, dt, J 15.1 and 6.2, CH₂CH=CH), 6.30 (1H, dt, J 15.1 and 1.7, CH₂CH=CH), 2.26 (2H, qdd, J 7.4, 6.1 and 1.7, CH₂), 1.05 (3H, t, J 7.4, CH₃); δₓ
(101 MHz, CDCl₃) 148.4, 140.7, 133.2, 129.6, 129.2, 127.5, 24.7, 11.6. These data are consistent with literature values.³⁰²

1-Methyl-4-(vinylsulfonyl)benzene, 58

![1-Methyl-4-(vinylsulfonyl)benzene](image)

According to the procedure of Kumar,⁷⁷ to a stirred solution of 2-(p-tolylsulfonyl)ethanol (1 g, 5 mmol) in CH₂Cl₂ (15 mL) at 0 °C was added first triethylamine (1.74 mL, 12.5 mmol) then methanesulfonyl chloride (0.46 mL, 6.0 mmol). The reaction mixture was stirred for a further 20 minutes and then concentrated under reduced pressure, re-dissolved in CH₂Cl₂, washed twice with NH₄Cl (sat. aq.), dried over Na₂SO₄ and concentrated under reduced pressure. Further purification via flash column chromatography (1:1 n-hexane:EtOAc) afforded the title compound as a crystalline white solid (700 mg, 77%); m.p. 65-66 °C (Lit.³⁰³ 65-66 °C); δH (400 MHz, CDCl₃) 7.78 (2H, d, J 8.2, 2 x ArH), 7.35 (2H, d, J 8.3, 2 x ArH), 6.65 (1H, dd, J 16.6 and 9.8, H₂C=CH), 6.42 (1H, d, J 16.6, HHC=CH), 6.00 (1H, d, J 9.8, HHC=CH), 2.44 (3H, s, CH₃). These data are consistent with literature values.⁷⁷

1-Fluoro-4-(vinylsulfonyl)benzene, 59

![1-Fluoro-4-(vinylsulfonyl)benzene](image)

Based on the procedure of Stirling,⁷⁸ to a stirred solution of 1-((2-chloroethyl)sulfonyl)-4-fluorobenzene (1 g, 4.5 mmol) in dry THF (100 mL) was added dropwise triethylamine (0.7 mL, 5.02 mmol). The reaction mixture was stirred at room temperature for a further 24 hours after which the reaction mixture was filtered, washed with toluene (2x 10 mL). The filtrate was washed with 1M HCl (aq.), NaHCO₃ (sat. aq.) then brine and the organic layer dried over Na₂SO₄ and concentrated under reduced pressure. Purification via flash column chromatography (4:1 n-hexane:EtOAc) afforded the title compound as a clear oil (768 mg, 93%); νmax / cm⁻¹ 3106, 3047, 1590, 1493, 1316, 1291, 1284, 1142, 1086, 976; δH (400 MHz, CDCl₃) 7.94-7.89 (2H, m, 2 x ArH), 7.26-7.20 (2H, m, 2 x ArH), 6.65 (1H, dd, J 16.5 and 9.7, H₂C=CH), 6.46 (1H, d, J 16.5, HHC=CH), 6.05 (1H, d, J 9.7, HHC=CH); δC (101 MHz, CDCl₃) 168.7 (d, Jₐₙ 256.3), 138.3, 135.6 (d, Jₐₙ 3.2), 130.7 (d, Jₐₙ 9.6), 127.9,
116.6 (d, $^2J_{CF}$ 22.6); $\delta$F (376.5 MHz, CDCl$_3$) 100.5; m/z (Cl+) 204 (100%, [M+NH$_4$]+); HRMS (Cl+) found 204.0502, C$_8$H$_{11}$NO$_2$FS requires 204.0495.

(Ethylsulfonyl)ethene, 60

\[
\begin{align*}
\text{SO}_2\text{Et} \\
\end{align*}
\]

To a stirred solution of mCPBA (380 mg, 2.2 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 °C was added dropwise ethylvinyl sulfone (100 μL, 1.0 mmol). The reaction mixture was warmed to room temperature and allowed to stir overnight. The reaction mixture was then diluted with CH$_2$Cl$_2$ (20 mL), washed with NaHCO$_3$ (sat. aq.), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Further purification via flash column chromatography (1:1 
$^6$hexane:EtOAc) afforded the title compound as a clear oil (131 mg, 98%); $\nu_{max}$ / cm$^{-1}$ 3061, 2922, 2852, 1457, 1385, 1305, 1276, 1126, 978. $\delta$H (400 MHz, CDCl$_3$) 6.62 (1H, dd, $^2J$ 16.6 and 9.8, H$_2$C=CH), 6.46 (1H, d, $^2J$ 16.6, HHC=CH), 6.19 (1H, d, $^2J$ 9.8, HHC=CH), 3.01 (2H, q, $^2J$ 7.4, CH$_2$), 1.35 (3H, t, $^2J$ 7.5, CH$_3$); $\delta$C (101 MHz, CDCl$_3$) 135.4, 130.8, 48.5, 7.0. m/z (Cl+) 138 (100%, [M+NH$_4$]+); HRMS (Cl+) found 138.0584, C$_4$H$_{12}$NO$_2$S requires 138.0589.

**General Procedure B: N-Boc-Aziridination of Vinyl Sulfones:**

To a stirred solution of the vinyl sulfone (0.2 mmol) in THF (2 mL) was added the N-Boc-O-(diphenylphosphinyl) hydroxylamine (133 mg, 0.4 mmol) and Cs$_2$CO$_3$ (195 mg, 0.6 mmol). The reaction mixture was allowed to stir for 4 hours at room temperature before quenching with NH$_4$HCl (sat. aq., 1 mL), extracted into CH$_2$Cl$_2$, dried over Na$_2$SO$_4$ and then concentrated under reduced pressure to afford the crude product mixture which was further purified via flash column chromatography.

($\pm$)tert-Butyl 2- (phenylsulfonyl)aziridine-1- carboxylate, 38

According to general procedure B, using phenyl vinyl sulfone (0.2 mmol). Purification via flash column chromatography (9:1 $^6$hexane:EtOAc) afforded the title compound as a white crystalline solid (36 mg, 64%); m.p. 119-121 °C; $\nu_{max}$ / cm$^{-1}$ 3096, 3003, 2981, 2935, 1729, 1369, 1323, 1280, 1145, 1021, 845; $\delta$H (400 MHz, CDCl$_3$) 8.00-7.95 (2H, m, 2 x ArH),
7.72-7.65 (1H, m, ArH), 7.61-7.55 (2H, m, 2 x ArH), 3.70 (1H, dd, $J_{5.7}$ and $J_{3.0}$, CHSO$_2$Ph), 2.87 (1H, d, $J_{2.9}$, CHCHSO$_2$Ph), 2.66 (1H, d, $J_{5.8}$, CHCHSO$_2$Ph), 1.25 (9H, s, C(CH$_3$)$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 158.5, 137.5, 134.1, 129.1, 128.8, 82.9, 51.0, 30.0, 27.5; m/z (ES+) 347 (100%, [M+MeCN+Na$^+$]), 266 (47%, [MH-$C_4$H$_9$]$^+$); HRMS (ES+/TOF) found 347.1049, for $C_{15}H_{20}N_2O_3$NaS requires 347.1041.

**tert-Butyl ((diphenylphosphoryl)oxy)(2-(phenylsulfonyl)ethyl)carbamate, 39**

Also, isolated from the crude product mixture of the reaction of phenyl vinyl sulfone and DppONHBoc affording tert-butyl 2-(phenylsulfonyl)aziridine-1-carboxylate (described above) was tert-butyl ((diphenylphosphoryl)oxy)(2-(phenylsulfonyl)ethyl)carbamate. The side product was unstable on SiO$_2$, but could be isolated with a significant loss of material using preparative HPLC; Sunfire C18 column (150mm x 30mm i.d. 5µm packing diameter). gradient 50:50 to 99:1 of 0.1% v/v solution of formic acid in H$_2$O: 0.1% v/v solution of formic acid in acetonitrile, flow rate 40 mLmin$^{-1}$, retention time 13.5 min.

When the reaction was carried out on a 0.5 mmol scale, the title compound was isolated via preparative HPLC as a white foam (45 mg, 18%); $\nu_{max}$ / cm$^{-1}$ 3062, 2983, 2936, 1748, 1717, 1441, 1307, 1289, 1233, 1148, 1131; $\delta_H$ (400 MHz, CDCl$_3$) 7.92-7.90 (2H, m, 2 x ArH), 7.87-7.82 (4H, m, 4 x ArH), 7.64 (1H, m ArH), 7.57-7.51 (4H, m, 4 x ArH), 7.47-7.41 (4H, m, 4 x ArH), 4.07 (2H, t, $J_{7.4}$, alkyl CH$_2$), 3.59 (2H, t, $J_{7.4}$, alkyl CH$_2$), 1.27 (9H, s, C(CH$_3$)$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 155.7 (d, $^3J_{CP}$ 3.1), 139.1, 134.0, 133.0 (d, $^4J_{CP}$ 2.8), 132.6 (d, $^3J_{CP}$ 10.3), 129.4, 128.6 (d, $^1J_{CP}$ 134.5), 128.5 (d, $^2J_{CP}$ 13.4), 128.1, 83.9, 52.4, 48.2, 27.8; m/z (ES+) 524 (45%, [MNa$^+$]), 502 (100%, [MH$^+$]), 446 (30%, [MH-$C_4$H$_9$]$^+$); HRMS (ES+/TOF) found 502.1450, $C_{25}H_{29}NO_6$SP requires 502.1453.
(±)tert-Butyl-2-(ethyloxysulfonyl)aziridine-1-carboxylate, 62

According to the general procedure B, using ethyl vinyl sulfone (0.15 mmol). Purification via flash column chromatography (1:1 n-hexane:EtOAc) afforded the title compound as a clear oil (8.3 mg, 24%); \( \nu_{\text{max}} / \text{cm}^{-1} \) 2980, 2937, 2886, 1729, 1370, 1320, 1280, 1258, 1139, 1115; \( \delta_H \) (400 MHz, CDCl\(_3\)) 3.74 (1H, dd, J 5.9 and 2.9, HHCH\(_{\text{T}}\)), 3.34-3.12 (2H, m, \( \text{CH}_2 \)), 2.87 (1H, d, J 2.9, HHCH\(_{\text{T}}\)), 2.67 (1H, d, J 5.9, HHCH\(_{\text{T}}\)), 1.53 (3H, t, J 7.5, \( \text{CH}_3 \)), 1.50 (9H, s, C(CH\(_3\))\(_3\)); \( \delta_C \) (101 MHz, CDCl\(_3\)) 158.7, 83.6, 47.5, 46.7, 21.0, 27.8, 6.5; m/z (Cl+) 253 (33%, [M+N\(_4\)H\(_4\)])\(^+\), 197 (47%, [M+NH\(_4\)-C\(_4\)H\(_9\)]\(^+\)), 153 (65%, [M+NH\(_4\)-CO\(_2\)\(_\text{tBu}\)]\(^+\)), 136 (100%, [M-CO\(_2\)\(_\text{tBu}\)]\(^+\)); HRMS (Cl+) found 253.1223, C\(_9\)H\(_{21}\)N\(_2\)O\(_4\)S requires 253.1222.

(±)tert-Butyl 2-tosylaziridine-1-carboxylate, 63

According to general procedure B, using 1-methyl-4-(vinylsulfonyl)benzene (0.15 mmol). Purification via flash column chromatography (4:1 n-hexane:EtOAc) afforded the title compound as a clear oil (21.9 mg, 49%); \( \nu_{\text{max}} / \text{cm}^{-1} \) 2980, 2943, 2852, 1734, 1326, 1285, 1152, 1086; \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.87-7.82 (2H, m, 2 x ArH), 7.39-7.35 (2H, m, 2 x ArH), 3.68 (1H, dd, J 5.8 and 2.9 HHCH\(_{\text{T}}\)), 2.85 (1H, d, J 2.9, HHCH\(_{\text{T}}\)), 2.64 (1H, d, J 5.8, HHCH\(_{\text{T}}\)), 2.45 (3H, s, \( \text{CH}_3 \)), 1.28 (9H, s, C(CH\(_3\))\(_3\)); \( \delta_C \) (101 MHz, CDCl\(_3\)) 158.6, 145.2, 134.5, 129.7, 128.8, 82.9, 51.1, 30.1, 27.6, 21.7; m/z (ES+) 361 (100%, [M+MeCN+Na]+), 336 (27%, [M+K]+), 315 (47%, [M+NH\(_4\)]\(^+\)), 239 (54%, [MH-C\(_4\)H\(_9\)]\(^+\)); HRMS (ES+/TOF) found 361.1197, C\(_{16}\)H\(_{22}\)N\(_2\)O\(_4\)Na requires 361.1198.

(±)tert-Butyl 2-((4-fluorophenyl)sulfonyl)aziridine-1-carboxylate, 64

According to general procedure B, using 1-fluoro-4-(vinylsulfonyl)benzene (0.15 mmol). Purification via flash column chromatography (4:1 n-hexane:EtOAc) afforded the title compound as a clear oil (27.1 mg, 46%); \( \nu_{\text{max}} / \text{cm}^{-1} \) 3107, 2981, 2929, 1733, 1592, 1493, 1330, 1291, 1152, 1086; \( \delta_H \) (400 MHz, CDCl\(_3\)) 8.03-7.92 (2H, m, 2 x ArH), 7.30-7.21 (2H, m, 2 x ArH), 3.69 (1H, dd, J 5.7 and 2.9, HHCH\(_{\text{T}}\)), 2.88 (1H, d, J 2.9, HHCH\(_{\text{T}}\)), 2.68 (1H,
d, J 5.8, HHCCH), 1.28 (9H, s, C(CH$_3$)$_3$); δ$_C$ (101 MHz, CDCl$_3$) 166.2 (d, $^1$J$_{CF}$ 256.9), 158.5, 133.5 (d, $^4$J$_{CF}$ 3.3), 131.8 (d, $^3$J$_{CF}$ 9.7), 116.5 (d, $^2$J$_{CF}$ 22.7), 83.1 and 51.1, 30.3, 27.6; δ$_F$ (376.5 MHz, CDCl$_3$) -102.7; m/z (CI$^+$) 319 (40%, [M+NH$_4$]$^+$), 263 (40%, [M+NH$_4$-C$_4$H$_9$]$^+$), 219 (98%, [M+NH$_4$-CO$_2$Bu]$^+$), 202 (100%, [M-CO$_2$Bu]$^+$); HRMS (CI$^+$) found 319.1132, C$_{13}$H$_{20}$N$_2$O$_4$SF requires 319.1128.

**tert-Butyl hydroxy(2-(phenylsulfonyl)ethyl)carbamate, 40**

![Boc HO N --- SO$_2$Ph](image)

To a stirred solution of *tert*-butyl (diphenylphosphoryl)oxy)(2-(fluorosulfonyl)ethyl)carbamate (15 mg, 0.030 mmol) in THF (0.5 mL) at room temperature was added sodium hydroxide (2.392 mg, 0.060 mmol). The reaction mixture was stirred at room temperature for 20 minutes then quenched with NH$_4$Cl (sat. aq., 0.5 mL). The reaction mixture was extracted into CH$_2$Cl$_2$ (3x), passed through a hydrophobic frit and concentrated under reduced pressure to afford the title compound as a clear oil (8 mg, 94%); $\nu_{\text{max}}$ / cm$^{-1}$ 3360, 3244, 2979, 2930, 1694, 1448, 1368, 1308, 1288, 1149, 1086; δ$_H$ (400 MHz, CDCl$_3$) 7.96-7.89 (2H, m, 2 x ArH), 7.74-7.65 (1H, m, ArH), 7.61-7.55 (2H, m, 2 x ArH), 3.88 (2H, t, J 7.6, alkyl CH$_2$), 3.42 (2H, t, J 7.6, alkyl CH$_2$), 1.46 (9H, s, C(CH$_3$)$_3$); δ$_C$ (101 MHz, CDCl$_3$) 156.1, 138.9, 134.0, 129.4, 128.0, 82.8, 53.1, 44.4, 28.2; m/z (ES$^+$) 365 (97%, [M+MeCN+Na]$^+$), 243 (100%); HRMS (ES$^+$/TOF) found 365.1141, C$_{15}$H$_{22}$N$_2$O$_5$Na requires 365.1142.

**2-Chloroethane-1-sulfonyl fluoride, 66**

![Cl SO$_2$F](image)

According to the procedure of Sharpless,$^{80}$ to a stirred solution of KHF$_2$ (890 mg, 11.4 mmol) in H$_2$O (2.3 mL) at 0 °C was added in one portion 2-chloroethan-1-sulfonyl chloride (810 mg, 5.0 mmol). The reaction mixture was stirred at room temperature for 3 hours, then diluted with CH$_2$Cl$_2$ (5 mL) and the aqueous layer was separated and extracted into CH$_2$Cl$_2$ (3x). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford the title compound as a pale yellow oil (721 mg, 99%); δ$_H$ (400 MHz, CDCl$_3$) 3.96-3.88 (2H, m, ClCH$_2$CH$_2$), 3.87-3.78 (2H, m, ClCH$_2$CH$_2$); δ$_C$ (101
MHz, CDCl₃) 52.6 (d, 2_JCF 17.6), 35.0; δ_F (376.5 MHz, CDCl₃) +57.2. These data are consistent with literature values.⁸⁰

**Ethenesulfonyl fluoride (ESF), 65**

![SO₂F]

According to the procedure of Sharpless,⁸⁰ to a stirred solution of 2-chloroethane-1-sulfonyl fluoride (387 mg, 2.65 mmol), in H₂O (0.7 mL) was added in portions magnesium oxide (59 mg, 1.45 mmol). The reaction mixture was stirred at room temperature for 2.5 hours, then diluted with CH₂Cl₂ (5 mL). The aqueous layer was separated and extracted into CH₂Cl₂, the combined organic layer was then dried over Na₂SO₄ and concentrated under reduced pressure (N.B. Care should be taken as the product is a volatile, highly toxic lachrymator.) to afford the title compound as a clear oil (184 mg, 64%); ν_max / cm⁻¹ 3124, 3083, 1404, 1388, 1197, 991, 952; δ_H (400 MHz, CDCl₃) 6.77-6.63 (2H, m, H₂C=CH), 6.39 (1H, dd, J 8.3 and 5.2, H₂C=C(H); δ_C (101 MHz, CDCl₃) 134.2 (d, 3_JCF 2.6), 130.2 (d, 2_JCF 28.3); δ_F (376.5 MHz, CDCl₃) +57.9; m/z (CI+) 128 (80%, [M+NH₄]⁺), 99 (100%, [M+NH₄-C₄H₉]⁺); HRMS (CI+) found 128.0176, C₂H₇NO₂SF requires 128.0182.

**tert-Butyl ((diphenylphosphoryl)oxy)(2-(fluorosulfonyl)ethyl)carbamate, 69**

![Ph₂P(O)NBOcSO₂F]

To a stirred solution of tert-butyl (bis(aryl)phosphoryl)oxycarbamates (166 mg, 0.4 mmol) and triethylamine (56 μL, 0.4 mmol) in DMF was added ethenesulfonyl fluoride (16.6 μL, 0.2 mmol). The reaction mixture was stirred for 10 minutes, diluted with EtOAc (5 mL) and washed with H₂O (10 x 1 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification via flash column chromatography (2:1 n-hexane:EtOAc) afforded the title compound as a white foam (87 mg, 98%); ν_max / cm⁻¹ 3477, 3063, 2984, 2935, 1751, 1723, 1440, 1409, 1370, 1232, 1207, 1150, 1130, 1073; δ_H (400 MHz, CDCl₃) 7.99-7.86 (4H, m, 4 x ArH), 7.64-7.55 (2H, m, 2 x ArH), 7.52-7.47 (4H, m, 4 x ArH), 433-4.23 (2H, m, NCH₂CH₂), 4.00-3.90 (2H, m, NCH₂CH₂), 1.31 (9H, s, C(CH₃)₃); δ_C (101 MHz, CDCl₃) 155.1 (d, 3_JCP 3.3), 133.0 (d, 4_JCP 2.7), 132.5 (d, 3_JCP 10.3), 128.4 (d, 2_JCP 13.5), 128.1 (d, 1_JCP 134.3), 84.4, 48.3, 47.5 (d, 2_JCF 17.2), 27.6; δ_F (376.5 MHz, CDCl₃) 56.3; δ_P (162 MHz, CDCl₃) 40.5. No molecular ion could be observed under the ionisation conditions tested, however Cl⁺ showed a peak at 220 which agrees with [Ph₂P(O)+NH₄]⁺.
(±)tert-Butyl 2-(fluorosulfonyl)aziridine-1-carboxylate, 67

To a stirred solution of tert-butyl ((diphenylphosphoryl)oxy)(2-(fluorosulfonyl)ethyl)carbamate (87 mg, 0.2 mmol) in DMF (0.5 mL) at 0 °C was added sodium hydride (60% dispersion in mineral oil, 5.4 mg, 0.136 mmol). The reaction mixture was stirred at 0 °C for 30 minutes then the reaction was quenched with H₂O (5 mL), extracted into EtOAc and dried over Na₂SO₄. Further purification via flash column chromatography (9:1 to 4:1 hexane:EtOAc) afforded the title compound as a white foam (8.5 mg, 19%); νmax / cm⁻¹ 2992, 2976, 2934, 1740, 1418, 1372, 1292, 1260, 1206, 1153; δH (400 MHz, CDCl₃) 4.07-4.04 (1H, m, HC₂C₃H), 2.83 (1H, dd, J₂.9 and 1.2 HHC=CH), 2.77 (1H, dd, J 5.6 and 1.2, HHC=CH), 1.49 (9H, s, C(CH₃)₃); δC (101 MHz, CDCl₃) 157.3, 84.5, 47.0 (d, 2JCF 33.4), 30.8, 27.7; m/z (ES+) 226 (36%, [MH⁺]), 208 (100%, [MH-19F⁺]); δF (376.5 MHz, CDCl₃) 53.2; HRMS (ES+/TOF) found 226.0540, C₇H₁₃NO₄FS requires 226.0549.

Also isolated was:

Diphenylphosphinic fluoride, 68

νmax / cm⁻¹ 3065, 2979, 2932, 1720, 1593, 1441, 1256, 1137, 833; δH (400 MHz, CDCl₃) 7.86-7.80 (4H, m, 4 x ArH), 7.63-7.60 (2H, m, 2 x ArH), 7.54-7.49 (4H, 4 x ArH); δC (101 MHz, CDCl₃) 133.4 (d, 4JCP 2.9), 131.4 (d, 3JCP 11.1), 128.8 (d, 2JCP 14.1), 128.7 (d, 1JCP 141.4); δF (376.5 MHz, CDCl₃) -75.2 (d, 1JFP 1017.1); δP (162 MHz, CDCl₃) -75.2 (d, 1JFP 1022.0); m/z (Cl+) 238 (9%, [M+NH₄]+), 221 (10%, [MH]+), 168 (100%); HRMS found 221.0527, C₁₂H₁₁POF requires 221.0532.

tert-Butyl 1,2,5-oxathiazolidine-5-carboxylate 2,2-dioxide, 70

m.p. 78-79 °C; νmax / cm⁻¹ 3036, 3006, 2982, 2939, 1728, 1373, 1363, 1321, 1244, 1170; δH (400 MHz, CDCl₃) 4.53-4.45 (2H, m, CH₂N), 3.46-3.40 (2H, m, CH₂S), 1.53 (9H, s,
C(CH₃)₃; δ C (101 MHz, CDCl₃)  155.9, 85.1, 48.7, 44.4, 27.9; m/z (Cl+) 241 (87%, [M+NH₄]⁺), 185 (100%); HRMS (Cl+) 241.0851, C₇H₁₇N₂O₅S requires 241.0858.
5.2.2 Experimental Details for Chapter 3: O-(Diphenylphosphinyl) Hydroxylamine (DppONH₂) as a Nitrogen Source in the Vicarious Nucleophilic Amination (VNA) of Electron-Deficient Aromatics

4-Amino-4-methylmorpholinium Iodide, 16a

According to the procedure of Armstrong,⁵⁷ to a solution of N-aminomorpholine (1.44 mL, 15 mmol) in THF (10 mL) at 0 °C was added MeI (0.98 mL, 15.7 mmol) dropwise over 5 min. The reaction mixture was warmed to room temperature and allow to stir for an additional for 30 min. Et₂O (20 mL) was added and the white solid was isolated by filtration and subsequently washed with Et₂O (4 x 10 mL) affording the title compound as a white powder which was recrystallised from hot EtOH:MeOH (3:1) to give clear plates (2.56 g, 70%); m.p. 181-183°C (softening at 176°C); δ_H (400 MHz, d_6-DMSO) 5.95 (2H, s, NH₂), 4.01-3.95 (2H, m, HHCOC=H), 3.86 (2H, dt, J 13.5 and 3.5, HHCOC=H), 3.61-3.55 (2H, m, HHCNCH=H), 3.40 (2H, br d, J 12.5 HHCNCH=H), 3.33 (3H, s, NCH₃); δ_C (101 MHz, d_6-DMSO); 62.6, 60.4, 56.6. These data are consistent with literature values.⁵⁷

General Procedure C: Amination of Electron-Deficient Aromatics using 4-Amino-4-methylmorpholinium Iodide

To a stirred solution of 4-amino-4-methylmorpholinium iodide (40 mg, 0.165 mmol) in DMSO (0.8 mL) was added substrate (0.15 mmol), followed by NaOH (14 mg, 0.36 mmol). The reaction mixture was allowed to stir at room temperature for an additional 20 hours, after which the reaction was quenched with NH₄Cl (sat. aq., 10 mL). The acidified solution was stirred at room temperature for 30 minutes and extracted with EtOAc (3x). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered and concentrated under reduced pressure. Further purification was achieved via flash column chromatography.
Nitroaniline, 92

According to general procedure C, using nitrobenzene (1.5 mmol). Purification by flash column chromatography (4:1 to 2:1 
\textsuperscript{6}hexane:EtOAc) afforded the title compound as two separate isomers;

2-nitroaniline as an orange crystalline solid (40 mg, 19\%); m.p. 68-69 °C (Lit.\textsuperscript{304} 67-69 °C); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 8.11 (1H, dd, J 8.6 and 1.5, ArH), 7.35 (1H, ddd, J 8.4, 7.0 and 1.5, ArH), 6.81 (1H, dd, J 8.5 and 1.2, ArH), 6.70 (1H, ddd, J 8.5, 7.1 and 1.4, ArH), 6.07 (2H br s, NH\textsubscript{2}). These data are consistent with literature values.\textsuperscript{153}

4-nitroaniline as an orange solid (112 mg, 54\%) m.p. 146-148 °C (Lit.\textsuperscript{304} 147-148 °C); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 8.07 (2H, d, J 9.1, 2 x ArH), 6.62 (2H, d, J 9.1, 2 x ArH), 4.40 (2H, br s, NH\textsubscript{2}). These data are consistent with literature values.\textsuperscript{153}

2,4-Dinitroaniline, 93

According to general procedure C, using 1,3-dinitrobenzene (0.15 mmol). Purification by flash column chromatography (1:1 
\textsuperscript{6}hexane:EtOAc) afforded the title compound as a yellow solid (21.5 mg, 79\%); m.p. 169-177 °C (Lit.\textsuperscript{305} 177 °C); δ\textsubscript{H} (400 MHz, d\textsubscript{6}-acetone): 8.94 (1 H, d, J 2.7, ArH), 8.21 (1 H, dd, J 9.4 and 2.7, ArH), 7.85-8.05 (2 H, br s, NH\textsubscript{2}), 7.25 (1 H, d, J 9.4, ArH). These data are consistent with literature values.\textsuperscript{153}

2-Amino-1-nitronaphthalene, 94

According to general procedure C, using 1-nitronaphthalene (0.15 mmol). Purification by flash column chromatography (4:1 to 2:1 
\textsuperscript{6}hexane:EtOAc) afforded the title compound as a yellow crystalline solid (24.5 mg, 88\%); m.p. 124-126 °C (Lit.\textsuperscript{306} 125-129 °C); δ\textsubscript{H} (400 MHz,
d$_6$-acetone) 8.57 (1 H, dd, J 8.7 and 0.8 ArH), 7.85 (1 H, d, J 9.1, ArH), 7.77 (1 H, dd, J 8.0 and 1.4, ArH), 7.59 (1 H, ddd, J 8.7, 7.1 and 1.5, ArH), 7.42 (2 H, br s, NH$_2$), 7.34 (1 H, ddd, J 8.0, 7.0 and 1.0, ArH), 7.22 (1 H, d, J 9.1, ArH). These data are consistent with literature values.$^{306}$

2-Aminobenzoxazole, 95

![2-Aminobenzoxazole](image)

According to general procedure C, using benzoxazole (0.15 mmol). Purification via flash column chromatography (1:1 $n$-hexane:EtOAc) afforded the title compound as an off-white solid (8.5 mg, 41%); m.p. 129-131 °C (Lit.$^{307}$ 129 °C); $\delta$$_H$ (400 MHz, CDCl$_3$) 7.36-7.33 (1 H, m, ArH), 7.29-7.26 (1 H, m, ArH), 7.18 (1 H, td, J 7.7 and 1.2, ArH), 7.07 (1 H, td, J 7.7 and 1.2, ArH), 5.59 (2 H, br s, NH$_2$). These data are consistent with literature values.$^{308}$

2-Aminobenzothiazole, 96

![2-Aminobenzothiazole](image)

According to general procedure C, using benzothiazole (0.15 mmol). Purification via flash column chromatography (1:1 $n$-hexane:EtOAc) afforded the title compound as an off-white solid (4.5 mg, 20%); m.p. 130-131 °C (Lit.$^{309}$ 129-130 °C); $\delta$$_H$ (400 MHz, CDCl$_3$) 7.60 (1 H, dd, J 8.1 and 1.2, ArH), 7.57-7.53 (1 H, m, ArH), 7.32 (1 H, ddd, J 8.1, 7.3 and 1.3, ArH), 7.13 (1 H, dt, J 7.6 and 1.2, ArH), 5.36 (2 H, br s, NH$_2$). These data are consistent with literature values.$^{310}$

2-Amino-6-nitrobenzothiazole, 97

![2-Amino-6-nitrobenzothiazole](image)

According to general procedure C, using 6-ntirobenzothiazole (0.15 mmol). Purification via flash column chromatography (1:1 $n$-hexane:EtOAc) afforded the title compound as a yellow solid (9 mg, 31%); m.p. 247-248 °C (Lit.$^{311}$ 249 °C); $\delta$$_H$ (400 MHz, d$_6$-DMSO) 8.53 (1 H, d, J 2.4, ArH), 8.23 (1 H, dd, J 8.9, 2.4, ArH), 7.57 (1 H, d, J 8.9, ArH), 5.58 (2 H, s, NH$_2$). These data are consistent with literature values.$^{312}$
1,2-Bis(phenylsulfinyl)ethane, 98

According to the procedure of White,\textsuperscript{167} to a stirred solution of 1,2-bis(phenylthio)ethane (1.25 g, 5.08 mmol) in glacial acetic acid (7.5 mL) was added dropwise a solution of hydrogen peroxide (30 wt.%, 10.1 mmol, 0.58 mL) in acetic acid (2.1 mL) and the reaction mixture allowed to stir overnight. The acetic acid was removed under reduced pressure and the white solid obtained was washed with cold EtOH (3 x 40 mL). The product was dried overnight under reduced pressure to afford the title compound as a white solid (1.01 g, 72%, 5:1 meso:rac); m.p. 116-120 °C; $\delta$H (400 MHz, CDCl\textsubscript{3}) 7.56-7.53 (10H, m, 10 x ArH \textit{meso}), 7.50 (10H, m, 10 x ArH \textit{rac}), 3.46-3.33 (2H, m, alkyl CH\textsubscript{2} \textit{rac}), 3.08-3.02 (4H, m, 2x alkyl CH\textsubscript{2} \textit{meso}), 2.81-2.68 (2H, m, alkyl CH\textsubscript{2} \textit{rac}). $\delta$C (101 MHz, CDCl\textsubscript{3}) 142.4, 142.2, 131.4, 131.3, 129.5, 123.93, 123.86, 47.72, 46.94. These data are consistent with literature values.\textsuperscript{167}

\textit{O}-(Diphenylphosphinyl) hydroxylamine, 20

According to the procedure of Nantz,\textsuperscript{313} to a stirred solution of hydroxylamine hydrochloride (6.46 g, 93 mmol) in H\textsubscript{2}O (20 mL) at -20 °C was added a solution of sodium hydroxide (3.58 g, ) in H\textsubscript{2}O (20 mL). Et\textsubscript{2}O (130 mL) was added and the biphasic mixture was cooled to -15 °C. Diphenylphosphinic chloride (10 g, 42 mmol) was added rapidly via a syringe and the reaction mixture was stirred vigorously for a further 10 minutes. The reaction mixture was then warmed to 0 °C and stirred for an additional 15 minutes. The resulting slurry was filtered and washed with cold H\textsubscript{2}O and then cold Et\textsubscript{2}O. The solid was dried under reduced pressure to afford the title compound as a white solid. The solid was then slurried in a 0.25 M solution of NaOH (120 mL) at 0 °C for 30 minutes, filtered and the solid washed with cold H\textsubscript{2}O. The solid was then dried under reduced pressure affording the title compound as a white solid (5.92 g, 60%); m.p. > 130 °C (gradual decomp.); $\delta$H (400 MHz, CDCl\textsubscript{3}) 7.88-7.82 (4H, m, 4 x ArH), 7.58-7.53 (2H, m, 2 x ArH), 7.50-7.45 (4H, m, 4 x ArH), 5.93 (2H, br s, NH\textsubscript{2}); $\delta$P (162 MHz, CDCl\textsubscript{3}) 37.5. These data are consistent with literature values.\textsuperscript{313}
General Procedure D: Amination of Electron-Deficient Aromatics with In Situ 4-
Amino-4-methylmorpholinium Formation

To a stirred solution of O-(diphenylphosphinyl) hydroxylamine (96 mg, 0.39 mmol) in
CH₂Cl₂ (2 mL) was added dropwise N-methylmorpholine (43 µL, 0.39 mmol). The solution
was stirred for 30 minutes at room temperature, after which substrate (0.36 mmol) and
NaOH (47 mg, 1.17 mmol) were added. The reaction mixture was stirred for a further 24
hours at room temperature, after which the reaction was quenched with NH₄Cl (sat. aq., 2
mL). The acidified mixture was stirred at room temperature for 30 minutes, extracted into
EtOAc, washed with H₂O, dried over MgSO₄ and concentrated under reduced pressure.
Further purification was achieved via flash column chromatography.

Nitroaniline, 92

![Nitroaniline structure]

According to general procedure D, using nitrobenzene (0.36 mmol) and using anhydrous
DMSO in place of CH₂Cl₂ and quenched 18 hours after the NaOH was added. Purification
via flash column chromatography (4:1 to 2:1 n-hexane:EtOAc) afforded the title compound
as two separate isomers; 2-nitroaniline as an orange crystalline solid (1 mg, 1%) and 4-
nitroaniline as an orange solid (8.5 mg, 17%). All data was in agreement with that reported
above.

2,4-Dinitroaniline, 93

![2,4-Dinitroaniline structure]

According to general procedure D, using 1,3-dinitrobenzene (0.36 mmol) and using
anhydrous DMSO in place of CH₂Cl₂ and quenched 18 hours after the NaOH was added.
Purification by flash column chromatography (1:1 n-hexane:EtOAc) afforded the title
compound as a yellow solid (14.0 mg, 21%). All data was in agreement with that reported
above.
**Amino-1-nitroaniline, 94**

![Structure of Amino-1-nitroaniline](image)

According to general procedure D, using 1-nitronaphthalene (0.36 mmol). Purification by flash column chromatography (4:1 to 2:1 hexane:EtOAc) afforded the title compound as two separate isomers;

2-Amino-1-nitronaphthalene as a yellow crystalline solid (42 mg, 62%); all data was in agreement with that reported above.

4-Amino-1-nitronaphthalene as yellow solid (4 mg, 6%); m.p. 190-193 °C (Lit. 306 190-191 °C); δ\(H\) (400 MHz, d\(_6\)-acetone); 8.96-8.93 (1H, m, ArH), 8.38 (1H, d, J 8.8, ArH), 8.28 (1H, dt, J 8.6 and 0.6, ArH), 7.75 (1H, ddd, J 8.8, 6.8 and 1.3, ArH), 7.57 (1H, ddd, J 8.4, 7.0 and 1.3, ArH), 6.82 (1H, d, J 8.8, ArH and 2H, br s, NH\(_2\)). These data are consistent with literature values. 306

**2-Amino-3-nitropyridine, 99**

![Structure of 2-Amino-3-nitropyridine](image)

According to the procedure D, using 3-nitropyridine (0.36 mmol). Purification by flash column chromatography (1:1 hexane:EtOAc) afforded the title compound as an orange solid (7 mg, 14%); m.p. 186-190 °C (Lit. 314 188 °C); δ\(H\) (400 MHz, DMSO); 8.84 (1H, d, 2.7, ArH), 8.11 (1H, dd, J 9.3 and 2.8, ArH), 7.54 (2H, br s, NH\(_2\)), 6.49 (1H, d, J 9.3, ArH). These data are consistent with literature values. 145

Also isolated was:

**5,5'-Dinitrobis(2-pyridyl)amine, 101**

![Structure of 5,5'-Dinitrobis(2-pyridyl)amine](image)

Yellow solid (33 mg, 35%); m.p. 230-231 °C (Lit. 315 223-226 °C); δ\(H\) (400 MHz, DMSO) 11.46 (1H, br s, NH), 9.19 (2H, dd, J 2.8 and 0.5, 2 x ArH), 8.57 (2H, dd, J 9.3 and 2.8, 2 x ArH), 7.99 (2H, dd, J 9.3 and 0.4, 2 x ArH); δ\(C\) (100 MHz, DMSO) 156.8, 150.0, 138.6,
133.7, 112.3; m/z (electrospray) 262 (MH\(^+\), 100%). These data are consistent with literature values.\(^{316}\)

2-Amino-3-nitrothiophene, 100

According to general procedure D, using 2-nitrothiophene (0.4 mmol). Purification by flash column chromatography (4:1 \(^{3}\)hexane:EtOAc) afforded the title compound as an orange solid (10 mg, 17%); m.p. 157-159 °C (lit\(^{149}\) 159-160 °C); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.32 (1H, d, \(J\ 5.9, \text{SCH}\)), 6.54 (1H, d, \(J\ 5.9, \text{SCHCH})\), 6.33 (2H, br s, NH\(_2\)). These data are consistent with literature values.\(^{149}\)

2-Aminobenzoxazole, 95

According to general procedure D, using benzoxazole (0.36 mmol). Purification by flash column chromatography (1:1 \(^{3}\)hexane:EtOAc) afforded the title compound as an off-white solid (15 mg, 31%). All data was in agreement with that reported above.

2-Amino-6-nitrobenzothiazole, 97

According to general procedure D, using 6-nitrobenzothiazole (0.36 mmol). Purification by flash column chromatography (1:1 \(^{3}\)hexane:EtOAc) afforded the title compound as a yellow solid (3.5 mg, 5%). All data was in agreement with that reported above.
5.2.3 Experimental Details for Chapter 4: [2,3]-Sigmatropic Rearrangement of Allylic Selenimides: The Synthesis of Enantioenriched Vinyl Glycine Peptides and Peptidomimetics

**(S)-**tert-Butyl 4-phenylselanyl-hex-2-(E)-enoate, 162

To a solution of butyraldehyde (576 μL, 6.4 mmol) in toluene (4.8 mL) at 0 °C was added **(S)**-2-[bis-(3,5-bistrifluoromethyl-phenyl)-trimethylsilyloxy-methyl]-pyrrolidine (384 mg, 0.64 mmol) and p-nitrobenzoic acid (106 mg, 0.64 mmol). The reaction mixture was stirred for 10 minutes after which N-(phenylselenyl)phthalimide (96%, 2.42 g, 7.68 mmol) added and stirred at 0 °C for an additional 20 hours. The reaction mixture was diluted with THF (32 mL) and cooled to -40 °C. To the reaction mixture was added a solution (**tert**-butoxycarbonylmethylene)triphenylphosphorane (3.13 g, 8.32 mmol) in THF (32 mL) at -40 °C via cannula. The reaction was stirred at -40 °C for an additional 2 hours before slowly warming to 0 °C and stirring for an additional 20 hours. NH₄Cl (sat. aq., 8 mL) was added and the reaction extracted into Et₂O, washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Crude NMR indicated a >99:1 E:Z ratio. Purification via flash column chromatography (20:1 *n*hexane:Et₂O) afforded the title compound as the pure E-isomer as a colourless oil (1.39 g, 67%); [α]D¹⁹ -128.7 (c = 0.886, CHCl₃); ν max / cm⁻¹ 3072, 2972, 2931, 2873, 1702, 1641, 1579, 1476, 1140; δH (400 MHz, CDCl₃) 7.50-7.40 (2H, m, 2 x ArH), 7.32-7.25 (3H, s, 3 x ArH), 6.77 (1H, dd, J 15.4 and 9.6, CH=CHCO₂Bu), 5.25 (1H, dd, J 15.5 and 0.9, CH=CHCO₂Bu), 3.62 (1H, dddd, J 9.5, 7.6, 6.4 and 0.9, CHSePh), 1.86-1.66 (2H, m, CH₂), 1.44 (9H, s, C(CH₃)₃), 1.01 (3H, t, J 7.4, CH₃); δC (101 MHz, CDCl₃) 165.7, 146.5, 136.5, 129.0, 128.4, 128.2, 121.9, 80.3, 47.8, 28.3, 27.1, 13.0; m/z (Cl+) 344 (80%, [M+NH₄⁺], 327 (20% [MH⁺]), 288 (100%, [M+NH₄-C₄H₉⁺]), 270 (5%, [M-(C₄H₉)⁺]); HRMS (Cl⁺) found 344.1134, C₁₅H₂₆NO₂Se⁸⁻ requires 344.1134; enantiomeric ratio was determined as 98:2 using HPLC; Chiralcel OD-H column, 100% hexane, flow 1.0 mLmin⁻¹, UV detection at 236 nm, 14.9 min (minor), 16.7 min (major).
(S)-Ethyl 4-phenylselanylbut-2-\(E\)-enoate, 163

To a stirred solution of propanal (200 μL, 2.79 mmol) in toluene (1.5 mL) at 0 °C was added (S)-2-[bis-(3,5-bistrifluoromethyl-phenyl)-trimethyl-silylanyloxymethyl]-pyrrolidine (87 μL, 0.279 mmol) and 4-nitrobenzoic acid (46.5 mg, 0.279 mmol). The reaction mixture was stirred for 10 minutes after which N-(phenylselenyl)phthalimide (1.01 g, 3.24 mmol) was added and stirred at 0 °C for an additional 17 hours. The reaction was diluted with THF (11 mL) and the temperature lowered to -40 °C. To the reaction mixture was added a solution of (carbethoxymethylene)triphenylphosphorane (1.26 g, 3.62 mmol) in THF (11 mL) at -40 °C via cannula. The reaction was stirred at -40 °C for 2 hours before slowly warming to 0 °C and stirring for an additional 20 hours. NH₄Cl (sat., aq., 5 mL) was added and the reaction was extracted into Et₂O, washed with brine, dried over MgSO₄ and concentrated under reduced pressure. Purification via flash column chromatography (40:1 to 20:1 n-hexane:Et₂O) afforded the title compound as a pale yellow oil (415 mg, 53%); \(\alpha\)D 21 -93.1 (c = 1.313, CH₂Cl₂); \(v\)max / cm⁻¹ 3072, 3056, 2978, 2924, 2866, 1712, 1643, 1438, 1259; δH (400 MHz, CDCl₃) 7.52-7.50 (2H, m, 2 x ArH), 7.34-7.25 (3H, m, 3 x ArH), 6.98 (1H, dd, J 15.5 and 8.6, CHCH=CH), 5.38 (1H, dd, J 15.5 and 1.1, CHCH=CH), 5.38 (1H, dd, J 15.5 and 1.1, CHCH=CH), 4.15 (2H, q, J 7.13, CH₂CH₃), 3.92-3.84 (1H, m, CH), 1.51 (3H, d, J 6.88, CH₂CH), 1.26 (3H, t, J 7.13, CH₂CH₃); δC (101 MHz, CDCl₃) 167.9, 148.9, 136.3, 129.1, 128.6, 128.1, 119.1, 60.4, 39.4, 19.7, 14.4; m/z (EI+) 284 (99%, [M]+), 157 (57%), 127 (79%), 99 (100%); HRMS (EI+) found 284.0314, C₁₃H₁₆O₂Se⁸₀ requires 284.0310; enantiomeric ratio was determined as 97:3 using HPLC; Chiralcel OD-H column, 100% hexane, flow 0.5 mLmin⁻¹, UV detection at 236 nm, 65.6 min (minor), 76.6 min (major).

(S)-Ethyl-2-methyl-4-(phenylselanyl)hex-2-\(E\)-enoate, 164

According to the procedure of Armstrong,²⁴⁹ to a solution of butyraldehyde (178 μL, 2.0 mmol) in toluene (1.5 mL) at 0 °C was added (S)-2-[bis-(3,5-bistrifluoromethyl-phenyl)-trimethylsilylanyloxymethyl]-pyrrolidine (119 mg, 0.2 mmol) and p-nitrobenzoic acid (33 mg, 0.2 mmol). The reaction mixture was stirred for 10 minutes after which N-phenylselenyl-phthalimide (95%, 763 g, 2.4 mmol) added and the reaction stirred for a further 20 hours.
The reaction was then filtered through a plug of cotton wool, washed with toluene (6 mL) and the filtrate was cooled to -78 °C. In a separate flask, to a solution of triethyl-2-phosphonopropionate (1.07 mL, 5.0 mmol) in CH₂Cl₂ (14.5 mL) at -78 °C was added ⁷BuLi (3.05 mL, 1.57 M in hexanes, 4.8 mmol) and stirred for 30 minutes before being added via a cannula to the reaction vessel at -78 °C. The reaction was held at -78 °C for a further 1.5 hours before the reaction was warmed to -45 °C for 1 hours, then warmed to 0 °C and stirred for a further 30 minutes. The reaction was quenched with NH₄Cl (sat. aq., 15 mL), extracted into Et₂O (3x), washed brine (2x) and dried over MgSO₄. Purification via flash column chromatography (1:1 ᵇhexane:Et₂O) gave a colourless oil (270 mg, 43%); \([\alpha]_D^{21} -66.0 \ (c = 0.66, \text{CH}_2\text{Cl}_2); \nu_{\text{max}} / \text{cm}^{-1} 3056, 2964, 2931, 2873, 1706, 1639, 1579, 1275, 1231, 1172; \delta_H (400 MHz, CDCl₃) 7.57-7.53 (2H, m, ArH), 7.34-7.27 (1H, m, ArH), 7.26-7.20 (2H, m, ArH), 6.67 (1H, dq, \(J_{11.3} \) and \(1.5, \text{CHC}H\text{C}H\)), 4.18 (2H, m, OC₃H₂CH₃), 3.95 (1H, ddd, \(J_{11.3}, 8.7 \) and \(5.6, \text{CHSePh}\)) 1.84 (1H, dqd, \(J_{13.0}, 7.4 \) and \(5.5, \text{CH₃CHHCH}\)), 1.76-1.65 (1H, m, CH₃CHHCH), 1.41 (3H, d, \(J = 1.5, \text{HC=C(CH₃)}\)), 1.29 (3H, t, \(J = 7.1, \text{OCH₂CH₃}\)), 0.98 (3H, t, \(J = 7.4, \text{CH₃CH₂CH₂}\); \delta_C (101 MHz, CDCl₃) 168.0, 141.8, 137.0, 128.9, 128.5, 128.0, 127.7, 60.7, 44.5, 28.2, 14.4, 13.1, 12.2; \(m/z \) (ES+) 313 (71% [MH⁺]), 282 (100%), 267 (74%), 155 (96%); HRMS (ES+/TOF) found 313.0711, C₁₅H₂₁O₂Se²⁸⁰ requires 313.0707; enantiomeric ratio was determined as 97.5:2.5 using HPLC; Chiralcel OD-H column, 100% hexane, flow 0.5 mLmin⁻¹, UV detection at 254 nm, 44 min (minor), 67 min (major).

tert-Butyl (S)-(2-oxooxetan-3-yl)carbamate, 182

![tert-Butyl (S)-(2-oxooxetan-3-yl)carbamate](image)

According to the procedure of Vederas,²⁵⁷ to a stirred solution of triphenylphosphine (2.62 g, 10 mmol) in THF (70 mL) at -78 °C was added diethyl azodicarboxylate (DEAD) (1.6 mL, 10.2 mmol). The reaction mixture was stirred for 20 minutes at -78 °C, then N-Boc-L-Ser-OH (2.05 g, 10 mmol) in THF (15 mL) was added dropwise over 20 minutes. The reaction mixture was allowed to warm to room temperature over 4 hours then concentrated under reduced pressure. Purification via flash column chromatography (1:1 ᵇhexane:EtOAc) afforded the title compound as a white solid (760 mg, 41%), m.p. 117-119 °C (Lit.²⁵⁷ 119.5-120.5 °C); \(\delta_H (400 MHz, CDCl₃) 5.24-5.37 \) (1H, br s, NH), 5.15-5.06 (1H,
m, NHCH$_3$), 4.40-4.48 (2H, m, CH$_2$), 1.45 (9H, s, C(CH$_3$)$_3$). These data are consistent with literature values.$^{257}$

**N-Boc-L-Ser-NH$_2$, 181**

![N-Boc-L-Ser-NH$_2$](image)

According to the procedure of Le Goffic,$^{258}$ to tert-butyl (S)-(2-oxooxetan-3-yl)carbamate (465 mg, 2.16 mmol) in a 100 mL round bottom flask at -78 °C was condensed NH$_3$(g) giving approximately 20 mL NH$_3$(l). The reaction mixture was held at -78 °C for 20 minutes before being slowly warmed to room temperature, allowing the ammonia to evaporate affording the title compound as a off-white solid (427 mg, 97%); m.p. 100-102 °C (Lit.$^{258}$ 101 °C); $\nu_{\text{max}}$ / cm$^{-1}$ 3384, 3340, 3199, 2970m 1683, 1644, 1523, 1297, 1249, 1158, 1005; $\delta_H$ (400 MHz, d$_6$-acetone) 7.04 (1H, br s, NH), 6.59 (1H, br s, NH), 5.98 (1H, br s, NH), 4.16-4.06 (2H, m, CH and OH), 3.81 (1H, dd, $J$ 10.9 and 5.0, CH$_2$OH), 3.71 (1H, dd, $J$ 10.9 and 5.5, CH$_2$OH), 1.41 (9H, s, C(CH$_3$)$_3$); $\delta_C$ (101 MHz, d$_6$-acetone) 173.8, 156.4, 79.4, 63.3, 56.9, 28.5; m/z (Cl+) 205 (100%, [MH]$^+$); HRMS (Cl+) found 205.1187, C$_8$H$_{17}$N$_2$O$_4$ requires 205.1188.

**N-Boc-L-Tyr-NH$_2$, 183**

![N-Boc-L-Tyr-NH$_2$](image)

Based on the procedure of Ley,$^{259}$ to a stirred solution of N-Boc-L-Tyr-OH (0.5 g, 1.77 mmol) in DMF (2.8 mL) was added EDCI (355 mg, 1.86 mmol) and HOBt (251 mg, 1.86 mmol) followed by aqueous ammonia (28%, 142 μL, 2.12 mmol). Stirred for 24 hours at room temperature, diluted with H$_2$O (30 mL), extracted into EtOAc (10 mL), washed with, alternately, 1M HCl (aq.), brine, sat. NaHCO$_3$ (sat. aq.), brine and dried over Na$_2$SO$_4$. The crude reaction mixture was concentrated under reduced pressure and purified via flash column chromatography (1:0 to 10:1 Et$_2$O:EtOAc) affording the title compound as a white solid (357 mg, 72%); m.p. 198-199 °C; $[\alpha]_D^{22}$ +20.0 ($c = 0.886$, EtOH); $\nu_{\text{max}}$ / cm$^{-1}$ 3410, 3331, 3212, 2977, 1688, 1659, 1515, 1250, 1163; $\delta_H$ (400 MHz, d$_6$-DMSO ) 9.14 (1H, s, OH), 7.30 (1H, s, CONH$_2$), 7.02 (2H, d, $J$ 8.1, ArH), 6.96 (1H, s, CONH$_2$), 6.68 (1H, d, $J$ 8.6, CHNH$_2$), 6.64 (2H, d, $J$ 8.1, ArH), 4.06-3.91 (1H, m, CH), 2.82 (1H, dd, $J$ 13.9 and 4.5,
CHCHH), 2.61 (1H, dd, J 13.8 and 9.8, CHCHH), 1.31 (9H, s, C(CH₃)₃); δC (101 MHz, d₆-DMSO) 173.8, 155.7, 155.2, 130.0, 128.3, 114.8, 77.9, 55.9, 36.8, 28.2; m/z (ES+) 303 (20%, [MNa]⁺), 242 (100%); HRMS (ES+/TOF) found 303.1326, C₁₄H₂₀N₂O₄Na requires 303.1321.

**N-Cbz-L-Trp-NH₂, 184**

Based on the procedure of Ley,²⁵⁹ to a stirred solution of N-Cbz-L-Trp-OH (0.5 g, 1.47 mmol) in DMF (3 mL) was added EDCI (296 mg, 1.55 mmol) and HOBt (210 mg, 1.55 mmol) followed by aqueous ammonia (28%, 118 μL). The reaction mixture was stirred overnight, diluted with H₂O (30 mL), extracted into EtOAc, washed with, alternately, with 1M HCl (aq.), brine, NaHCO₃ (sat. aq.), brine and dried over Na₂SO₄. The crude reaction mixture was concentrated under reduced pressure and recrystallized from EtOAc:hexane to afford the title compound as a white solid (436 mg, 88%); m.p. 190-192 °C (Lit.³¹⁷ 185-187 °C); [α]D²¹ -12 (c 1.0, MeOH) [lit.³¹⁷ [α]D²¹ -11.5 (c = 0.866, EtOH)]; νmax / cm⁻¹ 3427, 3400, 3296, 3196, 3055, 2913, 1661, 1608, 1538, 1461, 2415, 1296, 1256, 1235, 1047, 993; δH (400 MHz, d₆-DMSO ) 10.81 (1H, s, NH-indole), 7.64 (1H, d, J 7.8, ArH indole), 7.48 (1H, s, CONH), 7.39-7.22 (7H, m, 5 x ArH-Ph and ArH-indole and CONH), 7.13-7.02 (2H, m, ArH-indole and NHCbz), 6.97 (1H, t, J 7.4, ArH-indole), 5.00-4.84 (2H, m, CH₂Ph), 4.24 (1H, td, J 9.2 and 4.6, CHCONH₂), 3.12 (1H, dd, J 14.7 and 4.6, CH₂CHCONH₂), 2.92 (1H, dd, J 14.6 and 9.7, CH₂CHCONH₂); δC (101 MHz, d₆-DMSO) 173.8, 155.8, 155.2, 130.0, 128.3, 114.8, 77.9, 55.9, 36.8, 28.2; m/z (ES+) 360 (61%, [MNa]⁺), 259 (58%), 242 (100%); HRMS (ES+/TOF) found 360.1341, C₁₉H₁₉N₃O₃Na requires 360.1324.

**N-FMOC-L-Lys (N₃)-NH₂, 185**

Based on the procedure of Ley,²⁵⁹ to a stirred solution of N-Fmoc-L-Lys(N₃)-OH (238 mg, 0.6 mmol) in DMF (0.9 mL) was added EDCI (121 mg, 0.63 mmol) and HOBt (85 mg, 0.63
mmol) followed by aqueous ammonia (28%, 48 μL, 0.72 mmol). Stirred for 24 hours at room temperature, diluted with H₂O (10 mL), extracted into EtOAc, washed with alternately, 1M HCl (aq.), brine, NaHCO₃ (sat. aq.), brine then dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash column chromatography (1:1 to 1:0 hexane:EtOAc) afforded the title compound as a white solid (144 mg, 63%); m.p. 111-114 °C, [α]D²⁸ -3.8 (c = 1.06, CHCl₃); νmax / cm⁻¹ 3395, 3317, 3201, 2947, 2096, 1674, 1532, 1450, 1253; δH (400 MHz, CDCl₃) 7.76 (2H, dt, J 7.6 and 1.0, ArH), 7.57 (2H, d, J 7.4, ArH), 7.40 (2H, t, J 7.4 ArH), 7.31 (2H, td, J 7.5 and 1.2, ArH), 6.11 (1H, s, CONHH), 5.71 (1H, s, CONHH₂), 5.47 (1H, d, J 7.9, NH), 4.44 (2H, d, J 6.8, OCH₂CH), 4.20 (2H, t, J 6.7, 2 x CH), 3.26 (2H, t, J 6.7, CH₂N₃), 2.02-1.80 (2H, m, CHCH₂), 1.70-1.52 (2H, m, CH₂CH₂N₃), 1.49-1.36 (2H, m, CHCH₂CH₂); δC (101 MHz, CDCl₃) 174.1, 156.4, 143.8, 141.5, 127.9, 127.2, 125.1, 120.2, 77.2, 67.1, 54.3, 51.2, 47.3, 32.0, 28.6, 22.7; m/z (ES+) 416 (100% [MNa]+), 394 (83%, [MH]+), 338 (26%); HRMS (ES+/TOF) found 416.1695, C₂₁H₂₃N₅O₃Na requires 416.1699.

General Procedure E: Amination/Rearrangement of Allylic Selenides with Amino Acid Amides

To a solution of allylic selenide (0.30 mmol) in dry methanol (1 mL) was added amino acid amide (0.20 mmol), trimethylorthoformate (129 μL, 1.18 mmol) and para-toluene sulfonic acid (1 mg). The solution was stirred for 30 minutes at room temperature before cooling to 0 °C, diisopropylethylamine (209 μL, 1.20 mmol) then N-chlorosuccinimide (80 mg, 0.6 mmol) were added. The reaction was stirred at 0 °C for 20 minutes, then 1M HCl (aq., 1mL) was added, followed by saturated NaHCO₃ (1 mL). The reaction was extracted into EtOAc (3x), washed with brine (3x), dried over Na₂SO₄, concentrated under reduced pressure and further purified by flash column chromatography.
**tert-Butyl (2S,3E)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-hydroxypropanamido)hex-3-enoate, 186**

Following general procedure E, using \((S)-\text{tert-butyl 4-phenylselanyl-hex-2-}(E)\)-enoate (0.3 mmol) and \(\text{Boc-L-Ser-NH}_2\) (0.2 mmol). Purification via flash column chromatography (3:1 to 1:2 \(^7\)hexane:EtOAc) afforded the title compound as a light yellow foam (31 mg, 42\%); \([\alpha]_D^{21} -13.5 \ (c = 0.74, \text{CHCl}_3)\); \(v_{\text{max}} / \text{cm}^{-1} 3311, 2977, 2936, 1720, 1659, 1507, 1457\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.08 (1H, br d, \(J = 6.3\), \(\text{NHCO}_2\text{tBu}\)), 5.78 (1H, dt, \(J = 15.5, 6.4\) and 1.5, \(\text{CH}_2\text{CH}==\text{CH}\)), 5.57 (1H, d, \(J = 6.7\), \(\text{CHNH}\)), 5.45 (1H, ddt, \(J = 15.5, 6.0\) and 1.6, \(\text{CH}_2\text{CH}==\text{CH}\)), 4.92–4.87 (1H, m, \(\text{CHNH}\)), 4.22 (1H, br s, OH), 4.04 (1H d, \(J = 10.7\), \(\text{CHCH}_2\text{OH}\)), 3.68–3.62 (1H, m, \(\text{CHHOH}\)), 3.36 (1H, m, \(\text{CHHOH}\)), 2.09–2.01 (2H, m, \(\text{CH}_2\)), 1.45 (9H, s, C(\text{CH}_3)_3), 1.44 (9H, s, C(\text{CH}_3)_3), 0.97 (3H, t, \(J = 7.4\), CH\(_3\)); the following distinct signals for the Z-isomer were observed: 5.68 (1H, dt, \(J = 10.1\) and 7.5), 5.21 (1H, ddt, \(J = 10.1, 9.1\) and 1.6), 5.15–5.10 (1H, m), 2.26–2.19 (2H, m), 1.02 (3H, d, \(J = 7.5\)) and the \(E:Z\) ratio was determined to be 8.5:1 by integration of the signals at 2.09–2.01 and 2.26–2.19 respectively; \(\delta_C\) (100 MHz, CDCl\(_3\)) 170.9, 170.0, 156.0, 136.1, 122.7, 82.5, 80.3, 63.0, 54.8, 54.7, 28.3, 27.8, 25.2, 13.1; \(m/z (\text{ES}^+)\) 395 (100\%, \([\text{MNa}]^+\)), 373 (10\%, \([\text{MH}]^+\)); HRMS (ES\(^+\)/TOF) found 373.2346, \(\text{C}_{18}\text{H}_{33}\text{N}_2\text{O}_6\) requires 373.2339. The diastereomeric mixture was prepared by the same method from racemic tert-butyl 4-phenylselanyl-hex-2-\((E)\)-enoate. Spectroscopic data agreed with the material prepared above; the following additional NMR signals were observed for the other diastereomer: \(\delta_H\) (400 MHz, CDCl\(_3\)) 4.09 (1H, d, \(J = 11.0\)) 3.20 (1H, br s), 1.45 (9H, s), 1.44 (9H, s); \(\delta_C\) (100 MHz, CDCl\(_3\)) 136.2, 63.0, 25.2, 13.1.
tert-Butyl (2S,3E)-2-((S)-2-tert-butoxycarbonylamino-3-(4-hydroxyphenyl)propionyl-amido)-hex-3-enoate, 187

Following general procedure E, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.3 mmol) and N-Boc-L-Tyr-OH (0.2 mmol). Purification via flash column chromatography (4:1 to 2:3 n-hexane:EtOAc) afforded the title compound as a pale orange oil (28.6mg, 32%); [α]D<sup>20</sup> +29.04 (c = 0.619, CHCl<sub>3</sub>); ν<sub>max</sub>/ cm<sup>-1</sup> 3312, 2979, 1656, 1517, 1368, 1251; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.01 (2H, t, J 7.5, 2 x ArH), 6.76-6.66 (2H, m, 2 x ArH), 6.60 (1H, d, J 7.6, NHCHCO<sub>2</sub>Bu), 6.53-6.37 (1H, br s, OH), 5.71 (1H, dtd, J 15.5, 6.1 and 1.3, CH<sub>3</sub>CH<sub>2</sub>CH=CH) 5.36 (1H, ddt, J 15.5, 6.1 and 1.6 Hz, CH<sub>3</sub>CH=CH=CH), 5.16-4.99 (1H, m, NHCO<sub>2</sub>Bu), 4.90-4.79 (1H, m, NHCHCO<sub>2</sub>Bu), 4.48-4.20 (1H, m, CHCH<sub>2</sub>(C<sub>6</sub>H<sub>4</sub>)OH), 2.98 (2H, m, CHCH<sub>2</sub>(C<sub>6</sub>H<sub>4</sub>)OH), 2.06-1.98 (2H, m, CH<sub>2</sub>CH=CH), 1.43 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.41 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 0.95 (3H, t, J 7.4, CH<sub>2</sub>CH<sub>2</sub>); the following distinct signals for the Z-isomer were observed 6.89 (2H, d, J 7.6), 6.68 (2H, d, J 7.6), 5.66-5.61 (2H, m), 2.25-2.18 (2H, m), 1.01 (3H, t, J 7.4) and the E:Z ratio was determined to be 7:1 by integration of the signals at 0.95 and 1.01 respectively; δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 170.7, 169.7, 155.4, 155.1, 136.0, 130.5, 127.8, 123.0, 115.5, 82.4, 60.4, 54.6, 37.5, 28.2, 27.9, 25.2, 14.7, 13.1; m/z (ES+) 512 (23%, [M+MeCN+Na]<sup>+</sup>), 471 (100%, [MNa]<sup>+</sup>), 449 (21%, [MH]<sup>+</sup>), 369 (9%); HRMS (ES+/TOF) found 471.2457, C<sub>24</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>Na requires 471.2471. The diastereomeric mixture was prepared by the same method using racemic tert-butyl 4-phenylselanyl-hex-2-(E)-enoate. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.45 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.42 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 170.8, 115.6, 82.7, 54.7, 13.3.
**tert-Butyl** (2S,3E)-2-((S)-2-(benzyl oxy)carbonyl amino-3-(1H-indol-3-yl) propionylamino)hex-3-enoate, 188

![Chemical Structure](image)

Following general procedure E, using (S)-**tert**-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.3 mmol) and N-Cbz-L-Trp-NH₂ (0.2 mmol). Purification via flash column chromatography (4:1 to 1:1.5 hexane:EtOAc) afforded the title compound as a pale yellow oil (48.4 mg, 48%); [α]D20 + 11.9 (c = 1.844, CHCl₃); νmax / cm⁻¹ 3408, 3319, 2976, 1710, 1659, 1510, 1249, 1230; δH (400 MHz, CDCl₃) 8.19 (1H, br s, indole NH), 7.68 (1H, d, J 7.7, indole ArH), 7.38-7.28 (6H, m, 5 x phenyl ArH and 1 x indole NH), 7.19 (1H, t, J 7.7, indole ArH), 7.10 (1H, t, J 7.7, indole ArH) and 7.06 (1H, m, indole ArH), 6.40 (1H, d, J 6.9, NHCHCO₂Bu), 5.65-5.49 (2H, m, CH₃CH₂CH=CH and NHCO₂Bn), 5.29 (1H, app. dd, J 15.6 and 6.0, CH₃CH₂CH=CH), 5.11 (2H, s, OCH₂Ph), 4.80 (1H, t, J 6.7, CHNHCO₂Bn), 4.62-4.50 (1H, m, CHH(C₈H₅N)), 3.42-3.21 (1H, dd, J 14.6 and 7.2 CHH(C₈H₅N)), 1.97 (2H, app. p, J 7.2, CH₃CH₂CH=CH), 1.42 (3H, t, J 7.4, CH₃CH₂CH=CH); the following distinct signals for the Z-isomer were observed 4.89 (1H, t, J 6.9), 2.20 (2H, app. p, J 7.3), 1.01 (3H, t, 7.4) and the E:Z ratio was determined to be 7.5:1 by integration of the signals at 0.92 and 1.01 respectively; δC (101 MHz, CDCl₃) 170.5, 169.5, 155.9, 136.2, 135.9, 128.5, 128.1, 128.0, 127.4, 123.4, 122.9, 122.2, 119.7, 118.8, 111.2, 82.1, 69.9, 60.3, 55.4, 54.7, 27.9, 25.1, 13.3, 14.2, 13.0; m/z (ES⁺) 512 (23%, [M+MeCN+Na⁺]) 528 (100%, [MNa⁺]), 506 (56%, [MH]⁺), 450 (35%), 406 (12%); HRMS (ES+/TOF) found 528.2480, C₂₉H₃₅N₃O₅Na requires 528.2474; The diastereomeric mixture was prepared by the same method using racemic **tert**-Butyl 4-phenylselanyl-hex-2-(E)-enoate. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; δH (400 MHz, CDCl₃) 5.19 (1H, ddt, J 15.4, 6.1 and 1.5, CH₃CH₂CH=CH) 1.40 (9H, s, C(CH₃)₃); δC (101 MHz, CDCl₃) 170.5, 169.8, 136.4, 122.9, 122.5, 54.7.
tert-Butyl (2S,3E)-2-((S)-6-azido-2-(9H-fluoren-9-ylmethoxy)carbonylamino)hex-3-enolate, 189

Following general procedure E, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.3 mmol) and \(N\)-Fmoc-L-Lys(N\(_3\))NH\(_2\) (0.2 mmol). Purification via flash column chromatography (4:1 to 2:1 \(\text{hexane:EtOAc}\)) afforded the title compound as a pale yellow oil (43 mg, 77\%); \([\alpha]_D^{20}\) +2.67 (c = 2.24, CHCl\(_3\)); \(\nu_{\max}\) / cm\(^{-1}\) 3304, 2968, 2095, 1729, 1655, 1530, 1247, 1151; \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.76 (2H, d, \(J = 7.5\), 2 x ArH), 7.59 (2H, d, \(J = 7.4\), 2 x ArH), 7.44-7.35 (2H, m, 2 x ArH), 7.35-7.26 (2H, m, 2 x ArH), 6.58 (1H, d, \(N\)HCHCO\(_2\)tBu), 5.83-5.71 (1H, m, CH\(_3\)CH\(_2\)C=CH), 5.55-5.36 (2H, m, CH\(_3\)CH\(_2\)CH=CH and \(N\)HBoc), 4.90 (1H, t, \(J = 6.7\), CHNHFmoc), 3.27 (2H, t, \(J = 6.7\), CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)N\(_3\)), 2.11-1.97 (2H, m, CH\(_3\)CH\(_2\)CH=CH), 1.96-1.82 (1H, m, \(CH\)HCH\(_2\)CH\(_2\)CH\(_2\)N\(_3\)), 1.75-1.53 (3H, m, CH\(_3\)CH\(_2\)CH\(_2\)CH\(_2\)N\(_3\) and CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)N\(_3\)), 0.95 (3H, t, \(J = 7.4\), CH\(_3\)CH\(_2\)CH=CH); the following distinct signals for the Z-isomer were observed 6.70 (2H, m), 5.71-5.64 (2H, m), 2.26 (2H, m), 1.03 (3H, t, \(J = 7.4\)) and the \(E:Z\) ratio was determined to be 4:1 by integration of the signals at 5.83-5.71 and 5.71-5.64 respectively; \(\delta_C\) (101 MHz, CDCl\(_3\)) 170.7, 169.8, 156.1, 143.8, 143.7, 141.2, 136.3, 127.7, 127.0, 125.0, 122.8, 119.9, 82.4, 67.1, 54.6, 51.1, 47.1, 32.5, 28.4, 27.9, 25.2, 22.5, 13.1; m/z (ES+) 584 (100\%, [MNa\(^+\)], 562 (90\%, [MH\(^+\)]), 506 (53\%), 242 (41\%), 208 (34\%); HRMS (ES+/TOF) found 584.2858, C\(_{31}\)H\(_{39}\)N\(_5\)O\(_5\)Na requires 584.2849; The diastereomeric mixture was prepared by the same method using racemic tert-butyl 4-phenylselanyl-hex-2-(E)-enoate. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; \(\delta_C\) (101 MHz, CDCl\(_3\)) 170.0, 136.4, 82.7, 54.6, 32.5, 13.3.
General Procedure F: Amination/Rearrangement of allylic selenides With Amino Acid Esters

To a solution of allylic selenide (0.30 mmol) in dry methanol (1 mL) was added trimethylorthoformate (129 μL, 1.18 mmol) and para-toluene sulfonic acid (1 mg). The solution was stirred for 30 minutes at room temperature before cooling to 0 °C, diisopropylethylamine (209 μL, 1.20 mmol) then N-Chlorosuccinimide were added. The solution was stirred for 2 minutes and then the amino acid ester was added. The reaction mixture was held at 0 °C for 20 min, then 1M HCl (aq., 1mL) was added, followed by saturated NaHCO₃ (1 mL). The reaction was extracted into EtOAc, washed with brine, dried over Na₂SO₄, concentrated under reduced pressure and purified by flash column chromatography.

(2S,3E)-tert-Butyl 2-((S)-1-Benzzyloxycarbonylhexamino)hex-3-enoate, 190

Following general procedure F, using (S)-tert-butyl 4-phenylselenylhex-2-(E)-enoate (0.3 mmol) and H₂N-L-Ala-CO₂Bn (0.3 mmol). Purification via flash column chromatography (7:1 to 5:1 ᵃ-hexane:EtOAc) afforded the title compound as a light yellow oil (50 mg, 72%); [α]D²¹ +3.1° (c = 2.58, CHCl₃); νmax / cm⁻¹ 2975, 2934, 1730, 1498, 1456; δH (400 MHz, CDCl₃) 7.38-7.30 (5 H, m, 5 x ArH), 5.74 (1H, dtd, J 15.4, 6.3 and 1.0, CH₂C=CH), 5.35 (1H, ddt, J 15.4, 7.7 and 1.6, CH₂CH=C=CH₂), 5.18 (1H, d, J 12.4, CHCHPh), 5.11 (1H, d, J 12.4, CHCHPh), 3.72–3.70 (1H, m, C=CHCH=NH), 3.40 (1H, q, J 7.0, CHCH₃), 2.06–1.98 (2H, m, CH₂CH₃), 1.44 (9H, s, C(CH₃)₃), 1.32 (3H, d, J 7.0, CHCH₃), 0.96 (3H, t, J 7.4, CH₂CH₃); the following distinct signals for the Z-isomer were observed, 5.63 (1H, dtd, J 10.8, 7.4, 0.9, CH₂CH=CH₂), 0.92 (3H, d, J 7.5, CH₂CH₃) and the E:Z ratio was determined to be 8:1 by integration of the signals at 5.74 and 5.63 ppm, respectively; δC (101 MHz, CDCl₃) 175.0, 171.1, 136.7, 135.8, 128.5, 128.2, 128.1, 125.6, 81.3, 66.5, 62.8, 64.4, 28.0, 25.3, 19.1, 13.2; m/z (ES+) 370 (20%, [MNa]⁺), 348 (100%, [MH]⁺), 292 (40%); HRMS (ES+/TOF) found 348.2167, C₂₀H₃₀N₂O₄ requires 348.2175. The diastereomeric mixture was prepared by the same method from racemic (S)-tert-butyl 4-phenylselenyl-hex-2-(E)-enoate. The mixture was partially separable by careful column chromatography. Data for the minor diastereomer; δH (400 MHz, CDCl₃) 7.39-7.30 (5H, m, 5 x ArH), 5.67 (1H, dtd, J
15.4, 6.4 and 1.0, CH\(_2\)CH=CH\(_2\)), 5.32 (1H, ddt, J 15.3, 7.7 and 1.5, CH\(_2\)CH=CH\(_2\)), 5.18-5.12 (2H, m, CH\(_2\)Ph), 3.70-3.68 (1H, m, C=CHCHNH), 3.43 (1H, q, J 7.0, CHCH\(_2\)), 2.04 (2H, m, CH\(_2\)CH\(_3\)), 1.43 (9H, s, C(CH\(_3\))\(_3\)), 1.33 (3H, d, J 7.0, CHCH\(_3\)), 0.97 (3H, t, J 7.4, CH\(_2\)CH\(_3\)); \(\delta\)\(_C\) (100 MHz, CDCl\(_3\)) 174.9, 171.7, 137.1, 135.8, 128.5, 128.2, 128.1, 125.3, 81.4, 62.4, 62.0, 53.6, 28.0, 25.3, 19.0, 13.4; m/z (ES\(+\)) 370 (20%, \([\text{MNa}]^+\)), 348 (100%, \([\text{MH}]^+\)), 292 (40%); HRMS (ES\(+\)/TOF) found 348.2176, C\(_{20}\)H\(_{30}\)NO\(_4\) requires 348.2175.

\((2S,3E)-\text{-tert-Butyl 2-\((S)-1\text{-benzyloxy carbonyl ethylamino}\)}\text{-hex-3-enoate, 192\)

Following general procedure F, using (S)-\text{-tert-butyl 4-phenylselenylhex-2-(E)-enoate (0.3 mmol) and H\(_2\)N-L-Phg-CO\(_2\)Me (0.3 mmol). Purification via flash column chromatography (15:1 to 5:1 \(^9\)hexane:EtOAc afforded the title compound as a light yellow oil (40 mg, 60%); 

\([\alpha]_D^{21}+107\ (c = 2.13, \text{CHCl}_3); \nu_{\text{max}} / \text{cm}^{-1} \text{ 2970, 1730s, 1456, 1435, 1393, 1368; \(\delta\)_H (400 MHz, CDCl\(_3\)) 7.37-7.28 (5 H, m, 5 x ArH), 5.66 (1H, ddt, J 15.4, 6.3 and 0.9, CH\(_2\)CH=CH\(_2\)), 5.34 (1H, ddt, J 15.4, 8.0 and 1.6, CH\(_2\)CH=CH\(_2\)), 4.40 (1H, s, CHPh), 3.66 (3H, s, OMe), 3.56 (1H, d, J 8.0, C=CHCHNH), 2.66 (1H, br s, NH), 2.21-1.94 (2H, m, CH\(_2\)), 1.41 (9H, s, C(CH\(_3\))\(_3\)), 0.99 (3H, t, J 7.5, CH\(_2\)CH\(_3\)); \(\delta\)\(_C\) (101 MHz, CDCl\(_3\)) 172.9, 171.7, 137.7, 137.4, 128.7, 128.1, 125.3, 81.3, 62.6, 61.7, 52.2, 27.9, 25.3, 13.3; m/z (ES\(+\)) 334 (100%, 

\([\text{MH}]^+\)), 278 (40%, \(\text{[MH-C(CH\(_3\))\(_3\}]^+\)); HRMS (ES\(+\)/TOF) found 334.2013, C\(_{19}\)H\(_{28}\)NO\(_4\) requires 334.2018. The diastereomeric mixture was prepared by the same method from racemic \text{-tert-butyl 4-phenylselenylhex-2-(E)-enoate. The mixture was partially separable by careful column chromatography. Data for minor diastereomer: \(\delta\)_H (400 MHz, CDCl\(_3\)) 7.39-7.30 (5H, m, 5 x ArH), 5.75 (1H, ddt, J 15.5, 6.4 and 1.2, CH\(_2\)CH=CH\(_2\)), 5.39 (1H, ddt, J 15.4, 7.1 and 1.6, CH\(_2\)CH=CH\(_2\)); 4.43 (1H, s, CHPh), 3.68 (3H, s, OMe), 3.58 (1H, d, J 7.1, C=CHCHNH), 2.72 (1H, br s, NH), 2.09-2.01 (2H, m, CH\(_2\)), 1.5 (9H, s, C(CH\(_3\))\(_3\)), 0.98 (3H, t, J 7.4, CH\(_2\)CH\(_3\)); \(\delta\)\(_C\) (101 MHz, CDCl\(_3\)) 172.9, 172.0, 137.8, 136.3, 128.6, 128.1, 127.9, 125.4, 81.4, 62.8, 61.2, 52.3, 28.0, 25.4, 13.3. The diastereomeric ratio of the material derived from the enantiomerically enriched allylic selenide was determined to be 96:4 by integration of the 1H NMR signals at 5.67 (major) and 5.75 (minor) ppm.
Following general procedure F, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.3 mmol) and H$_2$N-L-Ser-CO$_2$Bn (0.2 mmol) with cooling to -40 °C prior to the diisopropylethylamine addition. The reaction was then held at -40 °C and allowed to stir for 12 hours after the NCS addition, purification via flash column chromatography (9:1 to 1:1 n-hexane:EtOAc) afforded the title compound as a pale yellow oil (39.5 mg, 54%); $\alpha_D^{18} +25.3$ (c = 0.71, CH$_2$Cl$_2$); $\nu_{max}$/ cm$^{-1}$ 3034, 2968, 2934, 2873, 1729, 1456, 1368, 1259, 1152, 1060; $\delta_H$ (400 MHz, CDCl$_3$) 7.37-7.32 (5H, m, 5 x ArH), 5.78 (1H, dtd, J 15.6, 6.3 and 0.8, CH$_2$CH=CH), 5.36 (1H, ddt, J 15.5, 8.1 and 1.7, CH$_2$CH=CH), 5.18 (2H, d, J 1.9, CH$_2$Ph), 3.79-3.70 (2H, m, CH=CHCH$_2$OH), 3.64 (1H, dd, J 10.9 and 6.2, CH$_2$OCH), 3.43 (1H, dd, J 6.2 and 4.1, CH$_2$CH$_2$OH), 2.21 (2H, br s, OH and NH), 2.02 (2H, ddd, J 7.6, 6.3 and 1.6, CH$_3$CH$_2$CH=CH), 1.45 (9H, s, C(CH$_3$)$_3$), 0.96 (3H, t, J 7.4, CH$_2$CH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 172.5, 171.9, 137.7, 135.3, 128.6, 128.4, 128.1, 125.1, 81.7, 67.0, 63.1, 62.5, 60.5, 27.9, 25.3, 13.2; m/z (ES+) 386 (51%, [MNa$^+$]), 364 (100%, [MH$^+$]), 308 (33%); HRMS (ES+/TOF) found 364.2136, for C$_{20}$H$_{30}$NO$_5$ 364.2124; The diastereomeric mixture was prepared by the same method from racemic (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; $\delta_C$ (101 MHz, CDCl$_3$) 128.7, 128.6, 128.5, 128.4, 81.8, 67.1, 62.8, 60.2, 28.2, 25.5 13.5.

Ethyl (2S,3E)-2-(((2S)-1-(benzyloxy)-1-oxopropan-2-yl)amino)-2-methylhex-3-enoate, 194

Following general procedure F, using (S)-ethyl-2-methyl-4-(phenylselanyl)hex-2-(E)-enoate (0.3 mmol) and H$_2$N-L-Ala-CO$_2$Bn (0.2 mmol). Purification via flash column chromatography (19:1 to 1:1 n-hexane:EtOAc) afforded the title compound as a colourless oil (15.4 mg, 46%); [$\alpha_D^{21}$] -8.9 (c = 0.89, CH$_2$Cl$_2$); $\nu_{max}$/ cm$^{-1}$ 3068, 3036, 2979, 2964, 2935, 1731, 1455, 1375, 1292, 1146, 974; $\delta_H$ (400 MHz, CDCl$_3$) 7.42-7.31 (5H, m, 5 x ArH), 5.39-5.31 (1H, m, 5 x CH$_2$), 5.17 (2H, d, J 1.9, CH$_2$Ph), 3.72-3.60 (2H, m, CH=CHCH$_2$OH), 3.51 (1H, dd, J 10.9 and 6.2, CH$_2$OCH), 3.32 (1H, dd, J 6.2 and 4.1, CH$_2$CH$_2$OH), 2.19 (2H, br s, OH and NH), 2.02 (2H, ddd, J 7.6, 6.3 and 1.6, CH$_3$CH$_2$CH=CH), 1.45 (9H, s, C(CH$_3$)$_3$), 0.96 (3H, t, J 7.4, CH$_2$CH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 172.5, 171.9, 137.7, 135.3, 128.6, 128.4, 128.1, 125.1, 81.7, 67.0, 63.1, 62.5, 60.5, 27.9, 25.3, 13.2; m/z (ES+) 386 (51%, [MNa$^+$]), 364 (100%, [MH$^+$]), 308 (33%); HRMS (ES+/TOF) found 364.2136, for C$_{20}$H$_{30}$NO$_5$ 364.2124; The diastereomeric mixture was prepared by the same method from racemic (S)-ethyl-2-methyl-4-(phenylselanyl)hex-2-(E)-enoate. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; $\delta_C$ (101 MHz, CDCl$_3$) 128.7, 128.6, 128.5, 128.4, 81.8, 67.1, 62.8, 60.2, 28.2, 25.5 13.5.
ArH), 5.71 (1H, dt, J 15.8 and 6.3, CH₂CH₂CH=CH), 5.49 (1H, dt, J 15.9 and 1.6, CH₃CH₂CH=CH), 5.23-5.19 (1H, d, J 12.1, CHHPh), 5.13 (1H, d, J 12.1, CHHPh), 4.16 (2H, q, J 7.1, OCH₂CH₃), 3.41 (1H, q, J 7.1, CHCH₃), 2.52 (1H, br s, NH), 2.01 (2H, m, CH₃CH₂CH=CH), 1.38 (3H, s, CH₃), 1.34 (3H, d, J 7.1, CHCH₃), 1.28 (3H, t, J 7.2, OCH₂CH₃), 0.98 (3H, t, J 7.4, (CH₃CH₂CH=CH); δC (101 MHz, CDCl₃) 176.4, 174.8, 135.7, 133.3, 130.8, 128.5, 128.3, 128.2, 66.4, 63.0, 61.1, 52.2, 25.4, 22.8, 21.3, 14.1, 13.3; m/z (ES+) 334 (100%, [MH]+), 208 (87%); HRMS (ES+/TOF) found 334.2030, C₁₉H₂₈NO₄ requires 334.2018. The diastereomeric mixture was prepared by the same method from racemic (S)-ethyl-2-methyl-4-(phenylselanyl)hex-2-(E)-enoate. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; δC (101 MHz, CDCl₃) 133.6, 130.7, 63.0, 61.2, 52.2, 23.8, 14.2.

**General Procedure G: Amination/Rearrangement of allylic selenides using aromatic amines**

To a solution of allylic selenide (0.20 mmol) in dry methanol (1 mL) was added trimethyl orthoformate (129 μL, 1.18 mmol) and para-toluenesulfonic acid (1 mg). The solution was stirred for 30 minutes at room temperature before cooling to -20 °C, diisopropylethylamine (209 μL, 1.20 mmol) then N-chlorosuccinimide (80 mg, 0.6 mmol) were added. The solution was stirred for 2 minutes and then the aromatic amine (0.30 mmol) was added. The reaction was stirred at -20 °C for 20 minutes, then 1M HCl (aq., 1mL) was added, followed by saturated NaHCO₃ (1 mL). The reaction was extracted into EtOAc, washed with brine, dried over Na₂SO₄, concentrated under reduced pressure and further purified by flash column chromatography.

**tert-Butyl (2S,3E)-2-[(1,3-thiazol-2-yl)amino]hex-3-enoate, 195**

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 2-aminothiazole (0.3 mmol). Purification via flash column chromatography (8:1 to 4:1 n-hexane:EtOAc) afforded the title compound as a colourless oil (39.4 mg, 73%); [α]D²⁴ +93.2 (c = 1.11, CHCl₃); νmax / cm⁻¹ 3326, 3198, 2969, 2933, 1726, 1619, 1523, 1368, 1255, 1148; δH (400 MHz, CDCl₃) 7.12 (1H, d, J 3.6, ArH), 6.50 (1H, d, J 3.6 ArH), 5.71 (1H, dt, J 15.8 and 6.3, CH₃CH₂CH=CH), 5.49 (1H, dt, J 15.9 and 1.6, CH₃CH₂CH=CH), 5.23-5.19 (1H, d, J 12.1, CHHPh), 5.13 (1H, d, J 12.1, CHHPh), 4.16 (2H, q, J 7.1, OCH₂CH₃), 3.41 (1H, q, J 7.1, CHCH₃), 2.52 (1H, br s, NH), 2.01 (2H, m, CH₃CH₂CH=CH), 1.38 (3H, s, CH₃), 1.34 (3H, d, J 7.1, CHCH₃), 1.28 (3H, t, J 7.2, OCH₂CH₃), 0.98 (3H, t, J 7.4, (CH₃CH₂CH=CH); δC (101 MHz, CDCl₃) 176.4, 174.8, 135.7, 133.3, 130.8, 128.5, 128.3, 128.2, 66.4, 63.0, 61.1, 52.2, 25.4, 22.8, 21.3, 14.1, 13.3; m/z (ES+) 334 (100%, [MH]⁺), 208 (87%); HRMS (ES+/TOF) found 334.2030, C₁₉H₂₈NO₄ requires 334.2018. The diastereomeric mixture was prepared by the same method from racemic (S)-ethyl-2-methyl-4-(phenylselanyl)hex-2-(E)-enoate. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; δC (101 MHz, CDCl₃) 133.6, 130.7, 63.0, 61.2, 52.2, 23.8, 14.2.
5.91 (1H, dtd, J 15.6, 6.4 and 1.4, CH$_3$CH$_2$CH=CH), 5.72 (1H, br s, NH), 5.48 (1H, ddt, J 15.4, 6.1 and 1.6, CH$_3$CH$_2$CH=CH), 4.67 (1H, ddd, J 7.3, 5.9 and 1.2, NHCHCO$_2$Bu), 2.10 (2H, ddt, J 7.6, 6.3 and 1.4, CH$_3$CH$_2$), 1.47 (9H, s, C(CH$_3$)$_3$), 0.99 (3H, t, J 7.4, CH$_3$CH$_2$); the following distinct signals for the Z-isomer were observed δ$_H$ (400 MHz, CDCl$_3$) 5.86 (1H, dtd, J 10.4, 6.5 and 1.4, CH$_3$CH$_2$CH=CH), 5.23 (1H, ddt, J 10.4, 8.9 and 1.4, CH$_3$CH$_2$CH=CH), 2.31 (2H, qd, J 7.4 and 1.6, CH$_3$CH$_2$), 1.06 (3H, t, J 7.5, CH$_3$CH$_2$) and the $E$/Z ratio was determined to be 28:1 by integration of the signals at 5.48 and 5.23 respectively; δ$_C$ (101 MHz, CDCl$_3$) 170.1, 168.2, 138.9, 136.7, 123.2, 107.3, 82.4, 60.1, 27.9, 25.3, 13.2; m/z (ES$^+$) 269 (100%, [MH$^+$]+), 224 (45%), 214 (61%); HRMS (ES+/TOF) found 269.1334, C$_{13}$H$_{21}$N$_2$O$_2$S requires 269.1324; enantiomeric ratio was determined as 94.5:5.5 using HPLC; Chiralpak IA-3 column, 98% hexane:IPA, flow 1 mLmin$^{-1}$, UV detection at 254 nm, 30.3 min (minor), 70.8 min (major).

tert-Butyl (2S,3E)-2-[(1,3-benzothiazol-2-yl)amino]hex-3-enoate, 196

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 2-aminobenzthiazole (0.3 mmol). Purification via flash column chromatography (14:1 hexane:EtOAc) afforded the title compound as an orange oil (46.8 mg, 74%); $[\alpha]_{D}^{23}$ +54.8 ($c = 0.99$, CHCl$_3$); $\nu_{\text{max}}$ / cm$^{-1}$ 3314, 2973, 2932, 2875, 1725, 1599, 1540, 1456, 1445, 1368, 1153; δ$_H$ (400 MHz, CDCl$_3$) 7.59-7.54 (2H, m, 2× ArH), 7.31 (1H, ddd, J 7.7, 7.4 and 1.3, ArH), 7.12 (1H, td, J 7.6 and 1.2, ArH), 6.14-5.93 (2H, includes (1H br s, NH) and (1H, ddt, J 15.5, 6.4 and 1.5, CH$_3$CH$_2$CH=CH)), 5.56 (1H, ddt, J 15.5, 5.9 and 1.6, CH$_3$CH$_2$CH=CH), 4.91 (1H, d, J 5.9, NHCHCO$_2$Bu), 2.18-2.05 (2H, m, CH$_3$CH$_2$), 1.51 (9H, s, C(CH$_3$)$_3$); 1.01 (3H, t, J 7.4, CH$_3$H$_2$) the following distinct signals for the Z-isomer were observed δ$_H$ (400 MHz, CDCl$_3$) 5.27 (1H, ddt, J 10.6, 90 and 1.5, CH$_3$CH$_2$CH=CH), 2.42-2.32 (2H, m, CH$_3$CH$_2$) and the $E$/Z ratio was determined to be 27:1 by integration of the signals at 5.56 and 5.27 respectively; δ$_C$ (101 MHz, CDCl$_3$) 169.9, 165.4, 152.1, 136.7, 130.8, 125.8, 123.1, 121.8, 120.8, 119.2, 82.6, 59.5, 28.0, 25.3, 13.2; m/z (ES$^+$) 319 (100%, [MH$^+$]$^+$), 263 (54%), 224 (59%), 208 (49%); HRMS (ES+/TOF) found 319.1495, C$_{17}$H$_{23}$N$_2$O$_2$S requires 319.1480; enantiomeric ratio was determined as 97:3 using HPLC;
Chiralcel OD-H column, 99:1 n-hexane:IPA, flow 1 mLmin⁻¹, UV detection at 254 nm, 22.6 min (minor), 35.0 min (major).

**tert-Butyl (2S,3E)-2-[(4-methoxy-1,3-benzothiazol-2-yl)amino]hex-3-enoate, 197**

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 2-aminobenzthiazole (0.3 mmol). Purification via flash column chromatography (9:1 n-hexane:EtOAc) afforded the title compound as a pale yellow foam (57.1 mg, 82%); [α]D¹⁷ +37.7 (c = 1.06, CHCl₃); νmax / cm⁻¹ 3396, 2971, 2937, 2906, 1729, 1589, 1546, 1479, 1369, 1327, 1254, 1154, 1048; δH (400 MHz, CDCl₃) 7.19 (1H, dd, J 7.9 and 1.0, ArH), 7.03 (1H, t, J 8.0, ArH), 6.79 (1H, dd, J 8.0 and 1.0, ArH), 6.13 (1H, br s, NH), 5.94 (1H, ddt, J 15.5, 6.0 and 1.6, CH₃CH₂CH=CH), 5.49 (1H, ddt, J 15.5, 6.0 and 1.6, CH₃CH₂CH=CH), 4.75 (1H, m, NHCH₂CO₂tBu), 3.20 (3H, s, OCH₃), 2.10-2.03 (2H, m, CH₃C₂H₂), 1.47 (9H, s, C(CH₃)₃), 0.97 (3H, t, J 7.4, CH₃C₂H₂); δC (101 MHz, CDCl₃) 169.5, 164.9, 150.7, 141.5, 136.8, 131.8, 123.1, 122.2, 113.1, 107.2, 82.6, 59.9, 55.8, 27.9, 25.2, 13.1; m/z (ES+) 349 (100%, [MH]+), 293 (47%); HRMS (ES+/TOF) found 349.1592, C₁₈H₂₅N₂O₃S requires 349.1586; enantiomeric ratio was determined as 97:3 using HPLC; Chiralcel AD column, 95:1 n-hexane:IPA, flow 1 mLmin⁻¹, UV detection at 254 nm, 19.7 min (minor), 23.9 min (major).

**tert-Butyl (2S,3E)-2-(phenylamino)hex-3-enoate, 198**

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and aniline (0.3 mmol). Purification via flash column chromatography (80:1 n-hexane:Et₂O) afforded the title compound as a clear oil (38.8 mg, 75%); [α]D²¹ +50.2 (c = 1.39, CHCl₃); νmax / cm⁻¹ 3405, 2970, 2933, 2872, 1730, 1604, 1505, 1369, 1316, 1256, 1152; δH (400 MHz, CDCl₃) 7.22-7.11 (2H, m, 2 × ArH), 6.72 (1H, tt, J 7.4 and 1.1, ArH), 6.65-6.57 (2H, m, 2 x ArH), 5.91 (1H, ddt, J 15.5, 6.4 and 1.3, CH₃CH₂CH=CH), 5.51 (1H, ddt, J 15.5, 5.7 and 1.6, CH₃CH₂CH=CH), 4.46 (1H, br d, J 6.4, NH), 4.41 (1H, br t, J 5.9,
NHCH\textsubscript{2}CO\textsubscript{2}Bu), 2.14-2.02 (2H, m, CH\textsubscript{3}CH\textsubscript{2}), 1.46 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 0.99 (3H, t, J 7.4, CH\textsubscript{3}CH\textsubscript{2}); δ\textsubscript{c} (101 MHz, CDCl\textsubscript{3}) 171.4, 146.6, 135.9, 129.1, 124.7, 117.9, 113.5, 81.9, 59.1, 28.0, 25.3, 13.4; m/z 262 (100%, [MH]\textsuperscript{+}), 214 (13%), 206 (37%); HRMS (ES+/TOF) found 262.1801 for C\textsubscript{16}H\textsubscript{24}NO\textsubscript{2} requires 262.1807; the enantiomeric ratio could not be determined using HPLC analysis of the above compound, reduction to the primary alcohol allowed the enantiomeric ratio to be determined as 97:3 see below.

**(2S,3E)-2-(Phenylamino)hex-3-en-1-ol**

![Chemical Structure](image)

To a stirred solution to tert-butyl (2S,3E)-2-(phenylamino)hex-3-enoate (0.11 mmol) in THF (0.8 mL) at 0 °C under argon was added dropwise a solution of LiAlH\textsubscript{4} in THF (1.0M, 0.33 mmol). The solution was stirred at 0 °C for a further 1.5 hours and then quenched with H\textsubscript{2}O (6 mL). The reaction was extracted into CH\textsubscript{2}Cl\textsubscript{2}, dried with Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Further purification by flash column chromatography afforded the product as a clear oil (17.8 mg, 79%); [α]\textsubscript{D}\textsuperscript{22} +39.0 (c = 0.81, CH\textsubscript{3}OH); ν\textsubscript{max} / cm\textsuperscript{-1} 3369, 3052, 3024, 2962, 2929, 2873, 1601, 1501, 1317, 1261, 1027, 957; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.17 (2H, td, J 7.5 and 2.1, 2 x ArH), 6.76-6.71 (1H, m, ArH), 6.70-6.66 (2H, m, ArH), 5.79 (1H, dtd, J 15.5, 6.3 and 1.3, CH\textsubscript{3}CH\textsubscript{2}CH=CH), 5.37 (1H, ddt, J 15.5, 6.1 and 1.5, CH\textsubscript{3}CH\textsubscript{3}CH=CH), 4.01-3.95 (1H, m, NHCH\textsubscript{2}CH\textsubscript{2}OH), 3.74 (1H, dd, J 10.8 and 4.6, CHOH), 3.61 (1H, dd, J 10.9 and 6.5, CHOH), 2.05 (2H, ddt, J 7.6, 6.3 and 1.3, CH\textsubscript{3}CH\textsubscript{2}), 0.97 (3H, t, J 7.4, CH\textsubscript{3}CH\textsubscript{2}); δ\textsubscript{c} (101 MHz, CDCl\textsubscript{3}) 147.2, 135.7, 129.2, 126.9, 118.1, 114.1, 56.5, 57.4, 25.4, 13.5; m/z (ES+) 192 (100%, [MH]\textsuperscript{+}), 135 (21%), 94 (12%); HRMS (ES+/TOF) found 192.1391, C\textsubscript{12}H\textsubscript{18}NO requires 192.1388; enantiomeric ratio was determined as 97:3 using HPLC; Chiralpak IA-3 column, 95:5 hexane:IPA, flow 1 mLmin\textsuperscript{-1}, UV detection at 254 nm, 13.1 min (major), 14.0 min (minor).

**tert-Butyl (2S,3E)-2-[(4-methylphenyl)amino]hex-3-enoate, 199**

![Chemical Structure](image)

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and p-toluidine (0.3 mmol). Purification via flash column chromatography (50:1
\( \text{hexane:Et}_2\text{O} \) afforded the title compound at an off white solid (33.3 mg, 61%); m.p. 44-46 \(^\circ\text{C}\); \([\alpha]_D^{23} +63.2 \ (c = 1.24, \text{CHCl}_3); \ \nu_{\text{max}} / \text{cm}^{-1} 3399, 2976, 2969, 2932, 2873, 1728, 1619, 1520, 1368, 1253, 1147; \delta_{\text{H}} \ (400 \text{ MHz, CDCl}_3) 6.98 \ (2\text{H, d, } J = 8.1, 2 \times \text{ArH}), 6.54 \ (2\text{H, d, } J = 8.2, 2 \times \text{ArH}), 5.90 \ (1\text{H, dtd, } J = 15.4, 6.4 \text{ and } 1.2, \text{CH}_3\text{CH}_2\text{CH} = \text{CH}), 5.50 \ (1\text{H, ddt, } J = 15.4, 5.8 \text{ and } 1.6, \text{CH}_3\text{CH}_2\text{CH} = \text{CH}), 4.39 \ (1\text{H, br d, } J = 5.0, \text{NHC}=\text{CO}_2\text{tBu}), 4.32 \ (1\text{H, br s, NH}), 2.24 \ (3\text{H, s, ArCH}_3), 2.14-2.01 \ (2\text{H, m, CH}_3\text{CH}_2), 1.46 \ (9\text{H, t, } J = 7.4, \text{CH}_3\text{CH}_2); \delta_{\text{C}} \ (101 \text{ MHz, CDCl}_3) 171.6, 144.3, 135.8, 129.6, 127.0, 124.9, 113.6, 81.9, 59.4, 28.0, 25.3, 20.4, 13.4; \ m/z \ (\text{ES+}) \ 276 \ (100\%, \ [\text{MH}]^+) , 220 \ (19\%); \ \text{HRMS (ES+/TOF) found } 276.1964, \ C_{17}H_{26}NO_2 \text{ requires } 276.1964; \ \text{enantiomeric ratio was determined as } 96.5:3.5 \text{ using HPLC; Chiralpak IA-3 column, 95-5 } \text{hexane:IPA, flow 1 mLmin}^{-1}, \ \text{UV detection at } 254 \text{ nm, } 4.9 \text{ min (major), } 5.7 \text{ min (minor).}

**tert-Butyl (2S,3E)-2-[(2-methylphenyl)amino]hex-3-enoate, 200**

Following general procedure G, using (S)-\textit{tert}-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and \alpha-toluidine (0.3 mmol). Purification via flash column chromatography (50:1 \text{hexane:Et}_2\text{O}) afforded the title compound as a pale yellow oil (26.9 mg, 49%); \([\alpha]_D^{23} +48.1 \ (c = 1.08, \text{CHCl}_3); \ \nu_{\text{max}} / \text{cm}^{-1} 3420, 2967, 2932, 2874, 1728, 1606, 1510, 1368, 1256, 1149; \delta_{\text{H}} \ (400 \text{ MHz, CDCl}_3) 7.12-7.03 \ (2\text{H, m, } 2 \times \text{ArH}), 6.67 \ (1\text{H, td, } J = 7.4 \text{ and } 1.0, \text{ArH}), 6.49 \ (1\text{H, dd, } J = 8.5 \text{ and } 1.0), 5.91 \ (1\text{H, dtd, } J = 15.4, 6.3 \text{ and } 0.9, \text{CH}_3\text{CH}_2\text{CH} = \text{CH}), 5.54 \ (1\text{H, ddt, } J = 15.3, 5.4 \text{ and } 1.5, \text{CH}_3\text{CH}_2\text{CH} = \text{CH}), 4.48-4.38 \ (2\text{H, m, NH and NHCHCO}_2\text{tBu}), 2.24 \ (3\text{H, s, ArCH}_3), 2.15-206 \ (2\text{H, m, CH}_3\text{CH}_2), 1.47 \ (9\text{H, s, C(CH}_3)_3, 1.00 \ (3\text{H, t, } J = 7.4, \text{CH}_3\text{CH}_2); \delta_{\text{C}} \ (101 \text{ MHz, CDCl}_3) 171.6, 144.7, 135.7, 130.1, 126.9, 124.8, 122.4, 117.3, 110.6, 81.9, 59.0, 28.0, 25.3, 17.5, 13.4; \ m/z \ (\text{ES+}) \ 276 \ (100\%, \ [\text{MH}]^+), 220 \ (15\%); \ \text{HRMS (ES+/TOF) found } 276.1964, \ C_{17}H_{26}NO_2 \text{ requires } 276.1964; \ \text{the enantiomeric ratio could not be determined using HPLC analysis of the above compound, reduction to the primary alcohol allowed the enantiomeric ratio to be determined as } 96.5:3.5 \text{ see below.}
(2S,3E)-2-[(2-Methylphenyl)amino]hex-3-en-1-ol

To a stirred solution of tert-butyl (2S,3E)-2-[(2-methylphenyl)amino]hex-3-enoate (34 mg, 0.12 mmol) in THF (0.8 mL) under argon at 0 °C was added dropwise a solution of LiAlH₄ in THF (1.0 M, 0.36 mmol). The solution was stirred at 0 °C for a further 1.5 hours and then quenched with H₂O (6 mL). The reaction was extracted into CH₂Cl₂, dried with Na₂SO₄ and concentrated under reduced pressure. Further purification by flash column chromatography provided the product as a clear oil (21.0 mg, 85%); [α]D²³ +65.3 (c = 0.76, CHCl₃); νmax / cm⁻¹ 3346, 2968, 2934, 2874, 1712, 1501, 1456, 1326, 1222, 1153, 1045; δH (400 MHz, CDCl₃) 7.15-7.04 (2H, m, 2 x ArH), 6.71-6.66 (2H, m, 2 x ArH), 5.78 (1H, dtd, J 15.4, 6.2 and 1.2, CH₃CH₂CH=CH), 5.40 (1H, ddt, J 15.5, 6.1 and 1.6, CH₃CH₂CH=CH), 4.03 (1H, tdd, J 6.1, 4.8 and 1.2, CH₂OH), 3.77 (1H, dd, J 10.9 and 6.4, CHCH₂OH), 2.19 (3H, s, CH₃C₆H₄), 2.06 (2H, ddt, J 6.3 and 1.3, CH₃CH₂CH=CH), 0.98 (3H, t, J 7.4, CH₃CH₂CH=CH); δC (101 MHz, CDCl₃) 145.1, 135.6, 130.2, 127.0, 126.8, 122.7, 117.6, 111.6, 65.3, 57.2, 25.4, 17.6, 13.4; m/z (EI+) 205 (32%, [M]+) 174 (100%, [M-CH₂OH]+); HRMS (EI+) found 205.1463, C₁₃H₁₉NO requires 205.1467; enantiomeric ratio was determined as 96.5:3.5 using HPLC; Chiralpak IB-3 column, 90:10 nhexane:IPA, flow 1 mLmin⁻¹, UV detection at 254 nm, 7.6 min (minor), 10.1 min (major).

tert-Butyl (2S,3E)-2-[(4-methoxy)amino]hex-3-enoate, 201

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and p-anisidine (0.3 mmol) with 1.1 equivalents of NCS. Purification via flash column chromatography (20:1 nhexane:EtOAc) afforded the title compound as an orange oil (31.8 mg, 54%); [α]D¹⁸ +41.3 (c = 0.93, CHCl₃); νmax / cm⁻¹ 3384, 2966, 2932, 1728, 1513, 1459, 1369, 1239, 1150; δH (400 MHz, CDCl₃) 6.76 (2H, d, J 8.9, 2 x ArH), 6.58 (2H, d, J 8.9, 2 x ArH), 5.89 (1H, ddt, J 15.5, 6.5 and 1.4, CH₃CH₂CH=CH), 5.49 (1H, ddt, J 15.4, 6.0 and 1.6, CH₃CH₂CH=CH), 4.34 (1H, br t, J 5.9, NHCH₂CO₂Bu), 4.15 (1H, br d, J
6.3, NH), 3.73 (3H, s, OCH$_3$) 2.13-2.01 (2H, m, CH$_3$CH$_2$), 1.44 (9H, s, C(CH$_3$_3)$_3$), 0.98 (3H, t, J 7.4, CH$_3$CH$_2$); $\delta$C (101 MHz, CDCl$_3$) 171.9, 152.6, 141.0, 136.1, 125.2, 115.1, 114.9, 81.9, 60.3, 55.9, 28.1, 25.2, 13.5; m/z (ES+) 292 (100% [MH]$^+$); HRMS (ES+/TOF) found 292.1925, C$_{17}$H$_{26}$NO$_3$ requires 292.1913; enantiomeric ratio determined as 96.5:3.5 using HPLC; Chiralpak IA-3 column, 90:10 n-hexane:IPA, flow 1 mLmin$^{-1}$, UV detection at 254 nm, 5.9 min (minor), 7.6 min (major).

**tert-Butyl (2S,3E)-2-[(4-nitrophenyl)amino]hex-3-enoate, 202**

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\text{\includegraphics{tert-Butyl_-2-[(4-nitrophenyl)amino]hex-3-enoate.png}}
\]

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 4-nitroaniline (0.3 mmol). Purification via flash column chromatography (19:1 n-hexane:EtOAc) afforded the title compound a yellow oil (52.2 mg, 85%); $[\alpha]_D^{15} +119.7$ (c = 1.38, CHCl$_3$); $\nu_{\text{max}}$ / cm$^{-1}$ 3377, 2972, 2933, 1726, 1597, 1504, 1475, 1313, 1148, 1110; $\delta$H (400 MHz, CDCl$_3$) 8.07 (2H, d, $J$ 9.2, 2 x ArH), 6.53 (2H, d, $J$ 9.2, 2 x ArH), 5.86 (1H, dtd, $J$ 15.6, 6.5 and 1.4, CH$_3$CH$_2$C=CH), 5.48 (1H, ddt, $J$ 15.5, 5.9 and 1.6, CH$_3$CH$_2$CH=CHF), 5.36 (1H, br s, NH), 4.47 (1H, dd, $J$ 5.9 and 1.4, NHCHCO$_2$Bu), 2.15-2.04 (2H, m, CH$_3$CH$_2$), 1.48 (9H, s, C(CH$_3$_3)$_3$), 0.98 (3H, t, J 7.4, CH$_3$CH$_2$); $\delta$C (101 MHz, CDCl$_3$) 170.0, 151.5, 138.5, 137.0, 126.2, 123.0 111.9, 83.0, 58.0, 27.9, 25.2, 13.3; m/z (ES+) 307 (100%, [MH]$^+$), 251 (49%, [M-CH$_3$CH$_2$CH=CH]$^+$); HRMS (ES+/TOF) found 307.1665, C$_{16}$H$_{23}$N$_2$O$_4$ requires 307.1658; enantiomeric ratio determined as 96.5:3.5 using HPLC; Chiralpak IB-3 column, 95:5 n-hexane:IPA, flow 1 mLmin$^{-1}$, UV detection at 224 nm, 6.3 min (minor), 6.8 min (major).

**tert-Butyl (2S,3E)-2-[[3-(hydroxymethyl)phenyl]amino]hex-enoate, 203**

\[
\text{\includegraphics{tert-Butyl_-2-[[3-(hydroxymethyl)phenyl]amino]hex-enoate.png}}
\]

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 3-aminobenzylalcohol (0.3 mmol). Purification via flash column chromatography (4:1 n-hexane:EtOAc) afforded the title compound as a pale yellow oil (27.3 mg, 62%); $[\alpha]_D^{23} +20.7$ (c = 0.868, CH$_3$OH); $\nu_{\text{max}}$ / cm$^{-1}$ 3391, 2968, 2932, 2874, 1726, 1608, 1488, 1369, 1323, 1256, 1148; $\delta$H (400 MHz, CDCl$_3$) 7.14 (1H, t, J 7.9, ArH),
6.70 (1H, ddd, J 7.6, 1.6 and 0.8, ArH), 6.61 (1H, t, J 2.0, ArH), 6.53 (1H, ddd, J 8.1, 2.4 and 0.9, ArH), 5.89 (1H, dtd, J 15.4, 6.4 and 1.4, CH$_3$CH$_2$CH=CH), 5.49 (1H, ddt, J 15.4, 5.7 and 1.6, CH$_3$CH$_2$CH=CH), 4.58 (2H, s, CH$_2$OH), 4.51 (1H, br s, NH), 4.42 (1H, app. br s, NHCO$_2$tBu), 2.14-2.01 (2H, m, CH$_3$C), 1.73 (1H, br s, OH), 1.46 (9H, s, C(CH$_3$)$_3$), 0.98 (3H, t, J 7.4, CH$_3$CH$_2$); δ$_c$ (101 MHz, CDCl$_3$) 171.4, 146.9, 142.0, 136.0, 129.4, 124.5, 116.3, 112.7, 111.9, 82.0, 58.9, 25.3, 13.4; m/z (ES+) 292 (100%, [MH]$^+$), 236 (16%); HRMS (ES+/TOF) found 292.1920, C$_{17}$H$_{26}$NO$_3$ requires 292.1913; enantiomeric ratio determined as 96.5:3.5 using HPLC; Chiralpak IA-3 column, 90:10 hexane:IPA, flow 1 mLmin$^{-1}$, UV detection at 212 nm, 10.6 min (minor), 13.4 min (major).

tert-Butyl (2S,3E)-2-[(pyridin-2-yl)amino]hex-3-enoate, 204

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 2-aminopyridine (0.3 mmol). Purification via flash column chromatography (19:1 hexane:EtOAc) afforded the title compound as a pale yellow oil (38.4 mg, 71%); [α]$_D$$_{21}$ +23.6 (c = 1.27, CHCl$_3$); $\nu_{max}$/ cm$^{-1}$ 3363, 2967, 2933, 2874, 1724, 1600, 1482, 1368, 1328, 1254, 1146, 967; δ$_H$ (400 MHz, CDCl$_3$) 8.07 (1H, ddd, J 5.2, 2.0 and 0.9, ArH), 7.38 (1H, ddd, J 8.2, 7.2 and 1.9, ArH), 6.57 (1H, ddd, J 7.2, 5.1 and 1.0, ArH), 6.40 (1H, dt, J 8.4 and 1.0, ArH), 5.87 (1H, dtd, J 15.6, 6.4 and 1.5, CH$_3$CH$_2$CH=CH), 5.55 (1H, ddt, J 15.5, 6.4 and 1.5, CH$_3$CH$_2$CH=CH), 5.07 (1H, br d, J 7.5, NH), 4.85 (1H, ddd, J 7.5, 5.8 and 1.4, NHCHCO$_2$tBu), 2.12-2.00 (2H, m, CH$_3$CH$_2$), 1.45 (9H, s, C(CH$_3$)$_3$), 0.97 (3H, t, J 7.4, CH$_3$CH$_2$); δ$_H$ (400 MHz, CDCl$_3$) 171.3, 157.4, 147.9, 137.2, 135.5, 124.3, 113.4, 108.1, 81.7, 56.9, 28.0, 25.3, 13.3; m/z (ES+) 263 (19%, [MH]$^+$), 207 (100%, [M-H-C(CH$_3$)$_3$]$^+$, 189 (9%), 161 (18%); HRMS (ES+/TOF) found 262.1765, C$_{15}$H$_{23}$N$_2$O$_2$ requires 263.1760; enantiomeric ratio was determined 94.5:5.5 using HPLC; Chiralpak IA-3 column, 94:5.5 hexane:IPA, flow 1 mLmin$^{-1}$, UV detection at 268 nm, 10.9 min (minor), 22.1 min (major).
**tert-Butyl (2S,3E)-2-[(6-bromopyridin-2-yl)amino]hex-3-enoate, 205**

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 2-amino-6-bromopyridine (0.3 mmol). Purification via flash column chromatography (20:1 \(^6\)hexane:EtOAc) afforded the title compound as a pale yellow oil (52.0 mg, 70%); \([\alpha]_D^{19} +23.6 \ (c = 1.19, \text{CHCl}_3\); \(\nu_{\max} / \text{cm}^{-1} \ 3353, 2971, 2934, 2876, 1722, 1594, 1557, 1491, 1150; \delta_H (400 MHz, CDCl\(_3\)) 7.20 (1H, t, \(J = 7.8, \text{ArH}\)), 6.73 (1H, d, \(J = 7.5, \text{ArH}\)), 6.28 (1H, d, \(J = 8.1, \text{ArH}\)), 5.86 (1H, dtd, \(J = 15.4, 6.4 \text{ and } 1.5, \text{CH\(_3\)CH\(_2\)CH=CH}\)), 5.48 (1H, ddt, \(J = 15.4, 6.1 \text{ and } 1.6, \text{CH\(_3\)CH\(_2\)CH=CH}\)), 5.26 (1H, br d, \(J = 7.4, \text{NH}\)), 4.74 (1H, ddd, \(J = 7.3, 6.1 \text{ and } 1.2, \text{NHCHCO\(_2\)tBu}\)), 2.12-2.09 (2H, m, CH\(_3\)CH\(_2\)), 1.46 (9H, s, C(CH\(_3\))\(_3\)), 0.97 (3H, t, \(J = 7.5, \text{CH\(_3\)CH\(_2\)}\)); \(\delta_C (101 MHz, \text{CDCl}_3) 170.7, 157.3, 140.1, 139.2, 136.2, 123.7, 116.4, 105.9, 82.0, 57.0, 27.9, 25.3, 13.3; \(m/z (\text{ES}^+) \ 343 (88%, [\text{MH}+2]^+)\). 341 (82% [\text{MH}^+]\), 287 (100%), 285 (91%) 224 (89%), 208 (91%); HRMS (ES+/TOF) found 341.0850, C\(_{15}\)H\(_{22}\)N\(_2\)O\(_2\)\(_7\)Br requires 341.0865; enantiomeric ratio was determined as 96.5:3.5 using HPLC; Chiralcel OD-H column, 95:1 \(^6\)hexane:IPA, flow 1 mLmin\(^{-1}\), UV detection at 236 nm, 8.6 min (minor), 12.3 min (major).

**tert-Butyl (2S,3E)-2-[(5-iodopyridin-2-yl)amino]hex-3-enoate, 206**

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 2-amino-5-iodopyridine (0.3 mmol). Purification via flash column chromatography (9:1 \(^6\)hexane:EtOAc) afforded the title compound as a clear oil (60.2 mg, 78%); \([\alpha]_D^{27} +34.9 \ (c = 0.97, \text{CHCl}_3\); \(\nu_{\max} / \text{cm}^{-1} \ 3359, 2967, 2933, 2873, 1722, 1586, 1476, 1368, 1256, 1149, 966; \delta_H (400 MHz, CDCl\(_3\)) 8.22 (1H, dd, \(J = 2.3 \text{ and } 0.7, \text{ArH}\)), 7.58 (1H, dd, \(J = 8.7 \text{ and } 2.3, \text{ArH}\)), 6.27 (1H, dd, \(J = 8.7 \text{ and } 0.8, \text{ArH}\)), 5.84 (1H, dtd, \(J = 15.5, 6.4 \text{ and } 1.5, \text{CH\(_2\)CH=CH}\)), 5.51 (1H, ddt, \(J = 15.5, 5.8 \text{ and } 1.5, \text{CH\(_2\)CH=CH}\)), 5.16 (1H, br d, \(J = 7.4, \text{NH}\)), 4.78 (1H, ddd, \(J = 7.4, 6.0 \text{ and } 1.3, \text{CHNH}\)), 2.12-2.30 (2H, m, CH\(_2\)CH\(_3\)), 1.45 (9H, s, C(CH\(_3\))\(_3\)), 0.97 (3H, t, \(J = 7.4, \text{CH}_3\)); \(\delta_C (101 MHz, \text{CDCl}_3) 171.0, 156.1, 153.6, 144.7, 135.9, 123.9, 110.4, 81.9, 77.4, 56.8., 28.0, 25.3, 13.3; \(m/z (\text{ES}^+) \ 389 (100%, [\text{MH}^+]\);
HRMS (ES+/TOF) found 389.0717, C_{15}H_{22}N_{2}O_{2} requires 389.0726; enantiomeric ratio was determined as 96.5:3.5 using HPLC; Chiralcel OD-H column, 95:5 hexane:IPA, flow 1 mL min\(^{-1}\), UV detection at 236 nm, 8.6 min (minor), 12.3 min (major).

tert-Butyl (2S,3E)-2-[(5-cyanopyridin-2-yl)amino]hex-3-enoate, 207

Following general procedure G using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 2-amino-5-cyanopyridine (0.3 mmol). Purification via flash column chromatography (9:1 hexane:EtOAc) afforded the title compound as an off-white crystalline solid (36.6 mg, 63%); m.p. 94-97 °C; \([\alpha]_D^{22} +74.0\) (c = 1.01, CHCl\(_3\)); \(\nu_{\text{max}} / \text{cm}^{-1}\) 3356, 2979, 2935, 2216, 1721, 1603, 1575, 1512, 1392, 1365, 1230, 1150; \(\delta_H\) (400 MHz, CDCl\(_3\)) 8.38 (1H, dd, \(J = 2.1\) and 0.8, 2 x ArH), 7.55 (1H, dd, \(J = 8.8\) and 2.2, 2 x ArH), 6.42 (1H, dd, \(J = 8.8\) and 0.8, ArH), 5.84 (1H, dt, \(J = 15.4, 6.4\) and 1.5, CH\(_3\)CH\(_2\)CH=CH), 5.67 (1H, br d, \(J = 6.3\), NH), 5.51 (1H, dt, \(J = 15.5, 6.0\) and 1.6, CH\(_3\)CH\(_2\)CH=CH), 4.90 (1H, br t, \(J = 6.1\), NHCHCO\(_2\)tBu), 2.07 (1H, dt, \(J = 7.6, 6.4\) and 1.4, CH\(_3\)CH\(_2\)), 1.47 (9H, s, C(CH\(_3\))\(_3\)), 0.98 (3H, t, \(J = 7.4\), CH\(_3\)CH\(_2\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 170.3, 158.4, 153.0, 139.4, 136.4, 123.2, 118.4, 107.9, 97.7, 82.5, 56.5, 27.9, 25.3, 13.2; \(m/z\) (ES+) 288 (36%, [MH]+), 232 (100%), 224 (17%); HRMS (ES+/TOF) found 288.1726, C\(_{16}\)H\(_{22}\)N\(_2\)O\(_2\) requires 288.1712; enantiomeric ratio was determined as 96.5:3.5 using HPLC; Chiralpak IA-3 column, 90:10 hexane:IPA, flow 1 mL min\(^{-1}\), UV detection at 236 nm, 7.6 min (minor), 33.4 min (major).

tert-Butyl (2S,3E)-2-[(1H-pyrazol-3-yl)amino]hex-3-enoate, 208

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 3-aminopyrazole (0.3 mmol). Purification with flash column chromatography (4:1 hexane:EtOAc) afforded the title compound as a pale orange oil (13.0 mg, 26%); \([\alpha]_D^{23} +16.2\) (c = 0.617, CHCl\(_3\)); \(\nu_{\text{max}} / \text{cm}^{-1}\) 3298, 2965, 2934, 1729, 1555, 1368, 1255, 1154; \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.31 (1H, d, \(J = 2.4\), ArH), 5.89 (1H, dt, \(J = 15.6, 6.4\) and 1.3, CH\(_3\)CH\(_2\)CH=CH), 5.63 (1H, d, \(J = 2.4\), ArH), 5.53 (1H, dt, \(J = 15.4, 6.0\) and 1.5, CH\(_3\)CH\(_2\)CH=CH), 4.51 (1H, d, \(J = 6.0\), NHCHCO\(_2\)tBu), 4.40 (1H, br s, NH), 2.13-2.01 (2H, m,
CH$_3$CH$_2$), 1.44 (9H, s, C(CH$_3$)$_3$), 0.98 (3H, t, J 7.4, CH$_3$CH$_2$); $\delta_C$ (101 MHz, CDCl$_3$) 171.9, 155.3, 135.6, 130.2, 125.0, 91.9, 81.5, 59.9, 28.0, 25.3, 13.3; m/z (ES+) 252 (92%, [MH]$^+$), 196 (100%); HRMS (ES+/TOF) found 252.1716, C$_{13}$H$_{22}$N$_3$O$_2$ requires 252.1707; enantiomeric ratio determined as 97:3 using HPLC; Chiralpak IA-3 column, 90:10 $^n$hexane:IPA, flow 1 mL min$^{-1}$, UV detection at 236 nm, 15.5 min (minor), 19.7 min (major).

tert-Butyl (2S,3E)-2-[(1H-1,3-benzodiazol-2-yl)amino]hex-3-enolate, 209

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and 2-aminobenzimidazole (0.3 mmol). Purification via flash chromatography (3:1 $^n$hexane:EtOAc) afforded the title compound as an off-white solid (52.0 mg, 43%); m.p. gradual decomp. at >155 °C; [a]$_D^{17}$ +32.9 (c = 1.03, CHCl$_3$); $\nu_{\text{max}}$ / cm$^{-1}$ 3303, 3060, 2970, 2934, 2877, 1707, 1602, 1463, 1369, 1259, 1041; $\delta_C$ (101 MHz, CDCl$_3$) 171.7, 154.0, 137.8, 136.0, 123.8, 120.5, 112.4, 82.6, 58.1, 27.9, 25.2, 13.1; m/z (ES+) 302 (100%, [MH]$^+$), 146 (69%), 219 (24%); HRMS (ES+/TOF) found 302.1876, C$_{17}$H$_{24}$N$_3$O$_2$ requires 302.1863; enantiomeric ratio determined as 97:3 using HPLC; Chiralpak IA-3 column, 90:10 $^n$hexane:IPA, flow 1 mL min$^{-1}$, UV detection at 254 nm, 11.2 min (minor), 26.0 min (major).

Ethyl (S,E)-2-(4-((1-(tert-butoxy)-1-oxohex-3-en-2-yl)amino)phenyl)oxazole-4-carboxylate, 210

Following general procedure G, using (S)-tert-butyl 4-phenylselanyl-hex-2-(E)-enoate (0.2 mmol) and ethyl 2-(4-aminophenyl)oxazole-4-carboxylate (0.3 mmol). Purification via flash
column chromatography (4:1 \textsuperscript{1}Hhexane:EtOAc) afforded the title compound as a white solid (56.2 mg, 70%); m.p. 98-102 °C; [\alpha]_D^{25} +57.7 (c = 0.84, CHCl\textsubscript{3}); \nu_{max} / \text{cm}^{-1} 3373, 3155, 3138, 2976, 2935, 2874, 1727, 1612, 1507, 1370, 1320, 1251, 1144, 1113; \delta_H (400 MHz, CDCl\textsubscript{3}) 8.17 (1H, s, ArH(oxazole)), 7.89 (2H, d, J 8.7, 2 x ArH(phenyl)), 6.60 (2H, d, J 8.7, 2 x ArH(phenyl)), 5.88 (1H, dtd, J 15.1, 6.4 and 1.3, CH\textsubscript{3}CH\textsubscript{2}CH=CH), 4.89 (1H, ddt, J 15.2, 5.8 and 1.4, CH\textsubscript{3}CH\textsubscript{2}CH=CH\textsubscript{2}), 4.89 (1H, br d, J 6.6, NH), 4.45 (1H, br t, J 5.9, NHCH\textsubscript{2}CO\textsubscript{2}Bu), 4.20 (2H, q, J 7.1, C(O)OCH\textsubscript{2}CH\textsubscript{3}), 2.13-1.99 (2H, m, CH\textsubscript{3}CH\textsubscript{2}), 1.46 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 1.38 (3H, t, J 7.2, C(O)OCH\textsubscript{2}CH\textsubscript{3}), 0.97 (3H, t, J 7.4, CH\textsubscript{3}CH\textsubscript{2}); \delta_C (101 MHz, CDCl\textsubscript{3}) 170.7, 163.2, 161.7, 148.8, 142.6, 136.4, 134.2, 128.4, 123.8, 115.7, 112.9, 82.4, 61.1, 58.3, 27.9, 25.4, 14.3, 13.3; \text{m/z} (ES+) 464 (28%), 401 (100% [MH]+); HRMS (ES+/TOF) found 401.2079, C\textsubscript{22}H\textsubscript{29}N\textsubscript{2}O\textsubscript{5} requires 401.2076; enantiomeric ratio determined as 96.5:3.5 using HPLC; Chiralpak IA-3 column, 90:10 \textsuperscript{1}Hhexane:IPA, flow 1 mL min\textsuperscript{-1}, UV detection at 236 nm, 15.5 min (minor), 30.8 min (major).

**tert-Butyl (2S, 3E)-2-\text{[(benzyloxy)carbonyl]amino}hex-3-enoate, 211**

According to the procedure of Armstrong\textsuperscript{249} to a solution of (S)-\textit{tert}-butyl 4-phenylselanyl-hex-2-(\textit{E})-enoate (110 mg, 0.33 mmol) and benzyl carbamate (151 mg, 1 mmol) in dry methanol (1.5 mL) was added trimethylorthoformate (255 \textmu L, 1.95 mmol) and para-toluene sulfonic acid (1 mg). The solution was stirred at room temperature for 30 minutes before cooling to 0 °C, diisopropylethylamine (350 \textmu L, 1.98 mmol) was added followed by \textit{N}-chlorosuccinimide (135 mg, 1.0 mmol). The reaction was stirred for a further 5 minutes then quenched with 1M HCl (aq., 2 mL) then NaHCO\textsubscript{3} (sat. aq., 1 mL). The reaction was extracted into EtOAc, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, concentrated under reduced pressure and purified by flash column chromatography (19:1 \textsuperscript{1}Hhexane:EtOAc) to afford the title compound as a clear oil (74.5 mg, 71%); [\alpha]_D^{24} +93.2 (c = 1.11, CHCl\textsubscript{3}); \nu_{max} / \text{cm}^{-1} 3342, 2968, 2930, 2958 1726, 1526, 1437, 1369, 1228, 1156; \delta_H (400 MHz, CDCl\textsubscript{3}) 7.40 (5H, m, 5 x ArH), 5.80 (1H, dtd, J 5.15, 6.2 and 1.0, CH\textsubscript{3}CH\textsubscript{2}CH=CH), 5.49-5.33 (2H, m, CH\textsubscript{3}CH\textsubscript{2}CH=CH and NH), 5.11 (2H, s, CH\textsubscript{2}Ph), 4.72 (1H, t, J 6.8, NHCH\textsubscript{2}CO\textsubscript{2}Bu), 2.06 (2H, app. p, J 7.3, CH\textsubscript{3}CH\textsubscript{2}), 1.46 (9H, s, C(CH\textsubscript{3})\textsubscript{3}), 0.98 (3H, t, J 7.4, CH\textsubscript{3}CH\textsubscript{2}); \delta_C (101 MHz, CDCl\textsubscript{3}) 170.3, 155.7, 155.6, 136.5, 135.9, 128.6, 128.3, 82.3, 67.1, 56.3, 28.1, 24.5, 13.4; \text{m/z} (ES+) 358 (100%, [MK]+), 342 (85%, [MN]a+), 220 (53%, [MH]+); HRMS (ES+/TOF)
found 342.1678, C_{18}H_{25}NO_4Na requires 342.1681; enantiomeric ratio was determined as 97:3 using HPLC; Chiralcel OD-H columns, 99:1 \text{\textit{\textalpha}}-hexane:IPA, flow 1 mLmin\(^{-1}\), UV detection at 215 nm, 24.1 min (minor), 27.2 min (major).

\textit{tert-}Butyl (2S)-2-\{[(benzylxy)carbonyl]amino\}-3-hydroxypropanoate, 212

Through a stirred solution of \textit{tert-}butyl (3E)-2-\{[(benzylxy)carbonyl]amino\}hex-3-enoate (60 mg, 0.189 mmol) in CH\(_2\)Cl\(_2\) (2 mL) at -78 °C was bubbled O\(_2\) for 15 minutes. Then ozone was bubbled through the reaction until the colourless solution turns to a blue solution (~10 min). Oxygen was then bubbled through the solution until the solution turns colourless. The reaction mixture was then diluted with MeOH (5 mL) and NaBH\(_4\) (71.5 mg, 1.89 mmol) and allowed to warm to room temperature over 2 hours. The reaction mixture was concentrated under reduced pressure and the crude reaction mixture dissolved in CH\(_2\)Cl\(_2\), washed twice with H\(_2\)O and then dried over Na\(_2\)SO\(_4\). Purification by flash column chromatography (2:1 \text{\textit{\textalpha}}-hexane:EtOAc) provided the title compound as an off-white solid (42.3 mg, 76%); m.p. 86-88 °C (lit.\textsuperscript{273} 89-90); \([\alpha]_D^{24}\) -11.7 (c = 1.02, EtOH), \([\text{lit.}\textsuperscript{273} [\alpha]_D^{22}\) -13.7 (c = 1.03, EtOH)); \(\nu_{\text{max}}\) / cm\(^{-1}\) 3401, 3263, 3063, 2952, 2892, 1710, 1550, 1455, 1366, 1274, 1236, 1154, 1087, 1050; \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.42-7.27 (5H, m, 5 x ArH), 5.72 (1H, br d, J 7.1, NH), 5.11 (2H, s, CH\(_2\)Ph), 4.36-4.27 (1H, m, CH\(_2\)O\(_t\)Bu), 2.39 (1H, br t, J 5.6, OH), 1.47 (9H, s, C(CH\(_3\))\(_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 169.6, 156.4, 136.3, 128.7, 128.34, 128.26, 83.0, 67.2, 63.9, 56.8, 28.1; \(m/z\) (ES\(^{+}\)) 334 (100%, [MK]\(^{+}\)), 318 (72% [MNa]\(^{+}\)), 196 (43%); HRMS (ES+/TOF) found 318.1335, C\(_{15}\)H\(_{21}\)NO\(_5\)Na requires 318.1317; enantiomeric ratio was determined as 91:9 using HPLC; Chiralcel OD column, 91:9 \text{\textit{\textalpha}}-hexane:IPA, flow 1 mLmin\(^{-1}\), UV detection at 214 nm, 11.1 min (major), 13.5 min (minor).

\((S)-\text{Ethyl-2-}((2)-1\text{-benzylxy})-1\text{-oxopropan-2-yl}amino)pent-3\text{-enoate, 218}

Following general procedure F, using (S)-ethyl 4-phenylselanylbut-2-(E)-enoate (0.3 mmol) and H\(_2\)N-L-Ala-CO\(_2\)Bn (0.2 mmol). Purification via flash column chromatography (20:1 to 4:1 \text{\textit{\textalpha}}-hexane:EtOAc) afforded the title compound as pale yellow oil (37.7 mg, 62%); \([\alpha]_D^{21}\)
+12.4 (c = 1.13, CHCl₃); v_max / cm⁻¹ 3036, 2981, 2939, 1733, 1456, 1370, 1240, 1154, 1028; δ_H (400 MHz, CDCl₃) 7.39-7.31 (5H, m, 5 x ArH), 5.73 (1H, ddd, J 15.5, 6.3 and 0.89, CH₃CH=CH). 5.39 (1H, ddq, J 15.5, 8.0 and 1.6, CH₂CH=CH), 5.14 (2H, app. q, J 12.3, OCH₂Ph), 4.17 (2H, qd, J 7.1, 1.8, OCH₂CH₃), 3.81 (1H, d, J 8.0, NHC₉H=CO₂Et), 3.39 (1H, q, J 7.0, CH₃), 1.94 (1H, br s, NH), 1.66 (3H, dd, J 7.0 and 1.6 CH₃CH=CH), 1.32 (3H, d, J 6.9, NHCH₂CH₃), 1.25 (3H, t, J 7.1, OCH₂CH₃); the following distinct signals for the Z-isomer were observed 5.26 (1H, ddd, J 11.0, 9.3 and 1.8, CH₃CH=C₃H), 1.59 (3H, dd, J 7.0 and 1.8) and the E:Z ratio was determined to be 10:1 by integration of the signals at 5.29 and 5.26 respectively; δ_C (101 MHz, CDCl₃) 175.0, 172.7, 135.7, 130.7, 128.6, 128.3, 128.1, 127.3, 66.6, 62.4, 61.1, 54.4, 19.1, 17.8, 14.1; m/z (ES⁺) 328 (100%, [MNa]⁺), 306 (95%, MH⁺), 232 (38%), 132 (12%); HRMS (ES+/TOF) found 306.17052, C₁₇H₂₄NO₄ requires 306.17080. The diastereomeric mixture was prepared by the same method from racemic phenylselanylbut-2-enoic acid ethylester. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; δ_C (101 MHz, CDCl₃) 174.9, 172.3, 135.9, 131.0, 127.3, 66.8, 61.8, 61.4, 53.7, 19.1.

(2S)-2-{[(2S,3E)-1-Ethoxy-1-oxopent-3-en-2-yl]amino}propanoic acid, 219

A suspension of (S)-ethyl-2-((2)-1-benzyloxy)-1-oxopropan-2-yl]amino)pent-3-enoate (65 mg, 0.24) and 10% Pd/C (6.5 mg) in dry methanol (0.4 mL) was stirred for 5.5 hours under hydrogen. Filtration through Celite and concentration under reduced pressure afforded the title compound as a white solid (44.1 mg, 97%); m.p. 158-160 °C; [α]_D +7.98 (c = 1.00, EtOH); v_max / cm⁻¹ 2694, 2937, 2735, 1750, 1568, 1397, 1351; δ_H (400 MHz, d₆-DMSO ) 4.08 (2H, q, J 7.0, OCH₂CH₃), 3.26 (1H, t, J 6.7, CHCO₂Et), 3.15 (1H, q, J 6.9, CHCH₃), 1.57-1.46 (2H, m, CH₃CH₂CH₂), 1.34-1.24 (2H, m, CH₃CH₂CH₂), 1.19-1.14 (6H, m, CHCH₃ and OCH₂CH₃), 0.85 (3H, t, J 7.8, CH₃CH₂CH₂); δ_C (101 MHz, d₆-DMSO) 175.6, 174.2, 60.1, 58.8, 54.5, 34.9, 18.8, 18.5, 14.2, 13.7; m/z (ES⁺) 218 (100%, [MH]⁺), 172 (53%), 116 (28%); HRMS (ES+/TOF) found 218.1398, C₁₀H₂₀NO₄ requires 218.1392.
(2S,3aS,7aS)-Octahydroindole-2-carboxylic acid benzyl ester, 215

According to the procedure of Pascard,\textsuperscript{318} a solution of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid (5 mmol), \textit{para}-toluenesulfonic acid (1.5 g, 8.5 mmol) in BnOH (2 g, 18.5 mmol) and toluene (15 mL) was stirred at reflux for 4 hours with H\textsubscript{2}O collected in a Dean-Stark trap. The solution was then concentrated under reduced pressure and triturated with Me\textsubscript{3}Bu overnight, filtered and concentrated under reduced pressure to afford the title compound as a white solid (2.17 g, 100%); m.p. 113-116 °C; \nu\textsubscript{max} / cm\textsuperscript{-1} 2949, 2873, 2724, 1745, 1519, 1454, 1388, 1202, 1152, 1030, 1008; \delta\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 10.19 (1H, br s, NH), 7.77 (2H, d, J 8.1, 2 x ArH), 7.40-7.25 (5H, m, 5 x ArH), 7.15 (2H, d, J 8.0, 2 x ArH), 5.22 (1H, d, J 12.5, CH\textsubscript{HPh}), 5.15 (1H, d, J 12.5, CH\textsubscript{HPh}), 4.68 (1H, app. dq, J 8.3 and 3.3, NCHCH), 4.14 (1H, br s, NH), 3.86 (1H, app. br s, CHCO\textsubscript{2}Ph), 2.54 (1H, dq, J 11.4 and 5.8, CH\textsubscript{HCHCO\textsubscript{2}Ph}), 2.39-2.30 (4H, m, includes 2.34 (3H, s, CH\textsubscript{3}) and CH\textsubscript{HCHCO\textsubscript{2}Ph}), 2.03-1.88 (2H, m, 2 x alkyl CH\textsubscript{H}), 1.67-1.11 (7H, m, 7 x alkyl CH\textsubscript{H}); \delta\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 169.9, 141.7, 140.2, 134.4, 128.8, 128.7, 128.6, 128.5, 68.4, 59.6, 57.9, 36.4, 31.5, 24.8, 22.4, 21.3, 20.3; m/z (ES+) 260 (15% [MH-C\textsubscript{7}H\textsubscript{7}O\textsubscript{3}S]\textsuperscript{+}), 211 (60%), 170 (100%, [MH-C\textsubscript{7}H\textsubscript{7}]\textsuperscript{+}); HMRS (ES+/TOF) found 260.1678, C\textsubscript{16}H\textsubscript{22}NO\textsubscript{2} requires 260.1645.

Benzy1 (2S,3aS,7aS)-1- (2S)-2-[(\textit{tert}-butyloxy carbonyl)-amino]-propionyl]-octahydro-1H-indole-2-carboxylate, 220

Based on the procedure of Fox,\textsuperscript{319} to a stirred solution of benzy1 (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester (900 mg, 2.08 mmol) in DMF (8.6 mL, 0.55 M) was added diisopropylethylamine (1.68 mL), N-Boc-L-Ala-OH (393 mg, 2.08 mmol), HOBT (365 mg, 2.70 mmol) and EDCI (517 mg, 2.70 mmol). The reaction was stirred at room temperature for 25 hours, concentrated under reduced pressure. The crude reaction mixture was then diluted with EtOAc (40 mL), washed with, alternately H\textsubscript{2}O (20 mL), 1M HCl (aq.), brine, NaHCO\textsubscript{3} (sat. aq.), brine then dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure to afford the title compound as a colorless oil (803 mg, 89%); \nu\textsubscript{max} / cm\textsuperscript{-1}
(2S)-1-[(2S,3aS,7aS)-2-[(Benzyloxy)carbonyl]-octahydro-1H-indol-1-yl]-1-oxopropyl-2-ammonium trifluoroacetate, 221

To a stirred solution of 4-phenylselanylbut-2-enoic acid ethyl ester (25.4 mg, 0.093 mmol) in methanol (1 mL) was added trimethylorthoformate (39.8 μL, 0.35 mmol) and para-toluenesulfonic acid (1 mg). The reaction mixture was stirred for 30 minutes at room temperature before cooling to 0 °C, diisopropylethylamine (61.6 μL, 0.36 mmol) then N-chlorosuccinimide (24.2 mg, 0.18 mmol) were added and after an additional 2 minutes (2S)-1-[(2S,3aS,7aS)-2-[(benzyloxy)carbonyl]-octahydro-1H-indol-1-yl]-1-oxopropyl-2-ammonium trifluoroacetate (20 mg, 0.6 mmol) was added. The reaction was stirred at 0 °C for 1 hour, then 1M HCl (aq., 1mL) was added, followed by NaHCO₃ (sat. aq., 1 mL). The reaction was extracted into EtOAc, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. Purification via flash column chromatography (99:1 to 95:5 EtOAc:MeOH) to afford (3S,5aS,9aS,10aS)-3-methyldecahydropyrazino[1,2-a]indole-1,4-dione (9.1 mg, 63%); m.p.168-169 °C; νₙₐₓ / cm⁻¹ 3493, 3225, 2926, 2864, 1686, 1637, 1426, 1299, 1163, 1116; δH (400 MHz, CDCl₃) 6.08 (1H, br s, NH), 4.14 (1H, dd, J 10.0 and 7.0, NCH(O)), 4.03-3.98 (2H, m, CHCH₃ and NCH(CH₃)), 2.41-2.19 (2H, m, NCHCH₂), 2.04 (1H, ddd, J 12.3, 7.0 and 5.2, NCHCH), 1.82-1.75 (2H, m, alkyl CH₂), 1.75-1.56 (2H, m, alkyl CH₂), 1.54-1.47 (1H, alkyl CHH), 1.43 (3H, d, J 6.9, CH₃), 1.36-1.25 (1H, m, alkyl CHH), 1.17 (1H, qt, J 12.6 and 2.8, alkyl CHH), 1.02 (1H, tdd, J 13.2, 10.6 and 7.0, alkyl CHH).
3.4, alkyl CHH; δC (101 MHz, CDCl₃) 171.6, 166.9, 59.5, 56.4, 51.2, 35.9, 29.0, 27.6, 25.9, 23.5, 20.9, 15.4; m/z (ES+), 264 (55%, [M+MeCN]+), 223 (100% [MH]+); HRMS (ES+/TOF) found 223.1450, C₁₂H₁₉N₂O₅ requires 223.1447.

(2S)-1-[(2S,3aS,7aS)-2-[(Benzyloxy)carbonyl]-octahydro-1H-indol-1-yl]-1-oxopropyl-2-ammonium trifluoroacetate, 222

Benzyl (2S,3aS,7aS)-1-((2S)-2-[amino]-propionyl)-octahydro-1H-indole-2-carboxylate (753 mg, 1.75 mmol) was added to a 1:4 mixture of TFA:CH₂Cl₂ (20 mL). The reaction mixture was stirred at room temperature for 45 minutes, then concentrated under reduced pressure, azeotroped (3x) with toluene to remove H₂O affording the title compound as a light brown oil (740 mg, 99%); νmax / cm⁻¹ 2934, 2862, 1743, 1651m 1444, 1169, 1023; δH (400 MHz, CDCl₃) 7.84 (3H, br s, NH₃), 7.37-7.28 (5H, m, 5 x ArH), 5.21 (1H, d, J 11.8, CHHPh), 5.07 (1H, d, J 11.8, CHHPh), 4.48 (1H, dd, J 10.2, 8.2, NCHCO₂Bn), 4.31 (1H, m, CH₃CH), 3.92 (1H, dt, J 12.2 and 6.2, NCHCH), 2.37 (1H, m, NCHCH₂), 2.18 (1H, ddd, J 12.4, 7.9 and 6.3, NCHCH₂), 1.98 (1H, m, NCHCH), 1.83-1.59 (4H, m, 4 x alkyl CHH), 1.52-1.47 (2H, m, 2 x alkyl CHH), 1.44 (3H, d, J 6.7, CH₃), 1.25-1.18 (2H, m, 2 x alkyl CHH), δC (101 MHz, CDCl₃) 171.3, 168.9, 161.3 (q), 135.4, 128.8, 128.7, 128.3, 67.4, 59.6, 59.1, 48.0, 37.4, 30.1, 28.3, 26.9, 25.3, 23.6, 19.7, 18.0; m/z (ES+) 353 (45%, [MNa⁺]), 331 (100%, [MH]+); HRMS (ES+/TOF) found 331.2020, C₁₉H₂₇N₂O₃ requires 331.2022.

Diphenyldiazomethane, 225

According to the procedure of Murray,²³⁰ to a stirred mixture of benzophenone hydrazone (981 mg, 5 mmol), anhydrous MgSO₄ (2.4 g, 20 mmol) in CH₂Cl₂ (3.75 mL) at 0 °C was added activated MnO₂ (1.74 g, 20 mmol). The reaction mixture was stirred for 2 hours at 0 °C, then 1 hour at room temperature. Solid material filtered off and washed with CH₂Cl₂.

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Volatiles were removed under reduced pressure as a dark red oil that upon cooling at -18 °C afforded the title compound as a red crystalline solid (920 mg, 95%); m.p. 31 °C (Lit\textsuperscript{320} 30°C). The diazo compound was used immediately.

\((2S,3aS,7aS)\)-Octahydroindole-2-carboxylic acid diphenylmethyl ester, 224

Based on the procedure of Li,\textsuperscript{321} to a stirred solution (2S,3aS,7aS)-octahydroindole-2-carboxylic acid (380 mg, 2.25 mmol) and \textit{para}-toluenesulfonic acid (428 mg, 2.25 mmol) in 1:1 MeCN:H\textsubscript{2}O (20 mL) was added diphenyl diazomethane (875 mg, 4.5 mmol). The reaction mixture was stirred for two minutes and then the pH was adjusted to 9 through the dropwise addition of 1M NaOH. The reaction mixture was extracted into Et\textsubscript{2}O, washed with H\textsubscript{2}O then brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc) afforded the title compound as a white solid (473 mg, 62%); m.p. 99 °C; [\(\alpha\)]\textsubscript{D}\textsuperscript{321} -29.0 (c = 0.966, CHCl\textsubscript{3}); \(v_{\text{max}}\) / cm\textsuperscript{-1} 3422, 3328, 3067, 3033, 2973, 2948, 2926, 2885, 2856, 1717, 1496, 1451, 1343, 1250, 1195, 1184, 1152, 1118, 1097, 966; \(\delta\textsubscript{H}\) (400 MHz, CDCl\textsubscript{3}) 7.36-7.27 (10H, m, 10 x ArH), 6.92 (1H, s, CHPh\textsubscript{2}), 3.94 (1H, dd, \(J = 10.1\) and 5.8, NCHCO\textsubscript{2}CHPh\textsubscript{2}), 3.11 (1H, q, \(J = 5.2\), NCH(CH)CH\textsubscript{2}), 2.51 (1H, s, NH), 2.24 (1H, ddd, \(J = 12.8, 10.1\) and 6.8, CH\textsubscript{2}HCHCO\textsubscript{2}CHPh\textsubscript{2}), 2.07-1.99 (1H, m, NCH(CH)CH\textsubscript{2}), 1.76 (1H, dt, \(J = 12.8\) and 5.4, CH\textsubscript{2}HCHCO\textsubscript{2}CHPh\textsubscript{2}), 1.69-1.58 (2H, m, NCH(CH)CH\textsubscript{2}), 1.48-1.31 (4H, m, 4 x alkyl CH\textsubscript{2}H), 1.26-1.15 (2H, m, 2 x alkyl CH\textsubscript{2}H); \(\delta\textsubscript{C}\) (101 MHz, CDCl\textsubscript{3}) 175.1, 140.0/140.0, 128.6/128.5, 128.1/128.0, 127.3/127.0, 77.4/77.2, 58.9, 58.3, 38.1, 35.9, 28.1, 27.0, 23.6, 21.6; m/z (ES+) 376 (52%, [M-MeCN]\textsuperscript{+}), 336 (100%, [MH]\textsuperscript{+}); HRMS (ES+/TOF) found 336.1966, C\textsubscript{22}H\textsubscript{26}NO\textsubscript{2} requires 336.1964.
(2S,3aS,7aS)-Benzhydryl 1-((S)-2-((tert-butoxycarbonyl)amino)propanoyl)octahydro-1H-indole-2-carboxylate, 226

To a stirred solution of (2S,3aS,7aS)-octahydropindole-2-carboxylic acid diphenylmethyl ester (400 mg, 1.19 mmol) and N-Boc-L-Ala-OH (225 mg, 1.19 mmol) in DMF (2.5 mL) was added diisopropylethylamine (876 μL, 5.36 mmol), followed by EDCI (255 mg, 1.34 mmol) and HOBT (180 mg, 1.34 mmol). The reaction mixture was stirred overnight at room temperature, diluted with H₂O (25 mL), extracted into EtOAc, washed, in sequence, with 1M HCl (aq.), brine, NaHCO₃ (sat. aq.), brine then dried over Na₂SO₄ and concentrated under reduced pressure to afford the title compound as a white foam (564 mg, 92%); [α]D²₁ -47.4 (c = 1.012, CHCl₃); νmax / cm⁻¹ 3343, 3298, 2979, 2933, 2859, 1749, 1705, 1639, 1455, 1366, 1253, 1169; δH (400 MHz, CDCl₃) 7.36 -7.26 (10H, m, 10 x ArH), 6.89 (1H, s, CHPh₂), 5.21 (1H, d, J 8.8, NH), 4.59 (1H, dd, J 10.3 and 8.0, NCHCO₂CHPh₂), 4.49 (1H, J 13.4 and 6.6, CHCH₃), 4.10 (1H, dt, J 12.1 and 5.5, NCHCH), 2.42 (1H, dq, J 12.1, 5.9 and 5.5, NCHCHH), 2.15 (1H, m, NCHCHH), 1.94-1.81 (2H, m, NCHCH and NCHCHHCH₂), 1.74-1.58 (3H, m, NCHCHHCH₂ and 2 x alkyl CHH), 1.55-1.36 (11H, m, C(CH₃)₃ and 2 x alkyl CHH), 1.28 (3H, d, J 6.8, CH₃), 1.21-1.15 (2H, m, 2 x alkyl CHH); δC (101 MHz, CDCl₃) 172.3, 171.3, 155.3, 140.9/139.9, 128.6/128.5, 128.1/128.0, 127.3/127.2, 79.9, 77.7, 59.0, 58.2, 41.2, 37.6, 30.4, 28.8, 28.5, 25.7, 23.8, 20.1, 20.0; m/z (ES⁺) 529 (100% [MNa⁺]), 507 (53%, [MH⁺⁺]); HRMS (ES+/TOF) found 529.2678, C₃₀H₃₈N₂O₅Na requires 529.2678.

(2S,3aS,7aS)-1-((Benzyloxy)carbonyl)octahydro-1H-indole-2-carboxylic acid

To a solution of (2S,3aS,7aS)-octahydropindole-2-carboxylic acid (1.0 g, 5.97 mmol) in 1M NaOH (7.5 mL) at 0 °C was added dropwise benzyl chloroformate (0.92 mL, 6.56 mmol). Solution was stirred overnight and the temperature allowed to increase to room temperature. The reaction was then diluted with H₂O (20 mL), washed with Et₂O, the aqueous layer acidified to pH 4 with 1M HCl (aq.), extracted with EtOAc. The combined
organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford the title compound as a white foam/colourless oil (1.49 g, 84%); $[\alpha]_D^{21}$ -29.3 (c = 1.025, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) peaks appear as rotamers, 9.13 (1H, br s, COOH), 7.40-7.20 (5H, m, 5 x ArH), 5.20-5.04 (2H, m, CH$_2$Ph$_2$), 4.14-4.28 (1H, m, NCHCOOH), 3.99-3.80 (1H, m, NCHCH), 2.40-2.26 (1H, m, NCHCH), 2.23-2.06 (2H, m, NCH(COOH)CH$_2$), 2.05-1.93 (1H, m, 1 x alkyl CHH), 1.80-1.55 (3H, m, 3 x alkyl CHH), 1.55-1.36 (2H, m, 2 x alkyl CHH), 1.35-1.05 (2H, m, alkyl CHH); $\delta_C$ (101 MHz, CDCl$_3$) 178.6/177.2, 155.4/154.1, 136.6, 128.5/128.4, 128.1/127.9, 127.7/127.6, 67.3/67.0, 59.3/58.9, 58.0/57.7, 37.0/36.6, 32.6/31.2, 27.9/27.3, 25.8, 23.8, 20.5/20.4. These data are consistent with literature values.

$\text{C}_{21}\text{H}_{29}\text{NO}_4\text{Na}$ requires 382.1994.

(2S,3aS,7aS)-1-Benzy1 2-tert-butyl octahydro-1H-indole-1,2-dicarboxylate

To a stirred solution of (2S,3aS,7aS)-1-((benzyloxy)carbonyl)octahydro-1H-indole-2-carboxylic acid (1.42 g, 4.7 mmol) in THF (25 mL) was added di-tert-butyl dicarbonate (2.05 g, 9.4 mmol) and DMAP (172.2 mg, 1.41 mmol). The reaction was stirred at room temperature for 6 hours and then the reaction mixture was then concentrated under reduced pressure. Purification via flash column chromatography (9:1 $n$hexane:EtOAc) to afford the title compound as a pale yellow oil (1.55 g, 92%); $[\alpha]_D^{21}$ -38.5 (c = 0.986, CHCl$_3$); $\nu_{\text{max}}$ / cm$^{-1}$ 2976, 2928, 2857, 1741, 1702, 1412, 1356, 1153, 1010; $\delta_H$ (400 MHz, CDCl$_3$) peaks appear as rotamers, 7.36-7.27 (5H, m, 5 x ArH), 5.14-5.04 (2H, m, CH$_2$Ph), 4.22-4.14 (1H, m, NCHCO$_2$Bu), 3.92 (0.5H, dt, $J$ 12.0 and 6.4, NCHCH), 3.81 (0.5H, dt, $J$ 12.0 and 6.4, NCHCH), 2.35-2.23 (1H, m, NC(CO$_2$Bu)CHH), 2.18-1.90 (2H, m, NC(CO$_2$Bu)CHH and NCHCH), 1.75-1.57 (4H, m, 4 x alkyl CHH), 1.53-1.21 (11H, m, C(CH$_3$)$_3$ and 2 x alkyl CH), CHH 1.20-1.07 (2H, m, 2 x alkyl CHH); $\delta_C$ (101 MHz, CDCl$_3$) 172.5/172.3, 154.7/154.2, 137.1/136.8, 128.6, 128.4, 127.9, 81.2/81.1, 66.9/66.8, 58.0/57.4, 36.9/36.5, 32.9/31.7, 28.2/28.0, 28.02, 27.3, 26.0/25.9, 23.9/23.8, 20.7/20.6; m/z (ES+) 382 (100%, [MNa]$^+$), 304 (42%), 208 (68%); HRMS (ES+/TOF) found 382.1988, C$_{21}$H$_{29}$NO$_4$Na requires 382.1994.
(2S,3aS,7aS)-tert-Butyl octahydro-1H-indole-2-carboxylate, 228

To a stirred solution of (2S,3aS,7aS)-1-benzyl 2-tert-butyl octahydro-1H-indole-1,2-dicarboxylate (1.07 g, 2.99 mmol) in MeOH (15 mL) was added 10% Pd on carbon (107 mg). The reaction was stirred for 24 hours under hydrogen, then the reaction mixture was filtered through Celite and concentrated under reduced pressure to afford the title compound as a white solid (672.2 mg, 99%); m.p. 150-151 °C; [α]D18 -28.7 (c = 0.766, CHCl3); νmax / cm⁻¹ 2976, 2928, 2857, 1741, 1702, 1412, 1356, 1153, 1010; δH (400 MHz, CDCl3) 7.38 (1H, br d, J 9.1, NH), 4.33-4.24 (1H, m, NCHCO2tBu), 3.79-3.69 (1H, m, NCCH), 2.50-2.40 (1H, m, NCHC(CH3)3), 2.30-2.16 (1H, m, NCH(CO2tBu)CH2), 2.07-1.98 (1H, m, NCH(CH)CH2), 1.92-1.84 (1H, m, NCH(CO2tBu)CHH), 1.60-1.12 (16H, m, C(CH3)3 and 7 x alkyl CHH); δC (101 MHz, CDCl3) 168.8, 84.6, 59.1, 57.6, 36.4, 31.4, 27.7, 24.6 (2 x CH2), 22.4, 20.2; m/z (ES+) 226 (100%, [MH]+), 211 (17%), 170 (90%); HRMS (ES+/TOF) found 226.1790, C13H24NO2 requires 266.1807.

(2S,3aS,7aS)-tert-Butyl 1-((S)-2-(((benzyloxy)carbonyl)amino)propanoyl)octahydro-1H-indole-2-carboxylate, 229

To a stirred solution of (2S,3aS,7aS)-tert-butyl octahydro-1H-indole-2-carboxylate (650 mg, 2.89 mmol) and N-Boc-L-Ala-OH (644.4 mg, 2.89 mmol) in DMF (3 mL) was added diisopropylethylamine (2.34 mL, 14.3 mmol), followed by EDCI (608 mg, 3.18 mmol) and HOBt (430 mg, 3.18 mmol). The reaction mixture was stirred overnight at room temperature, diluted with H2O (30 mL), extracted into EtOAc, washed sequentially with 1M HCl (aq.) brine, NaHCO3 (sat. aq.), brine, then dried over Na2SO4 and concentrated under reduced pressure. Purification via flash column chromatography (4:1 to 1:1 hexane:EtOAc) afforded the title compound as a white foam (1.0831 g, 95%); [α]D22 -37.0 (c = 1.29, CHCl3); νmax / cm⁻¹ 3297, 2977, 2933, 2860, 1717, 1636, 1529, 1459, 1367, 1244, 1157, 1067; δH (400 MHz, CDCl3) 7.39-7.27 (5H, m, 5 x ArH), 5.51 (1H, d, J 8.6, NH), 5.16-5.0 (2H, m, CH2Ph), 4.54 (1H, dq, J 8.7 and 6.8, CHCH3), 4.29 (1H, dd, J 10.4
and 7.9, NCHCO₂Bu), 4.05 (1H, dt, J 12.1 and 6.4, NCHCH), 2.37 (1H, dq, J 11.9 and 6.3, NCHCH), 2.10 (1H, dt, J 12.4 and 7.2, NCH(CO₂Bu)CHH), 1.98-1.84 (2H, m, NCH(CO₂Bu)CHH and alkyl CHH), 1.79-1.55 (3H, m, 3 x alkyl CHH), 1.54-1.40 (11H, m, C(CH₃)₃ and 2 x alkyl CHH), 1.39-1.12 (5H, CH₃ and 2 x alkyl CHH); δC (101 MHz, CDCl₃) 171.5, 171.3, 155.8, 136.5, 128.6, 128.1, 128.0, 81.2, 66.8, 59.9, 58.1, 47.7, 36.6, 30.5, 28.7, 28.04, 25.72 (2 x CH₂), 23.25, 20.0; m/z (ES+) 453 (100% [MNa]⁺), 431 (45%, [MH]⁺), 375 (14%); HRMS (ES+/TOF) found 453.2374, C₂₄H₃₄N₂O₅Na requires 453.2365.

(2S,3aS,7aS)-tert-Butyl 1-(2-aminopropanoyl)octahydro-1H-indole-2-carboxylate, 230

To a stirred solution of (2S,3aS,7aS)-tert-butyl 1-(((S)-2-(((benzyloxy)carbonyl)amino)propanoyl)octahydro-1H-indole-2-carboxylate (951 mg, 2.36 mmol) in MeOH (9.5 mL) was added 10% Pd on carbon (95.1 mg). The reaction was stirred for 15 hours under hydrogen, the reaction mixture was then filtered through Celite and concentrated under reduced pressure to afford the title compound as a white solid (697 mg, 99%); m.p. 207-209 °C; [α]D²⁰ = -72.3 (c = 0.933, CHCl₃); νmax / cm⁻¹ 3149, 2974, 2924, 2861, 2787, 2687, 2586, 1743, 1656, 1603, 1366, 1156; δH (400 MHz, CDCl₃) 6.01 (2H, br s, NH₂), 4.40 (1H, dd, J 10.3 and 7.8, NCHCO₂Bu), 4.21 (1H, q, J 6.6, CHCH₃), 4.11 (1H, dt, J 12.2 and 6.3, NCHCH), 2.58-2.44 (1H, m, NCHCH), 2.15 (1H, dt, J 12.5 and 7.3, NCH(CO₂Bu)CHH), 1.98-1.78 (2H, m, NCH(CO₂Bu)CHH and 1 x alkyl CHH), 1.77-1.62 (3H, m, 3 x alkyl CHH), 1.61-1.35 (14H, m, CH₃ and C(CH₃)₃ and 2 x alkyl CHH), 1.35-1.17 (2H, m, 2 x alkyl CHH); δC (101 MHz, CDCl₃) 171.1, 169.3, 81.3, 60.3, 58.7, 47.8, 37.2, 30.5, 28.6, 28.1, 25.6, 23.9, 20.1, 18.6; m/z (ES+) 360 (43%, [M+MeCN+Na]⁺), 297 (100%, [MH]⁺), 241 (48%); HRMS (ES+/TOF) found 297.2177, C₁₆H₂₉N₂O₃ requires 297.2178.
(2S,3aS,7aS)-tert-Butyl 1-((S)-2-(((S,E)-1-ethoxy-1-oxopent-3-en-2-yl)amino)propanoyl)octahydro-1H-indole-2-carboxylate, 231

To a stirred solution of (2S,3aS,7aS)-tert-butyl 1-(2-aminopropanoyl)octahydro-1H-indole-2-carboxylate (220 mg, 0.74 mmol) and (S)-ethyl 4-phenylselanylbut-2-(E)-enoate (325 mg, 1.11 mmol) in dry methanol (3.7 mL) was added trimethylorthoformate (479 μL, 4.38 mmol) and para-toluene sulfonic acid (1 mg). The solution was stirred at room temperature for 30 minutes and then cooled to -20 °C. Diisopropylethyl amine (776 μL, 4.45 mmol) then N-chlorosuccinimide (293 mg, 2.23 mmol) were added. The solution was stirred at -20 °C for 2 hours, then 1M HCl (aq., 5 mL) was added, followed by NaHCO₃ (sat. aq., 5 mL). The reaction was extracted into EtOAc, washed brine, dried over Na₂SO₄ and concentrated under reduced pressure. Purification via flash column chromatography (2:1 to 1:1 hexane:EtOAc) afforded the title compound as an clear oil (123 mg, 40%); [α]D²⁻35.9 (c = 1.17, CHCl₃); νmax / cm⁻¹ 2977, 2931, 1738, 1642, 1423, 1367, 1286, 1257, 1158; δH (400 MHz, CDCl₃) 5.77-5.56 (1H, m, CH₃CH=CH), 5.43 (1H, ddd, J 15.3, 8.1 and 1.7, CH₃CH=CHH), 4.30 (1H, dd, J 10.3 and 7.8, NCHCO₂Bu), 4.21-4.04 (3H, m, NH and CO₂CH₂CH₃), 3.79-3.63 (2H, m, NCHCH(CH₂)), 3.45 (1H, q, J 6.6, CHCH₃), 2.3-2.27 (1H, m, NCHC=C), 2.14-2.06 (1H, m, NCH(CO₂Bu)CHH), 1.97-1.87 (1H, m, NCH(CO₂Bu)CHH), 1.85-1.39 (18H, m, includes C(CH₃)₃, CH=CHCH₃ and 6 x alkyl CHH), 1.33-1.07 (8H, m, includes CO₂CH₂CH₃, CHCH₃ and 2 x alkyl CHH); the following distinct signals for the Z-isomer were observed 5.36 (1H, ddd, J 10.9, 9.3 and 1.8), 3.50 (1H, q, J 6.7) and the E/Z ratio was determined to be 4:1 by integration of the signals at 5.43 and 5.36 respectively; δC (101 MHz, CDCl₃) 173.8, 172.6, 171.4, 130.6, 127.9, 81.1, 63.1, 61.1, 60.0, 58.0, 56.1, 52.4, 37.8, 30.5, 28.0, 26.0, 23.9, 20.4, 20.1, 17.9, 14.3; the following distinct signals were observed for the Z-isomer δC (101 MHz, CDCl₃) 130.0, 81.2, 61.3, 56.3, 51.3, 37.9, 30.3, 28.7, 20.5; m/z (ES+) 423 (100%, [MH]+), 367 (15%); HRMS (ES+/TOF) found 423.2842, C₂₃H₃₉N₂O₅ requires 423.2359.

Also isolated was:
(2S)-1-[(2S,3aS,7aS)-2-[(Benzyloxy)carbonyl]-octahydro-1H-indol-1-yl]-1-oxopropyl-2-ammonium trifluoroacetate, 221

White solid (66 mg, 40%), m.p. 167-169 °C. All data was in agreement with that reported above.

(2S,3aS,7aS)-tert-Butyl 1-((S)-2-(((S)-1-ethoxy-1-oxopentan-2-yl)amino)propanoyl)octahydro-1H-indole-2-carboxylate, 232

Preparation of (2S,3aS,7aS)-tert-butyl 1-(((S)-2-(((S),E)-1-ethoxy-1-oxopent-3-en-2-yl)amino)propanoyl)octahydro-1H-indole-2-carboxylate (125 mg, 0.29 mmol) was dissolved in MeOH (2 mL) and was reduced using a H-Cube (10% Pd/C, 4 bar, 1 mLmin⁻¹). After one pass through the column, the reaction mixture was concentrated under reduced pressure to afford the title compound as a clear oil (121 mg, 96%); νₘₐₓ / cm⁻¹ 3460, 3329, 2973, 2874, 1734, 1644, 1468, 1449, 1422, 1366, 1156; δₕ (400 MHz, CDCl₃) 4.34 (1H, dd, J 10.3 and 7.9, NC₄H₂CO₂tBu), 4.20 (2H, q, J 7.1, CO₂CH₂CH₃), 3.77 (1H, dt, J 12.1 and 6.3, NCH(CH₂)), 3.52 (1H, q, J 6.6, CHCH₃), 3.11 (1H, t, J 6.8, NCHCO₂Et), 2.62 (1H, dt, J 12.2 and 6.0, NCHCH(CH₂)), 2.12 (1H, ddd, J 12.4, 7.9 and 6.6, NCH(CO₂Bu)CHH) 1.98-1.68 (3H, m, includes NCH(CO₂Bu)CHH and 2 x alkyl CHH), 1.84-1.49 (8H, m, 8 x alkyl CHH), 1.45 (9H, s, C(CH₃)₃), 1.37-1.20 (8H, m, includes O₂CH₂CH₃, CHCH₃ and 2 x alkyl CHH), 0.88 (3H, t, J 7.3, CHCH₂CH₃); δ_c (101 MHz, CDCl₃) 174.6, 173.5, 171.3, 81.0, 60.6, 60.0, 59.7, 58.0, 52.7, 27.6, 25.6, 30.3, 28.6, 27.0, 25.8, 23.9, 20.2, 20.0, 19.0, 14.3, 13.0; m/z (ES+) 425 (100%, [MH]⁺); HRMS (ES+/TOF) found 425.3016, C₂₃H₄₁N₂O₅ requires 425.3015.

The diastereomeric mixture was prepared over two steps from racemic (S)-ethyl 4-phenylselanylbut-2-(E)-enoate. Spectroscopic data agreed with the material above; the following additional signals were observed for the other diastereomer; δₕ (400 MHz,
CDCl$_3$ 3.25 (1H, t, $J$ 3.25); $\delta_C$ (101 MHz, CDCl$_3$) 172.0, 82.2, 60.4, 59.5, 58.5, 54.1, 33.1, 26.5, 25.5, 23.7, 20.3, 14.2. The diastereomeric ratio of the material derived from the enantiomerically enriched allylic selenide was determined to be 96:4 by integration of the 1H NMR signals at 3.25 (minor) and 3.11 (major) ppm.
6 References

(63) Page, P.; Bordogna, C.; Strutt, I.; Chan, Y.; Buckley, B. Synlett 2013, 24, 2067.
(64) Pullin, R. D. C. Amine-Promoted Alkene Aziridination, Imperial College London, 2011.
(86) Terrier, F. Modern Nucleophilic Aromatic Substitution; WILEY-VCH; Verlag GmbH & Co. KGaA: Weinheim, Germany, 2013.